Mark G. Robson
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Editors

Risk Assessment for Environmental Health

RISK ASSESSMENT FOR ENVIRONMENTAL HEALTH

JOSSEY-BASS

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Mark Robson
William Toscano
Editors

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PREFACE

Understanding risk to humans is one of the most important challenges in environmental public health. Over the past twenty-five years, schools of public health have developed courses to meet the growing needs of environmental health students as well as other public health disciplines to understand the risk assessment process used by government, industry, and academic researchers.

Courses in risk assessment in schools of public health vary in the approaches taken. In discussion with colleagues, it became apparent to us that there is no appropriate text that covers environmental health risk assessment and meets the needs of public health students. Because of the importance of risk assessment in environmental and occupational health sciences, the Environmental and Occupational Health Council of the Association of Schools of Public Health selected risk assessment as a topic for their annual summer meeting held in 2004 at the University of Minnesota. We organized and chaired the meeting and used it as the framework on which to build a risk assessment textbook. This textbook is the deliverable for the 2004 Minneapolis meeting. It is written primarily by faculty colleagues at the member schools of the Association of Schools of Public Health. The chapters and topics in this volume were identified at the meeting as the most relevant for textbook use in a graduate-level introduction to the risk assessment process. In addition, case studies used by faculty for illustrative purposes in their own courses are included.

This book should be considered a useful primary resource for students in public health, environmental science, environmental engineering, and other related disciplines. There are many other important references used by faculty: the classic "Red Book," *Issues in Risk Assessment* (1993) from the National Academy of Sciences, the WHO document *Human Exposure Assessment: An Introduction* (2001), and the EPA Superfund document *Volume I: Human Health Evaluation Manual, Part A* (1989).

Risk assessment is constantly changing with the advent of new exposure assessment tools, more sophisticated models, and a better understanding of disease processes. Risk assessment is also gaining greater acceptance in the developing world, where major environmental problems exist.

We hope you find this textbook of value in your teaching, and we welcome your comments on improving the chapters, adding case studies, and expanding the topics contained in the text.

Acknowledgments

We express our deep thanks to all the authors who contributed to this book. This volume was developed in response to a general agreement that there were few textbooks appropriate for graduate students studying environmental health risk assessment. We were overwhelmingly pleased when many of the faculty who expressed a need for a textbook on this subject were the very same authors who agreed to contribute to the text. We also thank the individuals from our public health partners who contributed to this book. We hope that the content of the textbook reflects the appropriately diverse backgrounds of the authors.

The staff of the Association of Schools of Public Health (ASPH) deserve credit for keeping this project on track—particularly in keeping its editors on task despite our most serious efforts to the contrary. Without the support of the ASPH staff on this project, this book would not have been published.

We also thank the staff of Jossey-Bass/Wiley for their support on this project. Their guidance and support made this a rich learning experience for all involved. In particular, we thank our editor, Andy Pasternack, for his unwavering support and for believing in this effort. We also thank Seth Schwartz and Kelsey McGee for their work in pulling these manuscripts together in final format.

We also acknowledge the support of our federal partners, which have provided support for the ASPH Environmental and Occupational Health Council over the past decade, enabling the council to meet and develop this book. These federal agencies include Centers for Disease Control and Prevention, Health Re-

sources and Services Administration, National Institutes for Health, and U.S. Environmental Protection Agency.

Lastly, we thank the deans of schools of public health for collectively supporting this project and making this an official publication of the Association of Schools of Public Health Environmental and Occupational Health Council.

September 2006

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RISK ASSESSMENT FOR ENVIRONMENTAL HEALTH

CHAPTER ONE

INTRODUCTION TO RISK ASSESSMENT IN PUBLIC HEALTH

Mark Robson
Fred Ellerbusch

Why did God invent risk assessment?
To give astrologers credibility!

—JOKE TOLD AT AN EPA RISK ASSESSMENT MEETING

Learning Objectives

Students who complete this chapter will be able to

1. Become familiar with the topic of risk assessment
2. Understand the process for developing this text
3. Understand the specific issues that relate to public health
4. Gain an overview of the book

Risk assessment is an important part of the training of environmental and occupational health (ENOH) students in schools of public health as well as in many programs in toxicology, environmental medicine, environmental engineering, and other fields of study. Most of the member schools of the Association of Schools of Public Health (ASPH) teach a risk assessment course. In some of the larger schools a student can select risk assessment as a major or minor. A number of texts on risk assessment are available; however, the Environmental and Occupational Health Council of ASPH asked us to write a book specifically designed to teach risk assessment for public health.

We are fortunate to be able to include in this book articles by a number of nationally and internationally recognized experts in the field who are on the faculties of many schools of public health. As a group we identified the major areas that are important for a public health graduate. We have also included a number of case studies to illustrate important principles and examples for our public health students.

Where to Begin?

When you woke up this morning and before leaving the comfort of your bed did you calculate the risk associated with each activity of the day ahead? Did you even know what you would be doing for the day—or, for that matter, think about risk at all? Looking at the day before, did you sum up the risks of what you experienced?

Unless we were in an accident or just missed one, few of us consciously think about risk. Few consider the risk of daily life, and fewer quantify those risks. Yet calculating risk, communicating risk, and managing risk in quantitative or qualitative ways are part of the human experience.

As this chapter was being written, one of us was in Bangkok, Thailand, and the other in Cape May, New Jersey. As each of us journeyed to our destination we thought more about finishing this chapter than about the risk associated with traveling, despite the very real hazards of how we traveled and where we were going.

For example, Thailand, though not the epicenter of SARS, was one of the first countries to record a death from the virus. West Nile Virus is now endemic in New Jersey, which for those with compromised immune systems can be deadly. In each country, and particularly during the summer months, exposure to the sun can lead to skin damage, sun poisoning, or skin cancer. Water pollution and air pollution are significant threats to populations in both locales, although to different degrees. Despite the vastly different cultures of Thailand and the United States, the hazards that concern public health professionals are quite similar.

While we did not quantify the risks associated with each of our journeys, we were aware of them and decided that the benefits outweighed the risks. For MR it was completing a research program that was set in Thailand beginning with the tsunami of 2004; for FE it was just sitting on the beach. Some of you would not have even considered flying more than 20 hours to Thailand, even though it is statistically less safe to drive to a more domestic destination. Others would not travel to Southeast Asia because of SARS, even though West Nile Virus has spread from the East Coast of the United States to the West in just a few years.

This illustrates that we face risks each day of our lives, whether we can quantify them, articulate them, or are even cognizant of them. Nevertheless, the exploration of risk can help inform priority setting, policy making, and decision making at global, national, regional, and local levels.

As we were putting the finishing touches on this chapter, the United States witnessed one of its worst natural disasters, Hurricane Katrina. This disaster made a previously hypothetical risk real. The physical and emotional devastation was undeniable, and the policy implications are only starting to emerge. For public health, it exposed a cultural bias of looking to the recent past (20 years) as a predictor of risk rather than a more comprehensive examination of the past (e.g., 100 years). It also exposed weaknesses in how the risk was managed from prevention to mitigation. Finally, it exposed how communicating risk-related information is itself a dangerous endeavor. At the core of this disaster, however, is the human dimension and a critical challenge to public health for this century: engaging the public to voluntarily take individual prophylactic action. We believe an informed public will be better equipped to understand and address risk, and we believe that an informed public health workforce is an essential first step.

What Is Risk?

For some risk means danger; for others, reward. It is a complex term that is best understood in context. In the investment world, risk is typically equated with reward, while in the insurance industry risk is equated with loss. These financial risks are very often quantifiable in terms of monetary gain or loss; for example, insurance risks are rooted in experience captured as actuarial data. For public health risk is usually framed as a potential harm to human health or the environment. Public health risk may have an actuarial component, but it is more likely to be based on a science and policy construct. Science is used to estimate the likelihood of the risk, while policy helps to define what is acceptable.

For our purposes, *risk* is defined as a function of hazard and exposure. Without either of these essential components risk is zero. For example, containers of drain cleaner are often found on supermarket shelves and in homes. The drain cleaner is hazardous, typically composed of caustic that is corrosive to skin if contact is made. If the container of drain cleaner is left unopened, the risk associated with the contained hazard is zero; no contact can be made with the contents. On the other hand, if the container is opened, the risk associated with using the drain cleaner can be determined; it will be greater than zero. How much greater than zero will depend on the exposure (such as length and frequency of use, concentration of

the material, precautionary measures, and how it is used). This simple framework of risk is often made more complicated by perception and emotion.

To see how emotion drives outcome, consider asbestos. Asbestos, a naturally occurring fiber, is also hazardous. It is listed by the International Agency for Research on Cancer (IARC) as a known human carcinogen, particularly when it is in friable form. Parents panicked when it was determined that many schools built before the 1970s had used asbestos as a fireproofing material and that the U.S. Environmental Protection Agency (EPA) had estimated that approximately three million school children in 8,500 schools could be exposed to friable asbestos (Environmental Protection Agency, 1980). Panic led to a public policy initiative called the Asbestos School Hazard Abatement Act in Schools, which made federal funds available for asbestos abatement. No one should doubt that some schools were in dire need of repair and abatement. However, no one predicted that over the next two decades demands for asbestos abatement were made regardless of its condition. Ironically, in some instances indoor asbestos levels were higher after abatement than before because the process of asbestos removal causes it to become friable. In these instances, an alternative approach—containment—would have achieved an equivalent or better outcome. Finally, the asbestos-removal hysteria may have created a new cohort of asbestos-related disease victims: workers in the asbestos abatement industry.

In many respects, the public's reaction to a threat such as asbestos in schools is understandable. First, their children could be in danger, and parents are instinctively protective of their children. Second, it is human nature to react to health threats, whether real or perceived. These two human reactions are deeply ingrained instincts.

Why is risk perception important to the study of risk assessment? Simply because public policy is set before a public who may or may not be informed by the truth. In 1962 John F. Kennedy wrote:

> As every past generation has had to disenthrall itself from an inheritance of truisms and stereotypes, so in our own time we must move on from the reassuring repetition of stale phrases to a new, difficult, but essential confrontation with reality. For the great enemy of the truth is very often not the lie—deliberate, contrived, and dishonest—but the myth—persistent, persuasive, and unrealistic. Too often we hold fast to the clichés of our forebears. We subject all facts to a prefabricated set of interpretations. We enjoy the comfort of opinion without the discomfort of thought [Kennedy, 1962].

In the graduate introduction to environmental health course we teach, one of us (FE) routinely asks students to complete a questionnaire during the first class

of the semester. This questionnaire, modeled after the Roper–NEETF Environmental Literacy survey, asks 15 questions on common environmental issues. The answers help students question their perceived environmental knowledge. One question asks about the cause of bird and fish entanglement. Over the course of five years 56 percent on average have answered that it is the six-pack rings; only 8 percent on average have given the correct answer: fishing lines. For the complete questionnaire, classes tend to answer about 35 percent of the questions correctly—a score slightly higher than that of the general public. The reason for this level of performance is quite simple: the images and information in the popular literature and television help perpetuate popular beliefs founded on a lack of environmental knowledge. So we focus on six-pack rings disposal rather than fishing lines and the result is—nothing. The behaviors that result in environmental risks associated with entanglements continue because we are focused on perception rather than reality. When the lack of environmental literacy is combined with priority setting, the results can lead to the funding of programs that may not represent the greatest opportunities for risk reduction.

Scientists at the USEPA (1987) discovered this truth during the course of an exercise that culminated in a report entitled *Unfinished Business.* Experts were asked to rank a number of risk-related issues and compare those rankings with priorities reflected in funding. We wish to emphasize that acknowledging perceptions is an important step toward understanding public concerns about a risk issue. In fact, the Presidential/Congressional Commission on Risk Assessment and Risk Management (1997a, 1997b) challenged the traditional approach to risk assessment. It incorporated the four steps of risk assessment—hazard assessment, dose response, exposure assessment, and risk characterization—into a more comprehensive framework that begins with understanding the context.

Acceptable Risk

Risk reduction as a public policy goal is laudable and implied in most government environmental and public health initiatives. The *protection of human health and the environment,* a common phrase found in many federal statutes, is based on a fundamental tenet: that of not harming health and therefore not increasing the risk to health. An extreme interpretation of this protective role is the notion of zero risk. Thus the answer to the question, Is zero risk achievable or even desirable? put bluntly is no. This statement might seem outrageous to some, but it is captured in the late Senator Patrick Moynihan's pithy statement, "Life is a risky proposition and it ends badly." The background risk for living on earth, which is bathed in radiation, means that zero risk is not achievable. Therefore, the notion of the

desirability of zero risk is purely theoretical. So for that matter is total risk. There are just too many variables subject to constant change applied to a population base that is also changing. That notion alone presupposes that all of the variables and members of a population can be identified.

If zero risk is not achievable, then it follows that it would be reasonable to determine an acceptable level of incremental risk for an exposed population. In the United States an acceptable level of incremental risk has been defined as one in one million. While a one-in-one-million incremental risk of, for instance, cancer seems to most a reasonably low level, it too must have some context. If a policy decision were made that could subject the entire population to this level of risk, with a theoretical result of 280 cancers, public outcry would be unthinkable, despite the fact that one of every four people in the United States will be diagnosed with cancer in his or her lifetime. On the other hand, if we were to establish a strict policy that no pharmaceuticals should carry an incremental risk greater than one in one million, most anticancer drugs would not be marketable. Dr. Michael Gallo, a researcher at the University of Medicine and Dentistry of New Jersey and a cancer survivor, put it this way: "I dodged a lethal bullet, and thanks to a series of well-placed bullets. . . . I could have been a dead man. Thank God for toxicity."

At the root of risk, real or perceived, is an inbred personal basis for hazard assessment and by extension, if exposure is assumed, risk. We tend to assess personal risk from a qualitative basis, and each of us has a personal and somewhat unpredictable tolerance for risk. If it were possible to categorize lifestyles as risk seeking or risk averse, it would not be possible to categorically apply the same term consistently for each person. For example, one friend considers parasailing to be a sport that is not risky, but refuses to install natural gas as a home fuel source, opting instead to burn wood. He is familiar and proficient at parasailing but not familiar and therefore suspicious of natural gas. This illustrates that preferences can modify our views about risk. But there remain deep ingrained aversions to hazards that reside among all humans.

The British Broadcasting Company in cooperation with researchers at the London School of Hygiene and Tropical Medicine (2006) has been conducting a global survey of what people find disgusting. For images that appear to contain evidence of bodily fluids, excrement, lice, rats, cockroaches, bad smells, and sweaty people, respondents were asked to rank each image from one (not disgusting) to five (very disgusting). The researchers hypothesized that an ancient protective mechanism could evoke a behavioral aspect of human immuno-response to protect us from organisms that would use our bodies as a source of food or shelter (e.g., bacterial contamination or parasites). First surveyed were respondents from six countries; now anyone can take the survey and learn how their responses compare

to others'. The researchers found that despite respondents' location, for similar images—one with and one without a disease threat, for example, towels, one with a blue stain, one with a yellow-brown stain, or a person, one healthy, one feverish—results were the same from every country tested. They found that a picture of a sick person was twice as disgusting as one of a healthy person, a picture of a yellow-brown stained towel was more than twice as disgusting as one with a blue stain, and a picture of a louse was more disgusting than one of a wasp, and so on. The researchers also found that women evidenced more disgust than men, which demonstrates that men can live in filth. On a more serious note, the researchers believe this is because women carry a double genetic burden (for themselves and their offspring). Overall, signs of disease and infection provoked more disgust, as did images linked to our sense of smell, which is often used to signal something that might be hazardous to eat, drink, or touch.

Risk Assessment Is Not New

The ancients institutionalized prophylactic behaviors to protect their populations. For example, the dietary laws of the ancient Hebrew people, commonly known as Mosaic Law, were a form of risk management in response to food-borne hazards. These and other precautionary instructions can be found in the book of Leviticus in the Old Testament.

The ancient Greeks believed that estimating risk was possible.

> We Athenians . . . take our decisions on policy and submit them to proper discussion. The worst thing is to rush into action before the consequences have been properly debated. . . . We are capable at the same time of taking risks and estimating them before hand [Thucydides (431 B.C.), 1954].

New Risks Arising from Common Public Health Practices

Public health as a discipline covers a wide range of topics. Public health measures or practices must, over time, be revaluated regarding their associated risks. It is common practice in many public water supplies to fluoridate water. In areas where people are served by an individual well, the family pediatrician or dentist often prescribes fluoride tablets for young children up to age 16. A recent National Academy of Sciences (NAS) report on fluoride in drinking water raised concerns about the current drinking water standard of 4 mg/L. There is, of course, concern about naturally occurring fluoride and the fluoride that is added to public

water supplies to prevent dental caries. The American Dental Association (ADA) (as of March 22, 2006) continues to support community water fluoridation as a safe, beneficial, and cost-effective way to prevent tooth decay. The ADA cites the Centers for Disease Control and Prevention's proclamation that community water fluoridation is one of the ten greatest public health achievements of the twentieth century. EPA has set the drinking water standard for fluoride at 4 mg/L. The optimal concentration range for fluoride in drinking water to prevent tooth decay is 0.7 to 102 mg/L. This standard was set by the U.S. Public Health Service more than 40 years ago. In 2000 it was estimated that about 162 million people used artificially fluoridated water. There are a range of effects, from moderate staining of teeth to serious dental fluorosis, depending on the concentration of fluoride. There are studies presented in the NAS report on skeletal effects of fluoride exposure as well as a discussion on the possible association of fluoride and cancer. There are some studies that suggest a possible increased risk of osteosarcoma in rodents (NAS, 2006).

This illustrates important issues in public health risk assessment: that new information leads to new thinking about risks and that a single action, in this case the fluoridation of the water supply with its clear benefit, can in fact also have a risk associated with it (if the natural or background levels exceed, in the case of fluoride, the EPA standard of 4 mg/L).

Risk assessment has been described as both an art and a science. There are often specific benefits from certain risks. The Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), which dates back to 1947, is a good example. The Act regulates pesticides, and this Act plus the Food Quality Protection Act and the Federal Food, Drug and Cosmetic Act serve as the major regulations that set standards of risk for the food we eat. FIFRA requires an assessment of the risk and the benefits. Pesticides are economic poisons; we know they kill things—that is what they are specifically designed to do. What we need to be certain about in the regulation, and most important in the use of pesticides, is that the benefits far exceed the risks associated with a particular type of application.

Risk in Context

Six years ago MR was invited to make a presentation in West Africa at a conference called Challenges and Opportunities for Environmental Heath Research. MR was specifically asked to present the topic of risk assessment and the one-in-one million risk standard that is in place in the United States. After delivering what was thought to be an organized and thoughtful presentation, MR was quickly challenged by one of the meeting participants:

> Thank you, Dr. Robson, for your interesting and informative presentation. I enjoyed your talk, but I have a very hard time understanding the relevance of your talk to my work here in West Africa. I am a pediatrician in rural northern Ghana. I cannot comprehend one in one million risks. But let me give you some risks that I face every day. One in five of the children I treat will die from diarrheal disease before they are eight years old, and likely another one in five will die of malaria before they are eight. For me, two in five is a real risk, and one in one million is so far from what I live with every day that I do not know why you even bothered to come and make this presentation.

This is a true story and it illustrates the importance, especially for those of us in public health, to look at the context of the risk, to understand what risks are real, immediate, and of greatest concern to the public. It was hard to respond to the comments raised by the young pediatrician. It is clear that her work presents her with real risks that are immediate, real, and difficult to ameliorate. Public health students are there in the field in real risk situations. The risks are clearly greater than one in one million. While they may not deal with a two-in-five level of risk, they deal with far more serious and concrete risks than the very abstract one-in-one million risk that is cited so often in risk assessment texts, journal articles, and regulations.

In this text we include areas that are of direct public health concern, an overview of the risk process, the toxicological basis for risk assessment, specific populations and media, regulatory issues, ecological risk, the precautionary principle, and emerging issues such as PBPK modeling and biomarkers. We also include an important chapter on risk communication, often thought of as the fifth step in the risk assessment paradigm.

Thought Questions

1. What is a reasonable risk standard for public health?
2. When do we apply the risk standard?
3. How can the regulatory process be improved to account for improvements in analytical capabilities? What do we mean by the vanishing zero?
4. What are reasonable methods of assessing benefit in the risk assessment process?

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CHAPTER TWO

THE RISK ASSESSMENT–RISK MANAGEMENT PARADIGM

Gilbert S. Omenn

Learning Objectives

Students who complete this chapter will be able to

1. Understand the fundamental concept of risk
2. Recognize the many roles of public health scientists and public health practitioners in analyzing and communicating with the public about risks
3. Adopt a useful framework for organizing and evaluating scientific inputs about risks
4. Learn about the major specific statutes that govern the activities of federal regulatory agencies and their state and local counterparts
5. Appreciate the particular contributions of toxicologists, exposure assessors, epidemiologists, biostatisticians, geneticists, and behavioral scientists

Definition of Risk

Risk is a fundamental concept in environmental health. *Environmental health risk assessment* has been defined as the "systematic scientific characterization of potential adverse health effects resulting from human exposures to hazardous agents or situations" (Faustman and Omenn, 2001; Omenn and Faustman, 2002). The short version is that risk is the probability of an adverse health effect from specified exposures.

Historical Perspectives

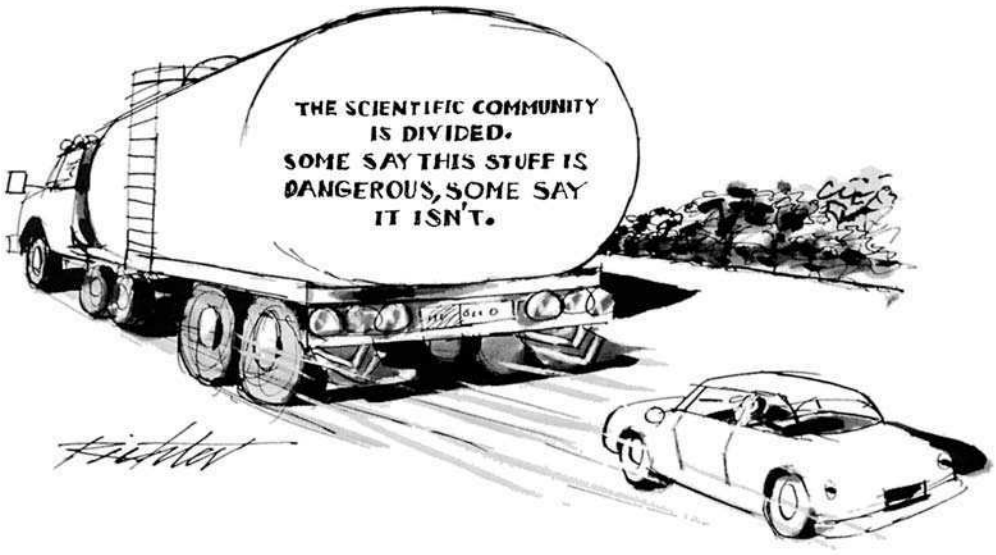
Over the past 30 years public health scientists and policy makers have developed and applied systematic approaches to understanding and evaluating the extent of exposures to environmental agents, the nature of potential hazards to health, the variation in susceptibility to such adverse effects, and the probability and magnitude of such impacts on populations. Concurrently, we have come to recognize the importance of risk perception and respectful two-way communication about risks in proactive interactions with potentially or already affected communities. The goal is to achieve feasible and cost-effective means of reducing such risks, actions acceptable to the public.

At the heart of such analyses and communication are probabilities. Most people, including most physicians and many scientists, are uncomfortable in evaluating probabilities, especially low probabilities with high consequences. Students and practitioners of public health are often called upon to interpret the conclusions, as well as make the scientific evaluations. The task is complicated by the fact that well-credentialed scientists, considered experts by the media and the public, may draw different conclusions or make different recommendations. Disclosure of such disagreements leads to confusion or even bewilderment among those who expect science to be about observable facts on which scientists should agree (see Figure 2.1).

In this context, David Bazelon, the widely admired longtime chief judge of the U.S. District Court for the District of Columbia, spoke in 1979 of "the perils of wizardry." He advised technical experts, both inside and outside regulatory agencies, to stay away from the ultimate policy decisions, which are not their charge or specific expertise. He urged us instead to delineate particular elements of the risk to be characterized, focus on those elements, and build a clear record of what is known, what is not yet known but feasibly could be learned, and what is beyond current methods of detection or evaluation. He advised us to expect to be asked again, since public health hazards and regulatory responses to them tend to recur. We hope our society will be better prepared each subsequent time.

The situation seemed simpler 50 years ago. In 1958 Congress enacted the Delaney Clause, which instructed the Food and Drug Administration (FDA) to prohibit the addition to the food supply of any substance ("food additive") found to cause cancer in humans or animals. In 1962, Rachel Carson published *Silent Spring*, decrying chemical contamination of streams and waterways. Air pollution in industrial cities and water pollution in such places as Lake Cuyahoga, Ohio, were all too visible. In response to Earth Day on April 1970, President Nixon and the Congress created the Environmental Protection Agency (EPA) and then the

FIGURE 2.1 WHY THE PUBLIC IS OFTEN CONFUSED ABOUT THE DIFFERING VIEWS OF SCIENTISTS ABOUT POTENTIAL HAZARDS AND HEALTH RISKS.



Source: Mischa Richter, *The New Yorker,* March 21, 1988.

Occupational Safety and Health Administration (OSHA). Multiple statutes (see Exhibit 2.1) required technical judgments about risks and remedies. Experimental protocols for testing chemicals in animals and schemes for extrapolating the findings to humans stimulated the emergence of risk assessment at the EPA (Anderson, 1983; Albert, 1994) and the formation of high-level federal working groups among the regulatory agencies and within the executive office of the President (Calkins and others, 1980; Omenn, 2003).

The Red Book

A landmark in this field was the publication in 1983 by the National Academy of Sciences of *Risk Assessment in the Federal Government: Managing the Process,* popularly known as *The Red Book* (National Research Council, 1983). The opening statement captured the challenge:

> This report explores the intricate relations between science and policy, . . . the assessment of the risk of cancer and other adverse health effects associated

EXHIBIT 2.1. MAJOR HAZARDOUS CHEMICAL LAWS IN THE UNITED STATES.

Environmental Protection Agency (EPA)
- Air Pollutants—Clean Air Act, 1970, 1977, 1990
- Water Pollutants—Federal WP Control Act, 1972, 1977
- Safe Drinking Water Act, 1974, 1996
- Pesticides Act (FIFRA), 1972
- Food Quality and Protection Act (FQPA), 1996
- Ocean Dumping Marine Protection Act, 1995
- Toxic Chemicals Act (TSCA), 1976
- Hazardous Wastes Act (RCRA), 1976
- Hazardous Waste Cleanup Act (CERCLA or Superfund), 1980, 1986

Food and Drug Administration (FDA)
- Foods, Drugs, Cosmetics (FDC) Acts, 1906, 1938, 1962, 1977, 1997

Council for Environmental Quality (CEQ; now Office of Environment Policy)
- Environmental Impacts Act (NEPA), 1972

Occupational Safety and Health Administration (OSHA)
- Workplace Act (OSH Act), 1970

Consumer Product Safety Commission (CPSC)
- Dangerous Consumer Products Act (CPS Act), 1972

Department of Transportation (DOT)
- Transport of Hazardous Materials Act (THM), 1975–1979, 1984, 1990

> with exposure of humans to toxic substances, . . . a search for the institutional mechanisms that best foster a constructive partnership between science and government, mechanisms to ensure that government regulation rests on the best available scientific knowledge and to preserve the integrity of scientific data and judgments in the unavoidable collision of the contending interests that accompany most important regulatory decisions. . . . The roots of the controversy lie in improvements in scientific and technologic capability to detect potentially hazardous chemicals, in changes in public expectations and concerns about health protection, and in the fact that the costs and benefits of regulatory policies fall unequally on different groups within American society.

The Red Book was commissioned by Congress after controversial assessments of the risks of saccharin as a nonnutritive sweetener (by FDA), of formaldehyde in home insulation (Consumer Product Safety Commission), of nitrites as preservatives in foods (FDA and U.S. Department of Agriculture), of asbestos removal from schools and homes (OSHA and EPA), of invisible air pollutants, and of many other chemicals in the general environment (primarily EPA). All of these issues were salient while I served in the Office of Science and Technology Policy in the Carter White House (1977–1980), as Associate Director of the Office of Management and Budget (1980-81), and on the Interagency Regulatory Liaison Group and the Regulatory Analysis Review Group. There was quite a struggle between those who insisted on "zero risk" and those who proposed methods of risk assessment to identify what Lowrance (1976) called "acceptable risk" and others called "negligible risk," realizing that such a conclusion lies in the eyes of the beholder (see Omenn, 2003).

The Objectives of Risk Assessment: Statutes and Programs

Exhibit 2.2 outlines the statutory and programmatic objectives for the use of risk assessment in decision making by regulatory agencies, manufacturers, environmental organizations, and public health departments. The laws governing pharmaceutical approvals and pesticide approvals recognize that these chemicals are designed to kill living cells or microbes; thus, a benefit/risk assessment is essential and care in their use is mandated. In contrast, the Clean Air Act requires national ambient air quality standards—for sulfur oxides, nitrogen oxides, hydrocarbons, carbon monoxide, particles, photochemical oxidants, and lead—to be set without regard to costs and to protect, with an adequate margin of safety, the most susceptible subgroups in the population. For contaminants in food and water, as opposed to deliberate additives, the statutes recognize that assurance of safety may be associated with some residual level of aflatoxin from a fungus that grows on peanut and corn crops or of byproducts from the chlorination of water. Not so well-recognized are objectives 3 and 4 (Exhibit 2.2). All parties have limited staff and financial resources, so deciding in a logical way which risks are most important, for various reasons, is necessary. Finally, the courts, which play a major role in contested regulatory decisions, have supported well-documented claims by agencies that it is time to turn their attention to more pressing remaining risks after taking actions that they consider to be adequate. But critics disagree on other risks. The classic case, decided by the U.S. Supreme Court, involved vinyl chloride (NRDC *v.* EPA, 1987).

EXHIBIT 2.2. OBJECTIVES OF RISK ASSESSMENT.

1. Balance risks and benefits.
   - Drugs
   - Pesticides
2. Set target levels of risk.
   - Food contaminants
   - Water pollutants
3. Set priorities for program activities.
   - Regulatory agencies
   - Manufacturers
   - Environmental and consumer organizations
4. Estimate residual risks and extent of risk reduction after steps are taken to reduce risks.

Biological End Points

Regulatory controls on chemicals started with a preoccupation about risks of cancer. Now we address multiple biological end points, as shown in Exhibit 2.3. The lowest concentration at which a given chemical may cause each of several adverse effects may vary quite a lot, so characterization of the dose-response relationship for each effect is necessary to guide the focus of risk management.

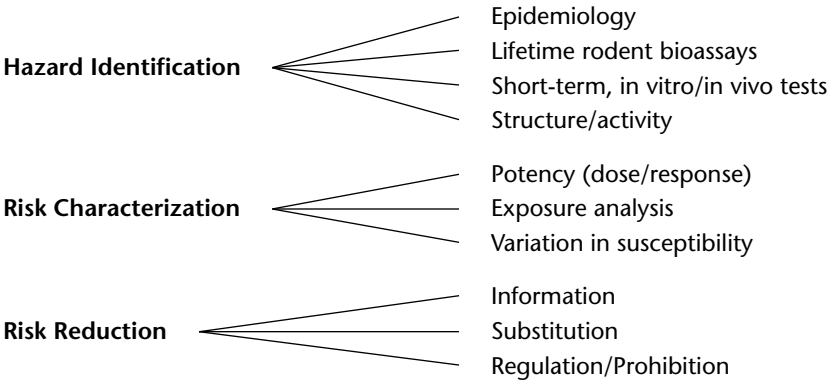
A Framework for Regulatory Decision Making

An elaborate scheme has evolved for evaluation of individual hazards and risks, as shown in Figure 2.2 from the Office of Science and Technology Policy (Calkins and others, 1980). The first step, hazard identification, seems to generate a yes/no decision about whether the agent, generally a chemical, has the potential to cause adverse effects. In fact, however, epidemiological studies of humans exposed at work or in the general environment, toxicological studies of animals or cells exposed with controlled concentrations of the agent, and structure-activity analysis of the chemical nature of the agent and its relationship to other known chemical hazards all generate quantitative data that must be evaluated with statistical cri-

EXHIBIT 2.3. BIOLOGICAL END POINTS.

- Cancers
- Mutations
- Birth defects
- Reproductive toxicity
- Immunological toxicity
- Neurobehavioral toxicity
- Organ-specific effects
- Endocrine modulation or disruption
- Ecosystem effects

FIGURE 2.2. FRAMEWORK FOR REGULATORY DECISION MAKING.



Source: Calkins and others (1980).

teria to determine whether a statistically significant excess occurrence of adverse events has been observed (Breslow and Day, 1980, 1987; Omenn and Faustman, 2002). These scientific studies lead into the second step, very importantly called risk characterization. This term supplanted *risk assessment* at a time when risk assessment had come to be synonymous with quantitative risk assessment, generating a number, sometimes an excessively precise number, for the potential risks from a given hazard under specified exposure conditions. It is essential to characterize the nature of the adverse effects, including their severity, reversibility or

prevention, the reasonableness of the exposure scenarios, the variation in susceptibility among people exposed or potentially exposed, and the quality of the evidence. Such risk characterization requires substantial narrative, which provides context for the point estimate(s) of risk and for various ways of expressing the uncertainty around that risk estimate.

Finally, the third step is about how the information is used to manage the risk(s). Even before definitive regulatory decisions and actions are taken, the release of information through advisories by public health or environmental agencies and through media coverage is often a powerful influence, however objective. Manufacturers may pull a product or modify its uses; end users, from companies to physicians to pesticide applicators to consumers, may modify their practices or behaviors. Ironically, prohibition or phaseout of one chemical and replacement by a designated substitute has often proved of little value—illustrated by the cases of red dye 2, which was replaced by red dye 40; the flame retardant TRIS in infants' clothes, which was replaced by son and grandson of TRIS; the sweetener cyclamate, which was replaced by saccharin; and the detergent nitrilo-tri-acetic acid (NTA), which was replaced by phosphates. Phosphates led to vast algal overgrowth in lakes, while all of the other replacements mentioned produced cancers in test animals. The primary reason substitutes must be viewed with caution is that we always know more about the toxicological or ecological consequences of an agent so well studied as to be removed from commerce than about the proposed substitute.

This framework was modified by *The Red Book* to have four parts, by breaking risk characterization into dose-response assessment and exposure assessment components, thereby emphasizing the need to greatly improve the data and response base for exposure assessments.

Adding Context for Risk Assessments

One of the biggest problems in the risk assessment/risk management paradigm above is the longstanding approach of analyzing one chemical at a time, usually for one predominant adverse effect and via one source of exposure. This approach was mandated in most of the statutes in Exhibit 2.1. In contrast, lay people complain very logically that we are exposed to a sea of chemicals in the air we breathe, the water we drink, the foods we eat, the products we touch, and the soil and dusts that contaminate all of the other sources. Thus, an analysis that builds information about the *context* of the exposure under analysis is critical. As outlined in Exhibit 2.4, this process begins by identifying multiple sources of the particular agent

EXHIBIT 2.4. BUILDING INFORMATION ABOUT CONTEXT.

- Multiple sources of same agent
- Multiple media or pathways of exposure
- Multiple risks and effects of same agent
- Multiple agents causing same effects
- Public health: status and trends
- Ecological health
- Social, cultural, and environmental justice considerations

under review and the multiple media of contamination and pathways of exposure. Then multiple potential effects should be considered, along with other agents that can cause the same effects. Sometimes people are exposed to several of these agents simultaneously or over time.

Then there are broader public health dimensions, like the overall incidence of cancers, birth defects, asthma, or other end points. Since health is dependent on a sustainable environment, ecological effects should be considered.

Finally, and very important, exposures and interventions are very unevenly experienced across the population, with lower-income economic groups and minority ethnic and racial groups at higher risk of exposures and less likely to benefit from risk-reduction action.

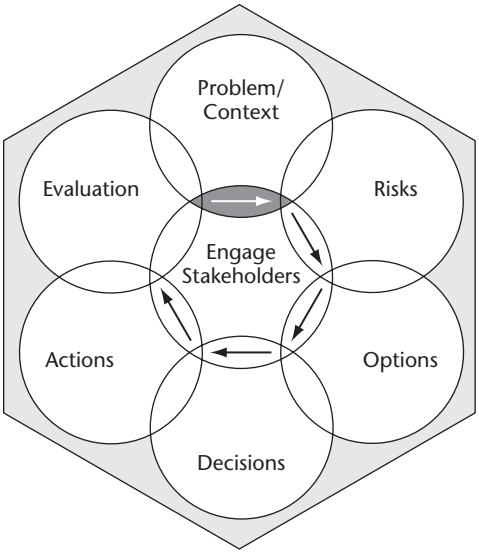
The Risk Commission

This focus on context (see Box 2.1) was developed explicitly during the 1990s by the Presidential/Congressional Commission on Risk Assessment and Risk Management, mandated by the Clean Air Act Amendments of 1990 (Omenn, 1996; Presidential/Congressional Commission on Risk Assessment and Risk Management, 1997a, 1997b). That commission created the more elaborate framework in Figure 2.3. Putting any new or current risk into public health (and ecologic) context is right at the top in step 1. An additional innovation is the emphasis, in the center of the hexagon, on proactive identification and engagement of stakeholders. Way too often elaborate risk assessments are performed and decisions made by regulatory agencies before they then go to the public to present the decision and seek support for implementation. However, thoughtful and practical questions are often neglected.

BOX 2.1. CONTEXT.

Moving beyond one chemical, one environmental medium (air, water, soil, or food), or one health effect (cancer or birth defect) at a time in risk assessment and risk management requires a comprehensive public health view.

FIGURE 2.3. HEXAGON SHOWING FRAMEWORK FOR ENVIRONMENTAL HEALTH RISK MANAGEMENT.



Source: Presidential/Congressional Commission on Risk Assessment and Risk Management (1997a).

For example, in a dramatic case involving expensive additional controls on sulfur oxide and arsenic emissions from a copper smelter in Tacoma, Washington, EPA administrator William Ruckelshaus called for public meetings to discuss risk assessment findings and build public understanding. At a televised local meeting, the EPA experts spoke of risk estimates and extrapolations from occupational exposures, including the most important study done with workers at that very smelter. The citizens asked practical questions about whether it was safe to eat vegetables

from their gardens, whether their children could safely play outdoors, whether the death of a dog might be due to the arsenic emissions, how they could possibly survive emissions of tons of arsenic per year when "a thimbleful can kill you." The questions and responses passed in the night. Such questions surely could have been addressed under the characterization of risks. Ruckelshaus proudly drew upon *The Red Book* for his decisions and commentaries (Ruckelshaus, 1983, 1985).

Special Challenges for Risk Assessment of Chemicals

Data and Testing

A basic problem is lack of data on potential toxicity. The organization Environmental Defense has called this situation "toxic ignorance" (Roe, Pease, Florini, and Silbergeld, 1997). A decade ago, only 7 percent of high-production-volume chemicals had a full set of studies for six basic end points, and 43 percent had no publicly available studies for any of the six basic toxicity end points. These revelations led by an agreement among the countries in the Organization for Economic Cooperation and Development (OECD) to require studies and data submission over several years. Progress has been significant for these 2,200 chemicals (Denison and Florini, 2003).

Alternative strategies for testing chemicals have been examined by modeling the social costs of testing and the consequences of false positives (declaring chemicals hazardous when they are not)—and especially of false negatives (not recognizing health hazards and thereby not avoiding exposures) (Lave and Omenn, 1986, 1988). Explicit efforts to deduce which chemicals will be carcinogenic in animal tests on the basis of chemical structure and preliminary in vitro assays have been disappointing (Tennant, Spaulding, Stasiewicz, and Ashby, 1990; Omenn, Stuebbe, and Lave, 1995).

Extrapolation

Many researchers have struggled with the challenge of extrapolation of the dose-response relationship. First we must determine the critical health effect, an adverse effect at the lowest dose, together with the strength of the evidence. What *The Red Book* called "default assumptions" must be applied to go from high-dose exposures (typically 20 to 100 percent of 50 rodents affected) to acceptable low-dose exposures (low enough that less than one person in ten thousand or one person in one million hypothetically exposed for a lifetime at the maximally permitted dose would be affected). Confidence limits are used in linear or linearized multistage models, generating what is recognized to be a (nearly) worst-case scenario

of potential risk. Less well-recognized is the need to utilize, generally, the most strikingly positive dataset, to better fit the extrapolation models (Faustman and Omenn, 2001).

The step from potential hazard to estimated risk depends on the scenarios of exposure—ambient concentrations, portals of entry into the body, time course over a period of years, and dose actually delivered to target organs with variables of absorption, distribution, metabolism, and excretion. A lot of modeling is usually required.

As noted in Box 2.1, real-world exposures often involve mixtures. Examples that have been studied extensively include diesel exhaust, urban smog, industrial effluents, pesticide combinations, and workplaces. On top of these chemical mixtures are exposures to microbial agents prevalent in our environments and to radiation of various kinds. With modern databases, we may be able to link unusual exposures and occupational disease states.

Variation and Uncertainty

The risk of any specific adverse effects from particular exposures to a single agent or a combination of potentially hazardous agents varies among individuals exposed. In addition, the extrapolation of the risk from observable events in test animals or in highly exposed workers to individuals in the general population with much lower exposures depends upon dose-response modeling and undescribed variation in metabolism and sites of action of the agent. These companion problems were called "variation and uncertainty" in a National Research Council report (1994), *Science and Judgment in Risk Assessment*. This report joins *The Red Book* and the later Risk Commission Report as landmarks.

The hazard identification step has been dominated by results from animal tests. Epidemiology is limited to observations of health conditions in relation to existing or past exposures. For new chemicals or for questions about risks from chemicals at levels below concentrations associated with observable effects in humans, it is essential to test animals and use cell assays for clues to mechanisms. The general presumption—reflecting the precautionary approach inherent in public health—is that a chemical that can produce cancers (or even benign tumors that have some likelihood of progressing to cancers) in animals should be considered capable of causing cancers in humans. The same applies to toxicity to the brain or liver or other organs. In a very few cases careful and extensive scientific studies have shown definitive evidence that the mechanism mediating the adverse effects in rodents is not at play in humans (see Presidential/Congressional Commission on Risk Assessment and Risk Management, 1997b, pp. 65–68). The classic example is the emergence of kidney tumors in male rats (not mice or monkeys

or female rats) from exposures to D-limonene or unleaded gasoline extract; they cause a very unusual accumulation of an alpha-2 euglobulin protein in the kidney tubules of male rats. This biochemical change can lead to cell death, sustained proliferation of remaining cells, and tumor formation. Both the International Agency for Research on Cancer, a unit of the World Health Organization, and the EPA in the United States now recognize a category of agents that are carcinogenic in rodents but not a risk to humans. For example, IARC/WHO classifies agents (or mixtures) as (1) carcinogenic for humans, (2A) probably or (2B) possibly carcinogenic to humans, or (3) not classifiable as to its carcinogenicity to humans. Category 3 is

> Used most commonly for agents, mixtures, and exposure circumstances for which the evidence of carcinogenicity is inadequate in humans and inadequate or limited in experimental animals. Exceptionally, agents (mixtures) for which the evidence of carcinogenicity is inadequate in humans but sufficient in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans [International Agency for Research on Cancer, 2005].

Emerging Contributions from Eco-Genetics

There are many reasons to be interested in individual variation in susceptibility. In the practice of occupational medicine we often encounter patients who are told that a particular set of symptoms may be due to exposures on the job and who then ask, "Why me, Doc? I'm no less careful that the next person." The Occupational Safety and Health Act requires that health standards be set "so that no worker . . . shall suffer adverse effects" even if exposed at the maximally permitted level for a full working lifetime. The Clean Air Act requires that ambient air standards be set to protect the "most susceptible subgroups" in the population. In the case of the air lead standard, the most susceptible subgroup was determined to be young children; in the case of photochemical oxidants (ozone), adults and children with asthma, chronic bronchitis, or emphysema were identified as such subgroups.

In the postgenomic era informed by the near completion of the human genome sequence for 22,000 genes coding for proteins, we can ask many more questions about the genetic predispositions to susceptibility or resistance to adverse effects from chemical, microbial, and physical agents. We can examine DNA and proteins for "molecular signatures" or "biomarkers" of exposure, early effects (genetic toxicology), and mechanisms of differential susceptibility.

This period should be a Golden Age for the public health sciences. Sequencing the human genome has generated an avalanche of genetic information to be linked with information about nutrition and metabolism; lifestyle behaviors; diseases and medications; and microbial, chemical, and physical agent exposures (Omenn, 2002; Collins, 2004). Both genetics and public health focus on populations. Both fields seek information about heterogeneity of predispositions, environmental exposures, disease risks, and responses to public health and medical interventions. Both explicitly recognize cultural, societal, ethnic, and racial contexts and are sensitive to risks of discrimination.

Contributions from All Public Health Sciences to Eco-Genetics and Risk Assessment

The public health sciences all bring essential capabilities. Epidemiology aims to identify and explain all the factors that influence risk of disease; with biomarkers we have greatly enhanced power to link qualitative and quantitative findings in test animals and humans. Biostatistics and bioinformatics provide the methods, platforms, and databases for designing studies and analyzing huge, complex datasets. Environmental health can apply molecular signatures to understanding host variation in host-agent interactions for risk assessment and risk management. Pathobiology focuses specifically on the host-pathogen genomic and environmental interactions; polymorphisms in genes controlling receptors essential to penetration of infectious agents (such as malaria-causing plasmodium vivax or AIDS-causing HIV) greatly influence the risk of infection and, hence, appearance of disease symptoms. Behavioral sciences can examine genetic predispositions to various aspects of cigarette smoking behavior and other unhealthful behaviors, which often interact with environmental chemical exposures. And health services researchers are active in designing and assessing well-targeted, cost-effective clinical and preventive genetic services that improve quality of life.

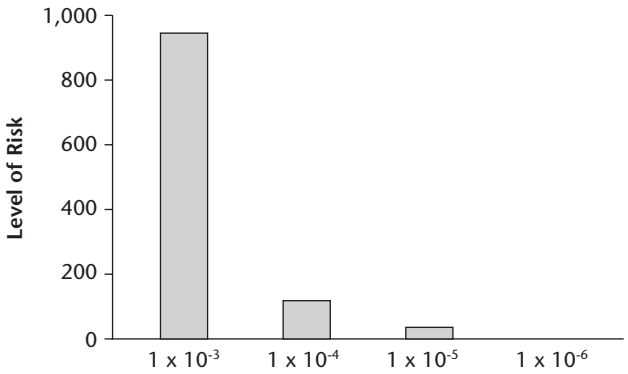
Risk Management–Risk Communication Approaches

Exhibit 2.5 shows the key components for risk management and risk reduction through a variety of communication strategies. Finding appropriate technical language for effective two-way communication is an important responsibility (National Research Council, 1989). We overuse powers of 10 (orders of magnitude) in our oral communication and documents, especially on the benefits of risk reduction. Many people seem to think that reducing estimated risks from 10^{-3} to 10^{-4} (from one in one thousand to one in ten thousand) is the same benefit as a further reduction to 10^{-5} (one in one hundred thousand). Figure 2.4 shows on a linear

EXHIBIT 2.5. ESSENTIAL COMPONENTS FOR RISK REDUCTION.

- Awareness of potential problems and context
- Engagement of the interested or affected publics
- Development of scientific knowledge
- Design of feasible alternative actions
- Affirmation of societal values
- Mobilization of political will

FIGURE 2.4. REDUCING RISK BY ORDERS OF MAGNITUDE VERSUS LINEAR REDUCTIONS IN RISK.



Source: Presidential/Congressional Commission on Risk Assessment and Risk Management (1997b).

scale for the *y*-axis that the first risk-reduction step removes 90 percent of the risk, leaving only 10 percent; thus, the next step can remove only 9 percent of the original risk, usually at a far higher cost ("Presidential/Congressional Commission on Risk Assessment and Risk Management," 1997b).

Words matter. For example, safety officials and public health practitioners have campaigned for many years to expunge the word *accidents*, which implies "acts of God" and unpreventable events; instead, words like *incidents*, *injuries*, and *crashes* should be used (see British Medical Journal, 2001).

Exhibit 2.6 lists a broad range of approaches for reducing risks judged to be too high for protection of the public.

Engagement. The first, emphasized by the Risk Commission, is proactive engagement of stakeholders to learn the issues that matter in the community, to

EXHIBIT 2.6. VARIOUS RISK MANAGEMENT AND RISK COMMUNICATION APPROACHES.

- Engagement of stakeholders: Learning the issues and questions; finding what might be "acceptable"
- Risk-based (chemicals): *de minimis*, maximal contaminant levels (foods, water), bright lines, comparisons of similar risks
- Precautionary principle: Hippocrates' "Do No Harm"; as low as reasonably achievable (ALARA); substantial equivalence (recombinant DNA)
- Best-available technology (Clean Air Act)
- Benefit-cost analysis

jointly formulate questions to be addressed in the risk assessment, and to build a basis for acceptable remedies. Such discussions, initiated as early as possible in the process (Figure 2.3), can help identify practical risk-reduction approaches that might be rejected by distant experts who do not compare the risks with the overall public health context in the community or are unaware of the modifications in behavior and therefore exposure that the affected community would consider quite acceptable. Such situations are well-documented in volume 1 of the Risk Commission reports.

Risk-based risk management approaches. These include determination by various methods (see Faustman and Omenn, 2001) of risks that policy makers may then declare to be *de minimis* levels of exposure and risk; bright lines for measurable levels of contaminants determined to be acceptable, as for food and water contaminants; and comparative analyses of similar risks from agents used for similar purposes, like pesticides or pharmaceuticals.

Intuitive approaches. Some alternatives do not require estimation of risk levels and uncertainty bounds. These include

- The traditional engineering approach of ALARA—*as low as reasonably achievable*—with judgments about feasibility and cost.
- The use of "best available technology," as mandated by Congress in the Clean Air Act Amendments of 1990, to be followed up later by risk-based determinations of whether additional reductions in emissions were warranted to be adequately protective of public health.
- The broad theme of *the precautionary principle,* which is a popular phrase in Europe and is compatible with traditional public health interventions in this country and with the dictum of Hippocrates to "do no harm." This last point highlights the importance of risk-risk tradeoffs, since many interventions them-

> "I know no safe depository of the ultimate powers of society but the people themselves; if we think them not enlightened enough to exercise their control with a wholesome discretion, the remedy is not to take it away from them, but to inform their discretion."
>
> —Thomas Jefferson

selves introduce new risks while reducing, hopefully, the targeted existing risks (Graham and Wiener, 1995).

Risk perception. Careful social science studies of risk perception (Slovic, 1987, 1993; Fischhoff, Bostrom, and Quadrel, 2002; Kasperson, Kasperson, Pidgeon, and Slovic, 2003; Slovic, Finucane, Peters, and MacGregor, 2004) have shown that people have somewhat predictable reactions to different kinds of risks. In general, exposures that are invisible or undetectable with the senses are feared more; dreaded consequences are magnified; and unfamiliar or new risks are more troublesome than such familiar, though much higher, risks as cigarette smoking, drinking alcoholic beverages, driving too fast, or engaging in hazardous recreational activities. Sometimes, public perceptions of risk and of acceptability of remedies change dramatically, as with seatbelts and infant car seats. Big changes in behavior generally require reinforcing and persistent actions and incentives, as occur in states with multimodality interventions to reduce cigarette smoking.

Information overload. Finally, there is a sense among many of the public that we inundate people with news about public health threats, some of which are quite unlikely, undercutting any sense of prioritization. A risk-based approach can help in this regard.

Thought Questions

1. Why do people who smoke or engage in very hazardous recreational sports seek extreme protection against low-level chemical risks?
2. Would health protection aimed at people at average risk be acceptable in light of presumed or known variation in susceptibility across the population?
3. How can we better evaluate risks from multiple simultaneous exposures?
4. How can public health practitioners and the media better communicate the nature and levels of risk?
5. What can be done to overcome the environmental injustice of location of hazardous facilities in poor neighborhoods or failure to clean up areas near poorer populations in our society?

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CHAPTER THREE

RISK ASSESSMENT AND REGULATORY DECISION MAKING IN ENVIRONMENTAL HEALTH

Felicia Wu
William H. Farland

Etymology of risk: *French* risqué, *from Italian* risco. *(1) possibility of loss or injury; (2) someone or something that creates or suggests a hazard; (3) the degree of probability of such loss.*

—MERRIAM-WEBSTER'S DICTIONARY

In addition to its French and Italian origins, the English word risk *has two other possible derivations which are interesting to contemplate: the vulgar Latin word* resecum, *meaning danger, rock, or risk at sea, and the Greek word* rhiza, *cliff, through the meaning "to sail round a cliff." Though unattested, these classical sources are appealing . . . for the visual image they evoke: Ulysses and his men making their perilous voyage between Scylla and Charybdis in the Strait of Messina.*

—BENTKOVER, COVELLO, AND MUMPOWER, 1986

Learning Objectives

Students who complete this chapter will be able to

1. Understand the history of risk assessment in U.S. environmental regulation
2. Understand the link between risk assessment and risk management in regulatory decision making
3. Assess pertinent environmental risk decisions in recent history

As can be seen in the description above, even the ancient Greeks were aware of the link between the environment and hazards to human health and life. Their myths of Scylla and Charybdis, in reality, described dangerous sea creatures, on the one hand, and whirlpools, on the other. In today's parlance, these mythical environmental hazards became risks only to those sailors who might be brave enough to sail near them. Today we know of real environmental hazards, physical and biological. However, today environmental risk assessment focuses more on chemical and microbiological hazards applied to and encountered in our environment.

The analysis of environmental risks to human health is increasingly being viewed as a field in itself, and there is high demand for a more orderly and formal treatment of information in assessing health risks. Risk assessment is an interdisciplinary field that draws on such disciplines as toxicology, molecular biology, ecology, engineering, statistics, and social sciences in order to evaluate the probability that a given hazard, if encountered, will cause some kind of harm. This chapter gives a primer on environmental risk assessment: what it is, its history, its main components, and how policy makers use it to regulate and manage environmental risks.

Addressing the risk to human health from exposure to environmental hazards consists of three interrelated processes:

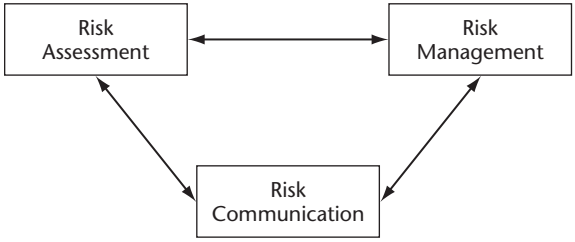
1. *Risk assessment,* defined above as a process of analyzing and characterizing information about a risk
2. *Risk management,* the process of integrating the results of a risk assessment with social, economic, political, regulatory, and other information to make decisions about how to manage the risk
3. *Risk communication,* the process of engaging in a dialogue with stakeholders to identify information that may improve the risk assessment, and to inform stakeholders about the implications of risk management decisions.

These three risk areas are interconnected as shown in Figure 3.1, as they inform and influence one another. Each of these three processes is itself the subject of many publications. While this chapter focuses primarily on environmental health risk assessment, it will at times touch on some aspects of the other two processes.

What Is Risk Assessment?

Risk assessment is the process of identifying the hazard at hand and attempting in some manner to bound or to quantify its level of potential harm under a prescribed set of conditions. Since the early 1980s, most health, environmental, and

FIGURE 3.1 INTERCONNECTEDNESS OF RISK ASSESSMENT, RISK MANAGEMENT, AND RISK COMMUNICATION IN DECISIONS AND ACTIONS BASED ON ENVIRONMENTAL RISK.



even technological risk assessments have been largely consistent with the basic human health risk assessment paradigm put forth by the National Academy of Sciences' National Research Council (National Research Council, 1983). The paradigm describes a four-step process for analyzing data, drawing inferences from all available related information and then summarizing the implications in a risk characterization that others, including risk managers and the public, can easily follow and understand. For each step, the relevant and scientifically reliable information is evaluated. In addition, the related uncertainties and science policy choices are described. The four steps described by the NRC are (1) hazard identification, (2) dose-response assessment, (3) exposure assessment, and (4) risk characterization. This paradigm has evolved somewhat to recognize that the first step in any risk assessment involves problem formulation, to account for the interactive nature of these steps, and to broaden their application beyond health risk assessment. For instance, in ecological risk assessment, hazard identification has been replaced by stressor identification, and dose-response assessment has changed to analysis of effects to account for the need to broaden the concept of *dose* in the ecological setting.

Problem Formulation

The first step in the risk assessment process is the planning and scoping step. Experience in implementing the risk assessment paradigm soon demonstrated that "one size does not fit all," that is, that one approach would not be ideal for all risk assessments. Problem formulation provides the opportunity for risk assessors to

engage risk managers and other stakeholders to define the problem to be addressed by answering such questions as:

- What are the key questions that must be answered in order for the assessment to be informative to decision makers?
- What information is available to answer these questions, and what gaps exist?
- Will time be available to collect additional information as data needs are identified, or will science policy-based inferences or default positions be sufficient?

Problem formulation does not determine what the results of the risk assessment should be; rather, it tries to ensure that it will be responsive to the needs of those who will use the assessment. Even with the best efforts at problem formulation, risk assessment is fundamentally an iterative process and the plan and scope of the assessment may have to be revisited and modified as the assessment proceeds.

Hazard or Stressor Identification

It is important to determine whether exposure to an agent has the potential, under some conditions, to cause an increase in the incidence of an undesirable effect such as ecological damage or human disease. In recent years, this process has become one of characterizing hazards rather than simply making a yes-no determination to "identify" hazards. As Paracelsus said back in the sixteenth century, "the dose makes the poison." Hazard is not an intrinsic property of a substance or agent but depends on the situation, such as the level of the exposure or the susceptibility of the receptor. Important advances in hazard characterization have come with an increased focus on understanding mode-of-action (MOA). Science now allows us to attempt to understand how environmental hazards interact with normal biology or environmental conditions to produce unwanted or deleterious effects. This understanding provides a basis for putting results of traditional animal toxicology or ecotoxicology in perspective to better characterize hazards.

Dose-Response Assessment or Analysis of Effects

These are attempts to place quantitative measurements on the magnitude of the hazard in question. If the hazard is expected to cause an undesirable human condition, one type of analysis of effects involves developing a *dose-response* curve to characterize the relationship between the dose of the agent received and the incidence of the adverse health effect as a function of human exposure to the agent. Dose-response characteristics may be as simple as a linear relationship or may be highly complex. The focus on understanding the relationships of dose to response

in both the pharmaceutical and environmental fields has spawned a keen interest in understanding toxicokinetic and toxicodynamic processes. Respectively, these are the studies of how organisms, including humans, handle a toxic chemical and how they respond.

Exposure Assessment

The process of determining the extent to which humans, animals, or other life forms are exposed to a hazardous agent is called *exposure assessment.* Exposure could be measured in terms of concentration of the agent or of duration or frequency of the agent's presence in the environment.

Risk Characterization

Risk characterization is the description of the nature and magnitude of the risk to human health, other life forms, or the environment, including attendant uncertainty. It involves combining the results of the analysis of effects and the exposure assessment.

Brief History of Risk Assessment in U.S. Environmental Regulation

The process of risk assessment in use today had its roots in safety assessment at the Food and Drug Administration in the 1950s and 1960s. Here, the recognition of the limits of our knowledge and understanding of hazards and risks based on animal toxicology and clinical trials was evolving into a process for safety assessment. Safety assessment typically involves determining a level below which the assessor believes no appreciable risk will be experienced under some specified conditions of exposure, such as a course of therapy or a lifetime consumption of certain foods. This process involved reducing the levels of allowable exposure to account for the uncertainty in extrapolating studies in animals to humans and to account for human variability of responsiveness or susceptibility. Dr. Arnold Lehman, an FDA scientist and "father" of safety assessment for regulatory purposes, believed that the data available at the time supported the use of a factor of 10 to account for each of these uncertainties in most cases. This formed the basis of the current approaches to safety assessment used as an input to environmental decision making.

By 1970 the mutation theory of cancer had spawned laws that banned intentional introduction of any level of an animal carcinogen to foods as a food

additive or pesticide residue, suggesting that any exposure carried some risk and therefore could not be considered safe. At the same time, President Nixon was declaring his "war on cancer" and increasing support to find a cure. This effort stimulated a stronger perception of cancer as a "dread" disease; a disease somehow different from many other adverse health outcomes. At just this time the Environmental Protection Agency was formed, and by the mid-1970s the first wave of environmental laws was being promulgated. These laws endorsed the use of risk-based standards, called for stringent goals, in some cases zero, for carcinogenic contaminants, and identified a suite of health endpoints in addition to cancer that must be assessed in the process of environmental regulation. Laws like the Toxic Substances Control Act, promulgated in 1976, sought to assess and control both existing chemicals and those that were entering the manufacturing process. Today some 2,200 or more chemicals are reviewed by the EPA in its new chemical review process. Cleanup laws of the early 1980s presented even greater challenges to the understanding and control of potential environmental risks. The risk assessment paradigm described above (National Research Council, 1983) provided a disciplined approach to considering available science in assessing the potential for risk from environmental exposures. The NRC also offered "inference guidance," which addressed the use of public health protective default positions in the absence of information to address some of the key questions in assessing risk. Use of these defaults has also stimulated additional research and data collection to allow defaults to be replaced by data in some cases, or, at a minimum, to refine and understand the implications of the use of defaults to address uncertainty in risk assessment. The NRC's advice was published by the EPA in 1986 and was captured in endpoint-specific risk-assessment guidelines for carcinogens, reproductive and developmental toxicity, neurotoxicity, mutagenicity, and exposure. These guidelines have been updated periodically as the field of risk assessment has evolved.

More recently, the NRC (1994) and the Presidential/Congressional Commission on Risk Assessment and Risk Management (1997), among others, have offered additional guidance for refining approaches to risk assessment. At the same time new environmental laws have presented further challenges to the field of risk assessment. In 1996, the Food Quality Protection Act and the Safe Drinking Water Act Amendments highlighted the need to assess risks to subpopulations or children and others at susceptible life stages. They also mandated consideration of aggregate (single chemical, multiple routes) and cumulative (multiple chemicals, single route) exposures in agency risk assessments. These challenges have stimulated further refinement of the risk assessment process as well as novel approaches to testing and data collection.

While risk assessment flourished at the federal level since the 1970s, it also took root in state approaches to evaluating environmental hazards. States like Cal-

ifornia and Massachusetts have developed a cadre of risk assessors to address their own laws and regulations. A thriving consulting industry, supported by academic and industrial scientists, exists to support or, in some cases, challenge federal and state risk assessment findings. Databases like the Integrated Risk Information System (IRIS; see www.epa.gov/iris/) provide practitioners with ready access to information on hazard and dose-response for hundreds of environmental chemicals. This information can then be applied, using local information on exposure, to produce site-specific risk assessments for use in local decision making or can inform federal or state regulatory efforts.

Risk Considerations in Environmental Decision Making

Which risk analysis method is most appropriate for environmental issues? Depending on the nature of the risk and the availability of historical or real-time environmental data, a variety of risk assessment methods can be used to attempt to bound or quantify the environmental risk. Here are several common methods that have been used by policy makers.

Hazard Classification/Characterization

The use of observational (epidemiology) or experimental data (toxicology) to identify potential environmental hazards has a long history. Approaches to systematically evaluate these data and to reach conclusions regarding potential hazards have resulted in a number of tools for use in environmental decision making. Hazard descriptors used in EPA's risk assessment guidelines (see, for example, Environmental Protection Agency, 2005), in the U.S. Department of Health and Human Services Report on Carcinogens (ROC), or in the World Health Organization's International Agency for Research on Cancer (IARC) monographs form the basis for specific regulatory action. For instance, under EPA's Safe Drinking Water Act, chemicals designated as *known* or *probable* carcinogens have a maximum contaminant level goal of zero.

This hazard-based approach to setting regulatory targets was also applied in California's famous Proposition 65. In 1986 California voters passed an initiative that became the Safe Drinking Water and Toxic Enforcement Act of 1986, better known as Proposition 65. This Act requires the governor to publish a list of chemicals that are known to the state to cause cancer, birth defects, or other reproductive harm. Over five hundred chemicals now appear on this list based on reference to the tools and databases discussed above. Specific controls are imposed on chemicals that appear on this list. These controls are designed to protect California's

drinking water sources from contamination by these chemicals, to allow California consumers to make informed choices about the products they purchase, and to enable residents and workers to perform whatever actions they deem appropriate to protect themselves from exposure to these harmful chemicals.

Safety Assessment

Building on the early history and approaches developed at the FDA, many regulatory bodies in the United States and around the world rely on safety assessment to inform their decisions. Using a variety of toxicological tests, safety assessment begins by using data to determine a level of exposure that produces low, or virtually no, effects. This level of exposure is converted to a human equivalent dose and is divided by *safety factors* or *uncertainty factors* to arrive at an exposure level that is unlikely to result in deleterious effects. This general approach to informing decision making has been widely adopted. Some groups have simply adopted the safety factor approach of dividing by one hundred to ensure that there is an adequate margin between observed effects and regulatory levels. Others, like the EPA, have chosen to develop a more elaborate scheme for determining a reference dose (RfD) (Barnes and Dourson, 1988) or reference concentration (RfC) (Jarabek and others, 1990) that embodies a detailed point of departure determination and application of uncertainty factors to account for incomplete information. These order of magnitude (factor of 10) uncertainty factors have a basis in empirical data and account for experimental, interspecies and intraspecies uncertainty (Environmental Protection Agency, 2002). This approach is considered to be conservative and public health-protective in informing regulatory decisions. Unlike quantitative risk assessment, safety assessment does not address the probability of a risk occurring but addresses a level below which appreciable risk is unlikely. It does not address a situation where risk might begin at higher levels of exposure or the nature or magnitude of such a risk. Nonetheless, safety assessment has become a useful tool for bringing science to bear on regulatory decisions.

Quantitative Risk Assessment

In the United States, quantitative risk assessment has become the norm for regulatory decision making, particularly with regard to environmental carcinogens. Mathematical models are applied to epidemiologic or toxicologic data and exposure information to determine upper-bound probabilities on cancer risk (Environmental Protection Agency, 2005). Using these approaches, scientists can provide decision makers with a perspective on the likelihood of cancer occurrence in a population of exposed individuals. This approach is designed to account for sensitive individuals in the population. Therefore, probabilities of risk are unlikely to be

underestimated and true risks are likely to be less. It is recognized that under certain conditions of exposure, there may be no risk at all. Despite these uncertainties, quantitative estimates of risk form the basis for many environmental decisions from setting national standards for air and water pollution to determining site-specific cleanup standards for hazardous waste sites. Advances in quantitative risk assessment have included the incorporation of an appreciation of how chemicals interact with underlying biology. This has spawned sophisticated, biologically based models. Recent work on formaldehyde provides an illustration of current approaches in the field of quantitative risk assessment (Conolly and others, 2003). Future directions will include quantitative assessment of noncancer effects. It is likely that these efforts will be informed by our understanding of susceptibility at the genetic level and will be aided by application of evolving tools of molecular biology.

Benefit-Cost Analysis

This is a set of procedures for defining and comparing benefits and costs of a particular risky event or undertaking; in this sense it is a way of organizing and analyzing data as an aid to decision making (Zerbe and Dively, 1994). The role of the benefit-cost analyst is to analyze impacts and their monetary values to inform the policy-making process. These values are important because they allow decision makers to directly compare costs and benefits using the same measure, namely dollars (Freeman, 1979). A complete benefit-cost analysis makes explicit the assumptions about the values of benefits and costs embedded in different policy choices (Environmental Protection Agency, 2000).

One could assert that benefit-cost analysis is a risk assessment method; in any case, it is a method used to justify the risks associated with many regulations (e.g., the Federal Insecticide, Fungicide and Rodenticide Act, enforced by the U.S. Environmental Protection Agency), as well as Executive Order 12866 requiring benefit-cost analysis for all significant regulatory actions. Some common criticisms of benefit-cost analysis are that (1) it cannot account effectively for ethical and moral issues regarding the environment, (2) it may seem ethically wrong, or in any case practically impossible, to accurately put dollar values on some intangibles, such as the value of a butterfly that may be harmed by a pesticide, and (3) it does not account sufficiently for distributional analysis—who wins and who loses from a given decision (Kelman, 1981; Environmental Protection Agency, 2000).

Fault Tree Analysis

This is applied in situations where there are multiple potential errors leading to specific adverse outcomes, such as the 1986 Chernobyl nuclear power plant explosion. Fault tree analysis takes dynamic (time-varying) aspects of a situation into

account so that it is relevant to situations where causes of risk occur over time. If there is only one type of error leading to one outcome, then this is not the most appropriate method. Also, this method is usually only useful when one can assign probabilities of risk with a high level of precision.

Fault trees are used most often to characterize hazards for which direct experience is not available. They may be used to map all relevant possibilities and to determine the probability of the final outcome. To accomplish the latter goal, the probabilities of all component stages, as well as their logical connections, must be completely specified (Slovic, Fischhoff, and Lichtenstein 1979). A very similar method is *root cause analysis,* which is applied to situations where specific risk events or errors have already occurred and data on these events are available, so that it is possible to do a detailed audit of the history of circumstances that led up to the event.

Focus Groups or One-on-One Interviews

Focus groups, in which a moderator leads a group of people in discussion of a given risk, are applied in situations where participants may have a range of different views. These groups are a good setting in which to learn about the range of views and to allow participants to explain the reasoning behind these views. It is also appropriate in settings where consensus is valued. One-on-one interviews are similar to the focus group approach except that these interviews are more appropriate for individual risk behaviors than community-based ones, such as smoking or applying pesticides within the home.

Despite initial fears of a particular risk, it is possible for people subject to that risk to think rationally about it, and for them to confront the hard truth that solutions to the problem may involve an uneven distribution of benefits and risks. Furthermore, effective risk management requires the cooperation of a large body of laypeople, because it is desirable that they vote sensibly, follow safety rules, and use the legal system responsibly (Ruckelshaus, 1985). In regard to risk events and public participation, Wildavsky (1979) points out: "Why, if accidents or health rates are mainly dependent on personal behavior, does the vast bulk of governmental resources go into engineering safety in the *environment* rather than inculcating it into the individual?" Indeed, knowing more about how people think and feel about a particular risk, and what they know about it, may in some cases be the most effective part of designing a risk management procedure.

Data-Based Methods

Data-based methods such as regression analysis/tornado analysis are appropriate when the number of errors or adverse outcomes and the circumstances under which they occur can be recorded. The goal of databased methods is to use sta-

tistical techniques to find out the relative contribution of potential contributing factors to the observed incidence of errors or adverse outcomes. (Tornado analysis has nothing to do with physical tornados; it deals with ranking the relative contribution each factor has to an outcome by diagrammatically putting the factor with greatest contribution at top, then the next, in a funnel shape.)

Databased methods can provide understanding and insight, but can never capture all the factors, such as quality of life, that are important in a problem. Moreover, they lead to the inclination of regulatory agencies to accept quantitative risk assessment tools as a substitute for science (Morgan, 1981).

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Notice that the preceding risk assessment methods differ in some important ways and therefore show various strengths and weaknesses when making a risk characterization of an environmental hazard. They differ in

1. The possible precision of risk estimation
2. The level of control professional staff have over risk factors
3. The extent to which an individual or a particular community is involved in the risk management process
4. The extent to which risks and errors occur as independent events or as part of a dynamic sequence of events
5. The extent to which one error contributes to one adverse outcome, or whether a series of errors leads to this outcome
6. The extent to which it is possible to record errors and the circumstances under which they occur
7. The extent to which the human performance contribution to error is understood

In reality, very few environmental regulatory decisions are based on use of just one of these risk assessment methods. Often, an integrated assessment is used, which is described in greater detail in the example on mycotoxins below. An integrated assessment, using several of these risk assessment methods, covers many of the flaws and gaps that using just one method might incur.

Going from Risk Assessment to Risk Management and Risk Communication

Risk management is as its name describes a method for managing risks. Ruckelshaus (1985) defines risk management as the process by which a protective agency decides what action to take in the face of risk estimates. In reality,

though, managing risks can be done on many different levels, from the individual decision maker to the highest policy decision maker. It is up to this decision maker, together with the community, to decide what constitutes "safety" or an acceptable level of risk (Rodricks and Taylor, 1983).

Risk management is best informed by the risk assessment process. At the same time, how risk is managed directly affects the risk assessment process by determining the level of risk with which the individual, group of people, or institution must live. For risk assessment to best inform the risk management process, a number of safeguards must be in place (Rodricks and Taylor, 1983). The risk analysts must make explicit all the assumptions going into their work and the uncertainties associated with them. Peer review ensures that significant departures from usual assumptions are justified. And decision makers, particularly government agencies, should ensure that their use of risk assessment is not tailored to fit a predetermined regulatory position; that is, the science and the policy should be kept separate.

Risk assessment does not purport to give risk managers one clear answer to any problem. For example, a local government may choose to manage the risk of arsenic in municipal drinking water by requiring water utilities to reduce arsenic to ten parts per billion. Perhaps this management decision was based on a risk assessment showing that *most* individuals, except for sensitive subpopulations, experience no adverse effects at that level. Meeting this management standard has a cost; at the same time, it may incur particular health benefits and yet leave some subpopulations still vulnerable to toxic effects. To ensure the safety of even those subpopulations, another risk management strategy may be to reduce the standard to five parts per billion. However, this could have enormous costs.

Thus, risk management almost always involves a cost-risk tradeoff, or a risk-risk tradeoff. Because these costs and risks can be incurred by multiple people, risk management is not merely a set of techniques for arriving at policy decisions; it must also include communication to the public about how those decisions are made (Ruckelshaus, 1985). Communication is crucial, as trust—whether between parties or on a wider public scale—is the ultimate goal of risk management.

Risk communication is the process by which persons or institutions with information of the risk at hand choose to communicate the risk to others, for example, to the general public, to loved ones, or to employees. Risk communication has benefited from a vast body of literature in behavioral economics and judgment and decision making, which has shown that the manner in which risks are communicated can have important effects on how people react and respond to the risks. (Some of these ways will be described in Tasks 3 and 5.)

Since the goal is to inform others in a way that helps them to make optimal decisions for themselves, the field of risk communication focuses on finding communication methods that will enable others to make those optimal decisions. It is also true, however, that risk communication can be a means by which people may

be led to act in suboptimal ways. The problem is that risk messages are difficult to formulate in ways that are accurate, clear, and not misleading (National Research Council, 1989).

Studies in risk communication have focused both on *what* risk information to present and *how* to present it. The mental models methodology (used in a variety of risk communication studies and most clearly outlined in Morgan and others, 2002) addresses the former problem. It seeks to answer the following questions:

- Who is the target audience for the risk communication?
- What are their mental models of the risk at hand—that is, what do they know about the risk, what don't they know, and what are their opinions of it?
- How do these compare to what experts know about the risk?
- How can a communication fill those gaps in the target audience's knowledge?

This method of risk perception elicitation not only seeks to fill gaps in the target audience's knowledge but also helps experts and risk managers to understand what concerns people, regardless of whether those concerns are grounded in science.

How to present this risk information is also important. A variety of studies (for example, Gatson and Daniels, 1988; Tinker and Silberberg, 1997; Connelly and Knuth, 1998; Small and others, 2002) have focused on language and visual aspects of risk communications. For example, these studies have indicated that to present risk information effectively to the general public, the best reading level to aim for, linguistically, is grade 8. Usually the lower the grade level, the broader the range of people who can read and understand the text, although it may be difficult to describe a complex risk at lower than a grade 8 level. Also, the tone of voice (Connelly and Knuth, 1998) is important; in getting people to comply with risk advisories, a commanding tone in which the communication reads "Do this" or "Avoid that" is less effective than declarative statements such as, "If you do this, that will happen." Including pictures and graphics is usually helpful as well.

Thus, policy makers use risk assessments to both manage and communicate environmental risks. Their job only begins when they receive the results of a risk assessment; the regulatory and educational aspects use the risk assessment as a starting point.

Three Examples of Risk Assessment

Chloroform in Drinking Water

Chloroform is one of a number of disinfection byproducts that occur from the use of chlorination. Although it is clear that chlorination of drinking water has had a huge beneficial effect on public health worldwide by controlling diseases

such as diarrhea and cholera, risk assessment has been used to determine the potential for chlorination to be used safely. The risk assessment for chloroform provides a good example of the modern application of risk assessment methods for informing public health

In the late 1990s, EPA proposed to raise the maximum contaminant level goal for chloroform, an animal carcinogen, from 0 to 300 parts per billion (ppb). In proposing to raise the goal level above zero, the Agency was relying on a risk assessment that had departed from the traditional risk assessment approach of using linear default models and assuming that any dose of a carcinogen carried with it some risk. It recognized the observations of various effects in laboratory animals, but applied emerging approaches to understand the mode-of-action underlying the toxicity of chloroform and apply them to the risk assessment. These approaches were consistent with the evolving field of cancer risk assessment that was captured in EPA's 1996 proposed cancer guidelines (Environmental Protection Agency, 1996). The resulting assessment concluded that cancer in animals was produced only after exposures had exceeded those needed to produce tissue damage. It was this tissue damage and the compensatory cell proliferation that gave rise to the tumors. If exposures were kept below the level associated with tissue damage, tumor formation was not expected to occur. This approach then relied on the concept of biological thresholds for a cancer response. (See Environmental Protection Agency, 2001a, for a full discussion of this risk assessment.)

This precedent-setting risk assessment illustrates the opportunity of bringing a large toxicological database to bear on decision making. It shows how the scientific community supported the development of a framework for judging the adequacy of the data to understand mode of toxic action. It provided an opportunity for the Agency to apply these concepts to an important chemical contaminant. It resulted in a science-based decision to depart from historical risk management approaches for chemicals in drinking water.

The debate surrounding the risk assessment of chloroform and its application to environmental decision making was highly contentious. On one side there were allegations that the Agency was abandoning public health in favor of uncertain data and models; on the other side there were discussions about the economic implications of zero as a goal for exposure to carcinogens. In the end, the best available science prevailed, and it was used to inform the Agency's regulatory approach.

Genetically Modified Bt Corn: The Risk of Gene Flow in the Environment

Bt corn is corn genetically modified to produce a protein that is toxic to lepidopteran insects, including common corn pests such as corn borers and earworms, but is harmless to other animal species. Thus far, eight nations worldwide have ap-

proved commercialization of Bt corn (James, 2003). However, about 90 percent of total Bt corn planting today takes place in industrial nations, with the United States comprising 85 percent of the total acreage devoted to Bt corn globally. Only four less-developed countries—Argentina, Honduras, South Africa, and the Philippines—have approved Bt corn commercialization and trade. However, many nations are now at the cusp of determining whether they will allow their farmers to plant Bt corn. Environmental risk assessment is crucial in informing policy makers' decisions in this case, because certain nations are particularly at risk of the potential environmental consequences of Bt corn genes spreading in the environment.

By virtue of its pest protection, Bt corn provides certain benefits both to growers and to consumers. Yield increase and pesticide reduction are primarily benefits that accrue to Bt corn growers, whereas mycotoxin reduction as a result of decreased insect damage provides economic benefits for growers and health benefits for both human and animal consumers. These benefits associated with Bt corn adoption have been demonstrated to various extents in different countries around the world, and could be particularly beneficial in some less-developed countries where corn is a staple in human and animal diets and pests and mycotoxins are poorly managed.

An important consideration when deciding whether to adopt an agricultural technology is that the technology poses no significant risks to human health, the environment, or trade; or, if it does, whether its benefits outweigh its risks. When Bt corn was first commercialized in the United States in 1996, the full suite of potential risks to human health and the environment had not yet been fully discovered and assessed. (Indeed, the full suite of risks of Bt corn, or any plant, may never be fully discovered and assessed.) In the last decade, more information has emerged to shed light on new potential risks—and in some cases, to repudiate those risks. Among the most notable potential risks of Bt corn that have since been repudiated by extensive scientific and governmental risk assessments are those of food allergenicity, horizontal gene transfer, and adverse impacts on nontarget species. Still of significant concern are issues of gene flow, insect resistance development, and trade barriers that could result from precautionary policies regarding genetically modified crops.

An important concern about the introduction of Bt corn is its potential for *gene flow*: spreading the Bt gene through sexual transmission to non-Bt corn (*gene outcrossing*) or wild relatives (*gene outflow*) that did not originally possess the genes. This potential for gene flow raises two main concerns:

1. Flow of the Bt gene could enhance the weediness of certain corn relatives, which could then lead to loss of biodiversity (Rhymer and Simberloff, 1996; Ellstrand, Prentice, and Hancock, 1999).

2. Flow of the Bt gene into corn that is not meant to contain genetically modified material (e.g., organically grown corn) could lead to an economic loss for farmers whose corn is pollinated with Bt pollen (Wu, 2004a).

The two relatives of corn that pose a concern are *tripsacum* and *teosinte,* as these are the only species related to corn that could survive without human cultivation. Field corn is of the species *zea mays,* which in the Americas is closely related to the *tripsacum* species as well as to wild *teosintes.* The species in the genus *tripsacum* are close relatives of corn, of which three species occur naturally in the United States (Hitchcock, 1971). Of these, *T. dactyloides,* or Eastern Gama Grass, is the only species of widespread occurrence and any agricultural importance, although it lacks the characteristics of many weeds (Environmental Protection Agency, 2001b). Because *tripsacum* differs from corn in chromosome number (usually 9 or 18), attempts at laboratory gene outcrossing have been difficult, and the resulting hybrids are primarily sterile. Also, such hybrids are not able to survive even the mildest winters (Environmental Protection Agency, 2001b).

The major concern is in the regions of native corn biodiversity primarily located in Mexico and Central America. *Teosintes* have coevolved in close proximity to maize in Central and South America for thousands of years. They have maintained separate genetic constitutions in spite of occasional introgression (Doebley, 1990; Environmental Protection Agency, 2001b). Like corn, two species of *teosintes* have 10 pairs of chromosomes and can be genetically compatible with corn, producing viable offspring. (Some *teosinte* species have 20 pairs of chromosomes and cannot form stable hybrids with corn (Edwards, Allen, and Coors, 1996).) One concern about introgression between Bt corn and *teosinte* is that the latter is self-sustaining in warm climates. *Teosinte* has a coblike fruit that shatters more easily than corn but still restricts the movement of seeds compared with other related weedy species (Environmental Protection Agency, 2001b).

Currently, Mexico has halted the planting of Bt corn, while it is assessing the potential impacts of Bt corn on the biodiversity of Mexican maize landraces and their ancestral forebear *teosinte.* Special concern was raised when a study published in *Nature* (Quist and Chapela, 2001) reported that promoter (CaMV 35S genes) and terminator (*nos* from *Agrobacterium tumafaciens*) elements from Bt corn were found in samples of Mexican native maize landraces. Later, Metz and Futterer (2001) and Christou (2002) cast doubt on the validity of the findings in the Quist and Chapela study, attributing the positive polymerase chain reaction (PCR) results to sample contamination as the most likely explanation. As an unequal number of samples tested positive for NOS and 35S, there seemed a lack of intact functional genes, which would have been expected from transgenic plant origin. However, Quist and Chapela's first conclusion, that transgenic DNA is present in

native landraces of Oaxacan corn, is certainly plausible, given the large-scale importation of U.S. corn. Whether or not Quist and Chapela conclusively proved that point, many scientists agree that it is likely that transgenic corn is growing in Mexico (Byrne and others, 2005).

Even if Bt corn were planted in close proximity so as to achieve gene flow to its native relatives, however, the probability of reducing biodiversity among native relatives or causing relatives to become weedy is remote. First, the Bt gene would need to be successfully incorporated into the native species. Next, the plant population would have to be contaminated with Bt corn multiple times, or Bt corn would need to be so dominant that a significant proportion of the plants would have acquired the transgenes. Finally, the plants that incorporated the transgenes would need to outcompete the non–Bt-contaminated plants in that same region. As the only advantage Bt confers is lepidopteran pest control, it is unlikely that outcompetition would occur (Dr. Christopher Wozniak, EPA, personal communication). In fact, because Mexican farmers rarely segregate different varieties, cross-pollination between local and nonlocal varieties has already been taking place. Yet, despite the history of gene flow from nonlocal to local cultivars, the varieties have survived intact as recognizable entities (Council for Agricultural Science and Technology, 2002).

It is also important, however, to consider the cultural value to humans of preserving the genetic integrity of those species. As Ignacio Chapela of the University of California-Berkeley stated of Mexico, "The people are corn, and the corn is the people." (Yoon, 2001). It may well be that concerns regarding the ecological effects of gene flow are scientifically unfounded, but the true concerns are cultural (Council for Agricultural Science and Technology, 2002).

The final risk of gene flow concerns organic corn growers whose fields lie in close proximity to Bt corn. All organic certification agencies worldwide prohibit the use of genetic engineering in organic production and processing (Codex, 2002). Hence, even if an organic grower plants no Bt corn, his corn may be rejected in the organic market if it is found to contain trace amounts of transgenic material through cross-pollination with Bt corn. In such cases, an organic grower could lose his premium of $0.20 to several U.S. dollars per bushel (Greene, 2001). Such concerns are important, as U.S. society is increasingly valuing organic produce (Good and Bender, 2001), although no federal statutes currently protect organic growers against GM gene contamination.

Mycotoxins in the Global Food Supply

Whereas the previous example describes a risk that we impose upon our environment, this case study describes a risk that the environment—through fungi and their toxins—imposes upon us.

As early as the eleventh century, the link between consumption of moldy grain and outbreaks of gangrenous disease was discovered in Europe. This disease was caused by consumption of the fungus *claviceps purpurea,* which produced a potent mycotoxin in rye (Council for Agricultural Science and Technology, 2003). Two more recent examples include an outbreak in Siberia in 1944 in which 10 percent of people who consumed moldy wheat and barley died of acute toxicosis (Kotsonis, 2001), and an incident in the southern United States in the mid-1930s in which several thousand horses died from consuming moldy corn (McCue, 1989).

Mycotoxins are chemicals produced by fungal molds that are toxic or carcinogenic to animals and humans. Although a low level of mycotoxins in food is generally regarded as safe and in any case unavoidable, conditions such as unusual weather, insect pest damage, improper breeding and harvesting, or poor storage can lead to high levels of mycotoxins in crops, causing severe disease outbreaks.

Aside from health risks, mycotoxin contamination can also reduce the price paid for crops. Losses from mycotoxins in the United States and other industrial nations are typically associated with market losses as opposed to illnesses or deaths resulting from the effects of the toxins. Vardon and others (2003) calculate that total mycotoxin-related losses to agriculture in the United States are as high as $1.4 billion annually ($630 million to $2.4 billion). In particular years and regions, one mycotoxin, aflatoxin, can contaminate crops so severely that farmers are forced to dispose of more than half of their total corn and peanut crop (Robens and Cardwell, 2003).

Far more severe, however, are the economic and health impacts of mycotoxins in the developing world. In these nations, many individuals are not only malnourished but also chronically exposed to high levels of mycotoxins in their diet (Miller and Marasas, 2002). Reported results of excess mycotoxin consumption range from deaths from severe toxicoses to various cancers to diseases of malnutrition, the last among children particularly. While industrial nations have well-developed infrastructures for monitoring internal food quality standards, developing nations often lack the proper enforcement and monitoring methods to protect their people from contaminated food.

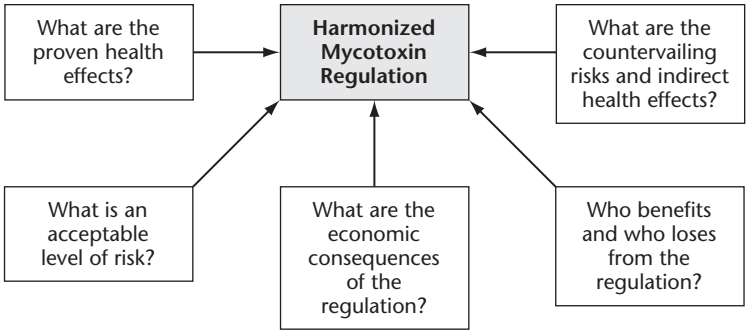
Today globalization of food trade has further contributed to losses due to mycotoxins in the developing world, in two important ways. First, stringent mycotoxin standards on exported foods mean that developing nations are likely to export their best-quality foods while keeping contaminated foods domestically, which inadvertently results in higher risk of mycotoxin exposure in those nations (Cardwell and others, 2001). Second, a large portion of even the best-quality foods produced in the developing world is rejected for export at these more stringent standards, meaning millions of dollars in losses. At the 2001 United Nations Conference on the Least Developed Countries in Brussels, Secretary-General Kofi Annan noted:

> A World Bank study has calculated that the European Union regulation on aflatoxins costs Africa $670 million each year in exports of cereals, dried fruit and nuts. And what does it achieve? It may possibly save the life of one citizen of the European Union every two years. . . . Surely a more reasonable balance can be found.

Mycotoxin regulations worldwide have largely been based on an analysis of demonstrated health effects to humans and to animals, with additional risk management considerations (e.g., safety factors). Integrated assessment takes the analysis several steps further. It includes available information about health effects, and also considers the questions, What is an acceptable level of risk? What are the economic consequences of the regulation? Among the different stakeholders affected by the regulation, who benefits and who loses? Finally, are there any *countervailing* risks and indirect health effects associated with the regulation? All these questions should be taken into account when considering harmonized mycotoxin regulations, as shown in Figure 3.2.

To address the economic consequences of mycotoxin regulations, an empirical economic model was developed to estimate a nation's total export loss of a particular food crop, given an internationally imposed mycotoxin standard. This is a function of the price of the food crop per unit volume on the world market, the total volume of that crop exported by a particular nation, and the fraction of that nation's export crop rejected as a result of a worldwide mycotoxin standard. The economic model allows a sensitivity analysis on how export losses for food crops in particular nations change as a function of the strictness of the mycotoxin

FIGURE 3.2. INTEGRATED ASSESSMENT TO INFORM DEVELOPMENT OF HARMONIZED MYCOTOXIN REGULATIONS.



standard. Model equations, parameters, their descriptions, and references for calculating economic impacts are given in Wu (2004b).

Next, an assessment was made of which nations would benefit and which would lose as a result of stricter mycotoxin regulations. Logically, those who would experience losses were food exporters, particularly those with higher mycotoxin concentrations in their food crops; while those who would experience the greatest health benefits from stricter standards were food-importing nations. These data were gathered from databases of the Foreign Agricultural Service of the U.S. Department of Agriculture, giving information on food crop imports and exports by nation and year. Potential health effects were considered through epidemiological studies of the effects of moving from one mycotoxin regulation to another.

Countervailing risks and indirect health effects were considered from two angles: the possibility of less-developed countries exporting their best crops while keeping the most contaminated food domestically, and the prevalence of predisposing factors among the populations of those countries (such as hepatitis B and C) that make them particularly vulnerable to toxic and carcinogenic effects of mycotoxin consumption. Finally, the question of an acceptable level of risk was explored from the integrated findings.

The empirical economic model presented in this study shows that moving from a harmonized fumonisin standard in corn of 2 mg/kg to 0.5 mg/kg would result in an increased worldwide annual market loss of over $200 million through rejected corn, with the United States, China, and Argentina bearing the brunt of the economic burden. Likewise, moving from a harmonized aflatoxin standard in peanuts of 20 μg/kg to 4 μg/kg would result in an increased worldwide annual market loss of about $350 million through rejected peanuts. Again, the United States, China, and Argentina would bear the brunt of the economic burden, with China and sub-Saharan African nations losing 90 percent of their peanut export market. Health benefits from moving to these stricter fumonisin and aflatoxin standards would be negligible; in fact, health risks could *increase* in less-developed countries if the best-quality crops were exported and the mycotoxin-contaminated food consumed domestically.

Thought Questions

1. How would a policy maker decide which of the different risk assessment methods was most appropriate in a given environmental context? What method(s) would you choose for assessing the risk of: (a) a hurricane that is predicted to hit a coast near your home, (b) a hazardous waste site located in your town, and (c) various cockroach control sprays found in your store?

2. Given the above case study of gene flow of genetically modified corn, if you were an environmental decision maker in an imaginary nation, would you decide to allow Bt corn planting? Why or why not? Would it make a difference if your nation were in Central America, Asia, or Africa?

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CHAPTER FOUR

TOXICOLOGICAL BASIS FOR RISK ASSESSMENT

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Learning Objectives

Students who complete this chapter will be able to

1. Explain basic concepts of toxicology
2. Describe the implications of toxicokinetic concepts for risk assessment
3. Describe each of the three exposure-response relationships: toxicological, epidemiological, and clinical
4. Explain how the mechanisms of carcinogenesis are modeled in quantitative risk assessment
5. Describe the problems one encounters in applying animal toxicity screening test results to human beings

Chemical agents present two fundamental problems in risk assessment: (1) consequence assessment for widespread, relatively frequent use of a chemical and (2) minimizing the frequency and consequences of an uncontrolled chemical release.

The first pertains to adverse health effects due to toxicity at levels more representative of production, emissions, or end use. This type of problem falls into the domain of toxicology. The modern paradigm of risk assessment was originally created to address this problem, particularly for carcinogens, and builds on basic principles of toxicology. The most common application of toxicological

knowledge in risk assessment is in modeling the risk of rare events, such as cancer, when the chemical is in common use or being considered for widespread use.

The second pertains to the physical and acute toxicity hazards of the chemical in bulk and the potentially catastrophic adverse effects due to uncontrolled release as in a transportation incident, spill, or facility malfunction (such as a valve leak). This problem is focused on the probability of an event occurring that results in a chemical release and the contingent probability of acute human illness or death following the release. It is best modeled as an example of a high-consequence, rare event. Engineers and risk management personnel have for many years addressed the latter problem using statistical methods and operations research methodology that also have applications in risk assessment.

Toxicology

Toxicology is the science that studies how chemicals are handled in the body and how they affect the body in causing injury or illness. It has been called the science of poisonings, but this definition is largely historical. Contemporary toxicology is concerned with the behavior of chemicals in the body (*toxicokinetics*), the effects of the chemicals on the body (*toxicodynamics*), and the body's responses and adaptations to these chemicals (metabolism and interactions with macromolecules). Therefore, in the modern sense, toxicology differs from pharmacology and nutritional sciences primarily in that the effects of interest are presumed to be adverse.

Toxicology is the basic science behind chemical risk assessment, and the problem of modeling the risk of chemical exposure has led to the foundations of modern quantitative risk assessment. Toxicology is therefore more than a tool for understanding the effects of chemicals on the human body; its principles underlie contemporary risk assessment as a discipline.

Orientation: Basic Concepts

The term *poisoning* is usually reserved for serious toxicity, either involving the total body or resulting in a recognized pattern, or syndrome, of clinical illness that is directly caused by a chemical. *Toxicity* is usually the preferred term for the adverse effects of chemicals on the body because it implies a range of toxic effects, including subclinical effects at low exposures, and the role of a chemical exposure as one risk factor among many others. For example, lead poisoning in children is a well-recognized clinical syndrome observed at high levels of exposure. Lead toxicity includes lead poisoning on a spectrum that includes lead exposure as a risk factor in brain development, along with nutrition, mercury, organochlorine exposure, mental stimulation, and myriad other risk factors. From the point of view

of risk assessment, poisoning is simply a question of how likely it is that an individual will encounter an exposure sufficient to cause clinical illness. Toxicity, however, is a more complex issue and requires that the probability of the effect due to exposure be teased out from that of other risk factors, separately calculated, and then compared to background.

Toxic effects may be acute or chronic. *Acute effects* occur quickly, as the result of relatively high exposure (by definition). *Chronic effects* are those that persist and are usually the result of exposure to relatively lower levels of exposures. Chronic effects may develop over a prolonged period, variously reflecting the cumulative effect of repeated exposures, the accumulation of a persistent chemical to the point of toxicity, or the irreversible or slowly reversible consequence of an acute exposure. Some toxic effects are reversible; when exposure stops, the adverse effect goes away. Others are irreversible, and the effect may be permanent or lead to further health consequences, which are called *complications.*

Allergy and immunity are different from toxicity. These conditions result when the body develops a particular response that is highly specific for the chemical or substance. These responses are programmed in the body as particular, stereotyped reactions. Only certain people develop this response to a particular chemical, and when they do the response lasts for a long time, often for the rest of their lives, and does not closely follow the exposure-response relationship described above.

In understanding the chronic effects of toxic chemicals at lower exposure levels, which is usually the issue in chemical risk assessment, it is useful to think first of their behavior in the body (toxicokinetics) and second of their effect on the body (toxicodynamics).

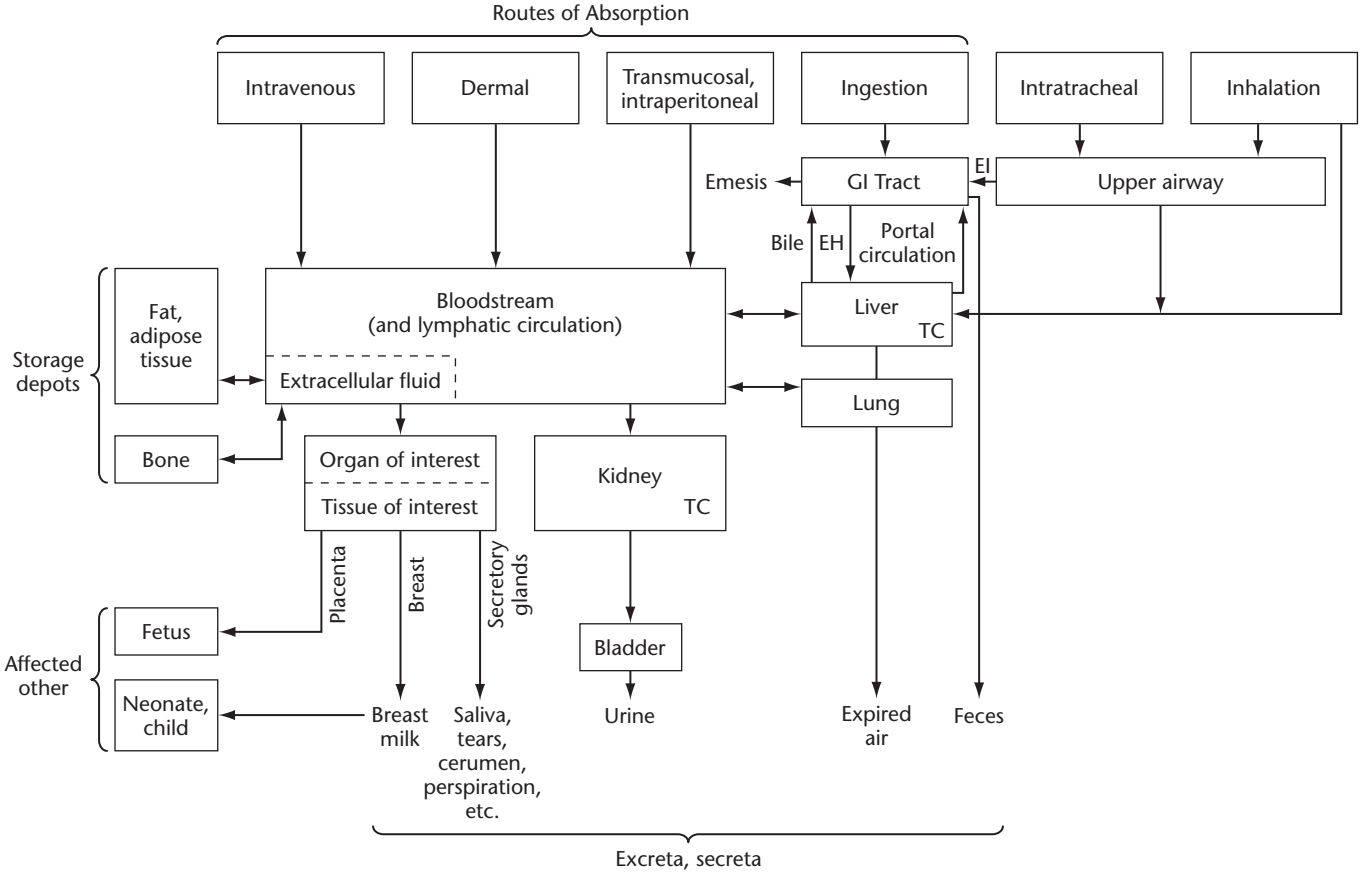
Toxicokinetics

Toxicokinetics refers to how the body takes in chemicals and what the body does with them. It is also the term used for modeling the concentration of the chemical as it rises or falls in the bloodstream or different parts of the body.

There are four recognized phases of toxicokinetics: absorption, distribution, metabolism, and excretion. In toxicology, chemicals originating externally to the body and having no nutritional value are called *xenobiotics,* literally "foreign compounds."

Regardless of their effect or origin, the behavior of xenobiotics in the body can be described by general terms and models reflecting the mechanisms by which exposure occurs and the body handles the chemical (Figure 4.1). These toxicokinetic models are very important in chemical risk assessment because they allow estimates to be made of how much of a chemical will be retained in the body, at what level, and for how long under various assumptions of absorption.

FIGURE 4.1. SCHEMATIC FLOW OF XENOBIOTICS THROUGH THE HUMAN BODY.



Absorption. The xenobiotic must reach the body through some pathway or *route of exposure*. In risk assessment applied to environmental health, the routes of exposure are primarily airborne, waterborne, or foodborne and applied to the skin. Applied to drugs and medical devices, there may be other, more invasive routes of exposure, such as injection into a muscle or a vein.

Once contact is made, the xenobiotic is then absorbed into the body or tissue and usually enters the bloodstream. Xenobiotics may enter the body through any of several *portals* or routes of entry, the first three of which are "natural" in the sense that they are the usual means by which exposure occurs in human beings and animals:

- Skin or mucous membranes
- Inhalation
- Ingestion
- Medical or therapeutic routes of exposure, such as subcutaneous injection, intramuscular injection or intravenous injection, implantation, anal suppositories, or intrathecal cannulation (to deliver chemotherapy to the central nervous system)
- Experimental routes of exposure used only in animal studies: intraperitoneal injection, intratracheal instillation (forced delivery into lungs), gavage (forced delivery to stomach)

The rate at which a xenobiotic enters the bloodstream is determined by absorption across the barrier specific to the given route of exposure. Absorption across membranes is determined for the most part by the chemical and physical properties of the agent. In general, lipid-soluble (*lipophilic* or *hydrophobic*) substances are absorbed more readily than water-soluble (*hydrophilic*) substances across barriers such as skin.

Another factor of importance in absorption is *bioavailability*. This term, usually expressed as a decimal fraction, describes how much of the xenobiotic is available to be absorbed given the route of exposure. For example, metallic mercury (Hg^0) is not efficiently absorbed in the gastrointestinal tract, but its vapor, in the gas form, is readily absorbed by the inhalation route. Differences in bioavailability may result in different absorption of drugs manufactured in different preparations.

The rate of absorption is the most important determinant of the peak levels in plasma. For many toxic substances, this becomes the prime determinant of acute toxicity.

Of the natural portals of entry, inhalation is the most rapid and complete route of absorption because the only barrier between an airborne, gaseous xenobiotic and the bloodstream is the thin, highly vascular respiratory membrane. An

inhaled gaseous xenobiotic reaches its peak in blood within seconds or minutes. Particles inhaled into the lung are taken up by special cells and broken down or dissolved to the extent they can be, and the soluble product is then absorbed.

The skin has many blood vessels and is a major route of entry into the bloodstream for many chemicals, particularly if they are lipid-soluble. Although absorption tends to be slow across the dessicated cells of the outer layer of skin (*keratinocytes*), there are shortcuts through hair follicles and sebaceous glands that facilitate entry of many xenobiotics. Absorption is also fast across wounds in the skin.

Ingestion tends to be an efficient route of absorption, but the blood from the stomach and intestines goes to the liver first (*via* the portal system of blood vessels), not directly into the circulatory system. For this reason, the liver is often the first organ to be injured by highly toxic xenobiotics, and xenobiotics that are metabolized in the liver appear as metabolites in the general circulation. There are also many specialized systems in the gastrointestinal tract that increase absorption of xenobiotics that are or resemble nutrients, such as lead or molecules that look like glucose.

For drugs, intravenous injection is the most rapid route of exposure. The xenobiotic goes from the vein directly to the heart and is then mixed with the general circulation, reaching its peak concentration in the blood almost immediately. Subcutaneous injection is much slower. Intramuscular injection is intermediate but variable, depending on blood flow through the muscle.

Distribution. Chemicals may not stay where they are first delivered. Once the xenobiotic is absorbed and enters the bloodstream, it is transported to the capillary level in tissues of the body, where it becomes available for uptake by the target organ. After one pass through the circulation the xenobiotic is uniformly mixed in with arterial blood regardless of its route of entry. When a bolus is absorbed, the peripheral tissues are therefore presented with an increasing concentration in the blood, which peaks and then declines as the xenobiotic is distributed to tissues throughout the body and removed by metabolism, excretion, or storage.

When a xenobiotic is dissolved in plasma, some fraction of the total usually binds to circulating proteins, particularly albumin (which binds many organic compounds and metals, such as calcium, copper, and zinc). Usually, only a small fraction persists as free xenobiotic in the bloodstream.

As the concentration of free xenobiotic falls in plasma, some molecules separate from their binding sites until a new equilibrium is reached. *Binding* therefore acts as both a storage and distribution mechanism, maintaining a more even blood concentration than would otherwise be the case and reducing the peak concentration that would otherwise be presented to tissues. Bound xenobiotics may be displaced by other xenobiotics. Some xenobiotics, such as barbiturates or sulfon-

amides, compete with others for binding sites and may increase the concentration of free xenobiotic in the plasma and therefore increase toxicity. As a practical matter, this is of greatest significance in drug-related toxicology as a mechanism of drug interaction and overdose and is seldom a consideration in environmental toxicology.

Some chemicals are kept out of certain parts of the body, such as the brain, by special barriers, and some are stored in certain parts of the body because they dissolve easily or are trapped there. Some mobilize under certain conditions and move around the body and others stay trapped in a particular tissue or organ.

The persistence of a xenobiotic in the bloodstream is an important determinant of the duration of its action and the penetration that may occur into tissues less avid in their uptake of the particular agent. However, the most important determinant of uptake by the target organ is the uptake of the xenobiotic from plasma into the tissue, which depends on the blood flow to the organ and the affinity of the tissue for the material. Special transport mechanisms exist at the cellular level for some xenobiotics, as in the gastrointestinal tract. As in absorption, *diffusion* of a xenobiotic from the bloodstream into the tissue depends on the solubility of the xenobiotic in fat.

Lipophilic agents accumulate in adipose tissue or lipid-rich organs such as the nervous system or the liver. These become *storage depots* for the xenobiotic or its metabolites, remaining in the tissue when the circulating levels in the bloodstream are relatively high but mobilized back into the bloodstream over weeks or months when circulating levels drop. Where the physicochemical properties of the organ attract and bind metals, as in bone, a metal may be *sequestered,* accumulating over time and turning over only very slowly and incompletely. Such storage depots hold much of the cumulative retained dose, or *body burden,* of a persistent xenobiotic and tend to maintain a low but persistent level in the circulation for a long time after exposure.

Entry into some tissues is restricted by special barriers to passage, such as the blood-brain barrier and the placenta. In most cases, however, delivery of a xenobiotic depends on the blood supply to a tissue relative to its weight. The brain receives a disproportionate fraction of the cardiac output but is partly protected by the blood-brain barrier; this barrier works well to keep out most polar xenobiotics but is permeable to most, but not all, lipophilic compounds.

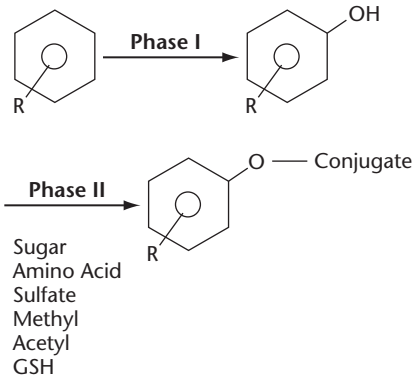
The mechanisms of distribution have important implications for exposure of a fetus or infants. The placenta is not an effective barrier to movement of xenobiotics. The fetus is generally exposed to levels similar to those in the bloodstream of the mother. As well, many lipophilic xenobiotics accumulate in breast tissue and are subsequently excreted into breast milk. This is the major route of exposure to a variety of xenobiotics for newborns who breast-feed.

Metabolism. Many chemicals are modified or even broken up by the action of cells and enzyme systems in the body, referred to as *metabolism*. Metabolism may transform one chemical into another, called a *metabolite,* which may be more toxic than the original chemical. There may be no, one, or many metabolites of a particular xenobiotic.

Xenobiotics that are metabolized are substrates for intracellular enzyme systems, most of which appear to have evolved as mechanisms for clearing endogenous metabolic products such as steroids, hormones, or substances taken in with food. These enzyme systems convert the xenobiotic into stable metabolites, often through intermediate unstable compounds. The most complicated metabolic pathways are those for organic compounds. Metals may also be metabolized, however. For example, the methylation pathway of arsenic is species-specific and this is thought to be the reason arsenic is a carcinogen in humans but not in animals. Some organic xenobiotics have many pathways of metabolism, resulting in multiple metabolites. In general, the major enzyme systems that metabolize xenobiotics tend to convert nonpolar, lipid-soluble compounds into polar, water-soluble products that are more easily excreted in urine or bile. The general pattern consists of two phases. These are illustrated in Figure 4.2.

Phase I of the metabolic process involves the attachment of functional chemical groups to the original molecule. Phase I metabolism may have the effect of either detoxification, detoxifying a toxic xenobiotic, by making it toxicologically harmless, or of *activation*, converting the native agent into a more toxic metabolite. In this way, an inactive precursor xenobiotic may be transformed into an active metabolite that exerts the true toxic effect. For aromatic organic molecules,

FIGURE 4.2. PHASES OF BIOTRANSFORMATION.



metabolism usually results in activation, especially when metabolized by the very important cytochrome oxidase-linked xenobiotic biotransforming enzymes.

Biotransformation requires a great deal of metabolic energy and is closely linked with the cytochrome oxidase system, which provides it. Phase I biotransformation enzymes are virtually ubiquitous in the body but are concentrated in the liver and lungs. They have a huge capacity and act on a wide variety of substrates. Many are inducible; when presented with suitable substrate, the cell synthesizes more Phase I biotransformation enzymes, increasing the capacity of the system and preparing itself for a greater load. The degree of inducibility and the level of baseline activity in a given tissue is genetically determined, so that at any one time Phase I biotransformation activity in a particular tissue reflects heredity combined with recent exposure. Activation of many polychromatic organic molecules results in a metabolite capable of interacting with macromolecules such as DNA, initiating the early steps of carcinogenesis.

Phase II involves the removal or conversion of chemical groups in such a way as to render the molecule more polar and therefore more easily excreted by the kidney (and less easily diffused back across the renal tubular epithelium after filtration). In the process, the activated metabolite from Phase I becomes inactivated. This process frequently involves *conjugation*, the attachment of a functional group such as sulfonate or glucuronic acid that makes the molecule much more hydrophilic. Conjugation, like Phase I biotransformation, requires energy and substrates from intermediary metabolism.

Excretion. Eventually, unless it is trapped in a storage depot in some tissue, the chemical or its metabolite may leave the body through the kidney, liver, or lungs. This is called *excretion*. If there were no mechanisms for excretion, the xenobiotic or its metabolites would accumulate and remain within the body. *Elimination* is the term used for removal of the xenobiotic from the bloodstream, whether by excretion, metabolism, or sequestration (storage).

The kidney is the major route of excretion for most water-soluble xenobiotics. The reserve capacity of the kidney is very great and is rarely saturated in healthy people, but individuals with renal insufficiency may show accumulation and persistence of the xenobiotic. Xenobiotics that are themselves nephrotoxic may injure the kidneys and reduce their own clearance, enhancing their own toxicity by further accumulation. Some metabolism occurs in the kidneys.

The liver, besides being an important metabolizing organ, secretes some xenobiotics, including heavy metals such as lead and mercury, into bile to pass out of the body in feces. Some xenobiotics may recirculate by reabsorption in the intestine, an important phenomenon called the *enterohepatic circulation*, which results in some xenobiotics or their metabolites persisting in the body for prolonged periods

of time. The enterohepatic circulation is particularly important for some pesticides and organochlorine compounds, but it also operates for mercury, manganese, and some other metals. Binding agents such as cholestyramine prevent reabsorption of some organic metabolites in the gut and therefore facilitate their excretion.

Volatile gases are readily excreted by the lungs through passive diffusion from the blood, crossing the alveolar-capillary barrier in reverse direction, and may be detectable in expired air for days or even weeks.

Xenobiotics and their metabolites are also eliminated by various minor routes, such as sweat glands or saliva. These are rarely important as effective means of excretion.

Kinetics. How fast the body can get rid of the xenobiotic, through metabolism, sequestration, or excretion, is called *elimination*. The rate of elimination describes the change in the concentration of the xenobiotic in the blood over time. The description of the rates of elimination of the agent is an important tool in understanding its behavior in the body. Each phase of the kinetics of a xenobiotic is governed by rates determined by properties of the agent and characteristics of the biological system. Each rate is described by a rate constant (k) that determines how rapidly the process proceeds. A xenobiotic with complex toxicokinetics may have several elimination pathways operating at the same time, with different rates.

Rate constants are described by their *order* or the number of notional compartments or spaces involved. A *zero-order rate constant* describes an elimination curve in which the rate is limited intrinsically by the fixed ability of the body to eliminate the agent, regardless of its concentration. In practice, the only important example of this is, ironically, the most common exposure of toxicological concern: ethanol (ethyl alcohol). Alcohol dehydrogenase, which metabolizes ethanol and other alcohols, has a low capacity and is easily saturated, resulting in a bottleneck that follows zero-order kinetics. Regardless of how much alcohol a person ingests, elimination occurs at the same rate, and that rate of elimination is fixed rate regardless of the dose or plasma concentration.

A *first-order rate constant* describes a process in which the rate of elimination is independent of the dose and the concentration of the xenobiotic in plasma is proportional to the concentration of the agent in tissue. Over time the concentration of the xenobiotic in plasma decreases by a constant proportion per unit time. This is called a *one-compartment model* because the agent behaves as if it were restricted to one compartment of the body such as the vascular space. First-order kinetics are most common for water-soluble xenobiotics other than alcohols. In such systems, elimination of the agent, being proportional to concentration, results in an exponential decay or reduction in plasma concentration over time. The period (τ) required for the plasma concentration to drop by half is called the *half life* ($\tau_{1/2}$).

The $\tau_{1/2}$ can be calculated easily and accurately and is related to the elimination rate for first-order systems using the following equation:

$$\tau_{1/2} = 0.693/\text{kel} \tag{4.1}$$

A multicompartment, or multiexponential, function of elimination suggests that the agent equilibrates in more than one compartment and is eliminated at different rates from each. The rate of elimination is biphasic and varies with the concentration in plasma and the initial dose. The elimination will not fit a simple exponential decay (or straight line on a logarithmic scale) but will be described by a more complex equation with two (or more) rate constants, usually a fast rate constant and a slow one, each of which may be described by a $\tau_{1/2}$. Organohalides typically show at least two-compartment kinetics because of their storage and slow release from fatty tissue. (The term *second order* is not used because it would imply that elimination rate is a function of the *square* of the concentration, which is not the case.)

Increasingly, the behavior of such xenobiotics is modeled using *physiologically based pharmacokinetic* (PBPK) models, so named because they were first worked out for drugs. Xenobiotics often have multiple compartments and complicated toxicokinetics, especially metals. These models are used to estimate the tissue concentrations at various sites of action to predict blood levels and to determine the rates of clearance of xenobiotics from the bloodstream.

Toxicodynamics

Toxicodynamics refers to how the chemicals affect the body. For centuries, poisons were considered to be a special class of chemicals and the toxicity of poisons were understood to be intrinsic properties of the chemical, or magic. Now, it is well-understood that all chemicals have the potential for toxicity at some level of exposure, but at very low levels of exposure any chemical can, in theory if not in practice, be safe.

Chemicals can interfere with every natural process in the body. However, there are some general rules. The dose, or intensity of exposure, to a chemical determines whether exposure results in toxicity, how much toxicity results (from barely detectable to death), and how many people (or animals) in a community or group suffer from the toxic effect. Therefore, the dose-response, or exposure-response, relationship (usually plotted as a curve) is one of the most important principles of toxicology and defines the action of a chemical for a particular effect on a particular species (human or animal).

Toxic exposures may interact. When two chemicals act the same way to produce the same result, their effects are typically *additive*—the same as the combined

effect of one on top of the other. When two chemicals act in different ways to produce a similar or related effect, or one modifies the way the other acts, together they may produce a much greater response, called *synergy* or a *positive interaction*. One important example is that of cigarette smoking: Cigarette smoking interacts with exposure to asbestos to produce more lung cancer in exposed workers than the combined effect of either smoking or asbestos alone would predict. Another example is *potentiation* of liver damage by combined exposures: Carbon tetrachloride is highly toxic to the liver; ethanol can also damage the liver when ingested in excess, but normally not in small quantities; isopropanol (isopropyl alcohol), on the other hand, is not hepatotoxic; however, when an otherwise nontoxic dose of ethanol is added to exposure to carbon tetrachloride, the combination causes much worse liver damage that would be predicted from adding together their individual effects; when isopropanol is added to carbon tetrachloride, it greatly increases the damage caused by carbon tetrachloride, even though it would have no effect by itself.

Xenobiotics exert toxic effects by interfering with the normal functions of the body. These effects occur at the molecular and cellular levels. Thus, an understanding of normal function and biochemistry is essential for understanding toxicodynamics.

Certain organs of the body are in harm's way because they may be the first to encounter a toxic exposure, receive a large blood flow, are highly active metabolically, actively metabolize xenobiotics themselves, concentrate toxic substances or their metabolites, or have biochemical characteristics that render them vulnerable. The liver, kidney, lungs, skin, and bladder are particularly susceptible to toxic effects. These organs are most often affected by environmental and organic carcinogens, for example.

The *exposure-response relationship* is fundamental to toxicology and was one of the first great insights contributed to modern toxicology by Paracelsus, the great medieval toxicologist and physician, who said, "It is the dose that makes the poison." By this, he meant that poisons were not a magical form of matter—all chemicals have toxic properties that may only become apparent as increasing quantities are consumed or absorbed. It follows from this simple observation that there may be safe levels of exposure to even the most toxic substances, a much more controversial assertion that is, however, basic to chemical risk assessment and risk management.

Dose is the total quantity of a toxic substance that has been administered within a relevant period. *Exposure* is the level of concentration available for absorption by any or all routes at or over a given period of time (see Chapter Five for more details). Thus, dose is best understood as total or cumulative exposure over a relevant time period. If the dose is given all at once, the dose-response rela-

tionship is most meaningful, as it is when the toxic substance is accumulated in the body. If the exposure takes place over a prolonged period of time, the internal dose at any given time tends to vary, and it is more useful to think of an *exposure-response relationship.* When a xenobiotic such as lead accumulates and persists in the body over a period of weeks, or dioxin and pesticides over a period of months and years, cumulative exposure approximates dose in toxicological terms. When a xenobiotic does not readily accumulate and is quickly eliminated, cumulative exposure over a long time period does not equal effective dose in toxicological terms.

The three distinct varieties of the exposure-response relationship that need to be distinguished conceptually are shown in Figure 4.3. These are the toxicological dose-response relationship, the clinical dose—or exposure—response relationship, and the epidemiological exposure-response relationship.

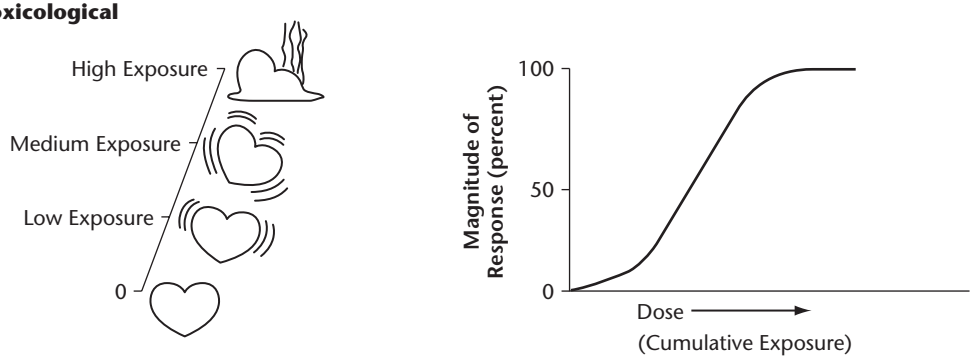
The most fundamental building block of toxicology is the dose-response relationship demonstrable in the laboratory, often called the *toxicological* dose—or exposure-response relationship. The fundamental principle is that the physiological response depends on the amount of the agent in the blood and presented to the tissue. As exposure increases at the tissue level, the response (for example, smooth muscle contraction, inflammation, cell injury or other outcomes) increases up to the maximum that the tissue can sustain.

The toxicological exposure-response relationship is usually studied in the laboratory in isolation, to characterize each important effect. However, in the intact animal or person, several toxicological exposure-response relationships develop at the same time. Some result in visible toxicity earlier than others. In a given individual, exposure to an increasing amount of a toxic substance leads to the progressive appearance of new and usually more severe health problems that finally lead to death—a sort of stepladder to lethality.

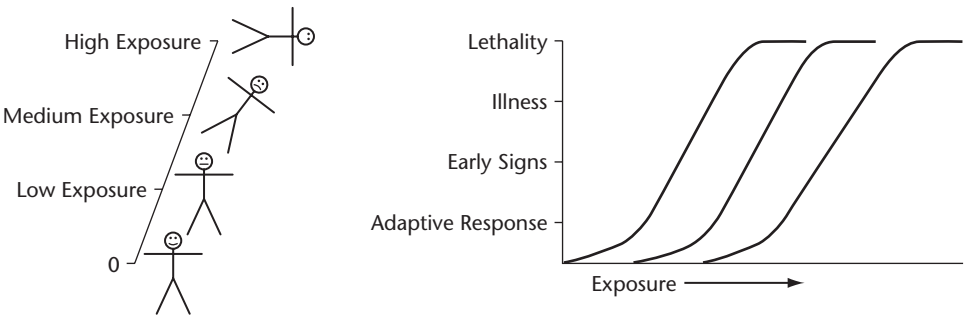
This gives rise to another type of dose- or exposure-response relationship, which might be termed the *clinical* exposure-response relationship. At a given level of exposure, often referred to clinically (if colloquially) as a *threshold*, one can usually expect a given constellation of symptoms and signs. This clinical exposure-response relationship depends importantly on susceptibility. In a given exposure situation, one person because of personal susceptibility may show one symptom and another, a different symptom. At relatively low levels of lead toxicity, some patients show elevated uric acid levels because of reduced renal clearance; however, many do not. The detection of the expected clinical response depends on the sensitivity of clinical examination and laboratory tests. Clinical tests are often inadequate for early detection of equivocal cases because they are designed to make specific diagnoses in people known to be sick in a way that strongly suggests a particular type of disease.

FIGURE 4.3. EXPOSURE-RESPONSE RELATIONSHIPS.

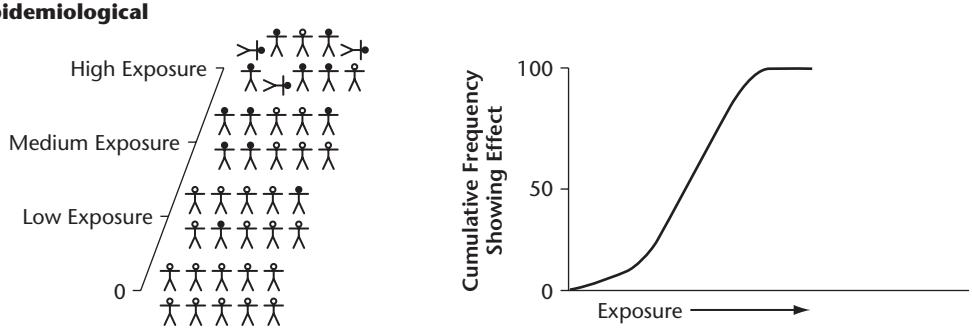
Toxicological



Clinical



Epidemiological



The third type of exposure-response relationship relates exposure levels to the frequency of the response in a population. If we are interested in the personal characteristics of those exposed that render them vulnerable to a toxic effect or in how frequently a response is associated with a given level of exposure in a population, we may count the number of individuals who are observed to show the response. This is the essential method of epidemiology and yields what is usually called the *epidemiological* exposure-response relationship.

At higher levels of exposure, the exact shape of these exposure-response relationships is not critical and the general relationship is usually obvious. At lower exposure levels, however, interpretation of the population response is very dependent on an interpretation of the general mechanism of the toxic effect, and extrapolation to low exposures is very sensitive to the biological model applied.

A particularly important, if confusing, term in toxicology is *threshold*, which means the level of exposure at which an effect is first observed. Thresholds are well documented for most toxicological phenomena but the existence of thresholds for certain effects, particularly carcinogenesis and immune sensitization, is controversial.

Carcinogenesis

Much of chemical risk assessment is concerned with the risk of cancer. Indeed, concern over chemical carcinogenesis gave rise to the classical approach to risk assessment as embodied in the original *Red Book* published in 1983 by the National Academy of Sciences.

Chemical carcinogens are demonstrable by their effect in increasing the frequency of cancers observed in exposed as compared to unexposed subjects. They may produce malignant tumors that are often different in tissue type and wider in diversity from those usually observed among unexposed subjects. They also produce malignant tumors at characteristic or unusual sites in the body and produce these malignant tumors earlier in the life span of subjects than would otherwise be seen. Two classic examples of tumors that are specific for environmental exposures are mesothelioma, associated with exposure to asbestos, and hepatic angiosarcoma, associated with several environmental exposures (vinyl chloride, arsenic, and Thorotrast™, a now-discontinued radioactive medical imaging medium); both are exceedingly rare except in exposed populations. Often, however, chemical carcinogens produce malignancies identical in tissue type, location, and onset to those seen in unexposed populations, and the only clue is an increased frequency of cancers in exposed groups. Examples of the capacity of environmental chemicals to cause common malignant diseases are legion but include

lung cancer associated with asbestos or arsenic, skin cancer associated with arsenic, and bladder cancer also associated with arsenic. These examples also demonstrate another important point: one agent (in this case, arsenic) may cause several malignant outcomes.

Carcinogenesis is usually modelled as a point probability or confidence interval in which the upper bound is accepted in order to be actively protective. In general terms, chemical carcinogenesis is a *stochastic*, or probabilistic, process, like a roulette wheel or radioactive decay. Once it occurs, it progresses according to a predetermined, biological program that is not much modified by the circumstances of chemical exposure except in timing and latency. In this sense, modelling carcinogenesis resembles modelling the risk of infection, without implications of communicability, or of allergic sensitization. In any one individual, an exposure may increase the odds of getting cancer, but it does not make it certain.

A deep understanding of the biology of cancer helps to explain many of the phenomena critical to regulation and control, such as latency periods and cancer promotion. For example, health effects of low-dose ionizing radiation and radiomimetic chemicals (which act like ionizing radiation) have been difficult to unravel because three competing theoretical models exist for low-dose extrapolation (linear, quadratic, and linear-quadratic). The divergence in goodness-of-fit to available response data results from differences in the underlying assumptions involving adaptive mechanisms, threshold effects, receptor behavior, and transport to the target organ. Similarly, modelling the population response to exposure to chemical carcinogens at low exposure levels depends importantly on whether a one-hit model or an interactive model is operative. *One-hit* refers to a single interaction with DNA in a single cell being theoretically sufficient to cause cancer, no matter how improbable; an interactive model assumes that more than a one-hit is required to sustain the carcinogenic process. The discovery of the various oncogenes and emerging evidence as to their distribution in the genome among individuals in the general population and, perhaps, high-risk subgroups have led to a rethinking of our concepts of cancer risk and susceptibility.

Thus, from the standpoint of biology, carcinogenesis is not a straightforward, deterministic process. At each step in the sequence, there is a finite probability of events leading to the next step. Carcinogenesis is therefore more appropriately thought of as a series of contingent probabilities, rather than a single probability of an event.

As our understanding of the basic mechanisms of cancer improves, concepts of risk based on chemical carcinogenesis grow more refined and the capacity to predict cancer risk in populations improves. Recent advances in research on carcinogenesis have identified new and rather complicated mechanisms of carcinogenesis. However, the overall effect has been to simplify our understanding by

providing common pathways and unitary, comprehensible mechanisms by which many causes may act in a similar way. Specific causes within each category may act by similar mechanisms, as by activation of oncogenes.

The principal categories of chemical carcinogenesis are

- Genotoxic mechanisms
- Organic chemical genotoxicity
- Metal genotoxic carcinogenesis
- Clastogenesis, including radiomimetic exposure, mimicking the effects of radiation, by genotoxic mechanisms
- Nongenotoxic mechanisms
- Film and fiber carcinogenesis
- Hormonal carcinogenesis
- Organic chemicals acting through nonhormonal and nongenotoxic mechanisms

Other categories of causation may be acting simultaneously in human carcinogenesis, for example, viral carcinogenesis, radiation carcinogenesis, and heredity. In the real world, carcinogens are usually encountered in mixtures or combined exposures so that at any given time the body is dealing with several exposures of carcinogenic potential, of greater or lesser potency and intensity (see Chapter Six). The resistance of the body to carcinogenesis is a form of host defense mechanism.

The basic contemporary model of carcinogenesis is based on the concept of genotoxicity. As previously described, most chemical carcinogens are procarcinogens before they are metabolized within a cell, and converted into active carcinogenic metabolites, which may have only a fleeting existence in the cell. These activated carcinogens, which tend to be electron-depleted (*electrophilic*), are attracted to the electron-dense (*nucleophilic*) sites of macromolecules, such as proteins and nucleic acids, and bond covalently to them. These covalently bonded sites, when detached from the macromolecule, are called *adducts* and may be found in the cell or in the circulation, serving as biomarkers for exposure and genotoxic risk.

When the activated carcinogens bind to proteins or to RNA, their effect is silent. When they bind to DNA, however, they may change the genome, the genetic information encoded in it. If this occurs in a part of the genome that is not critical, undergoes repair by one of several mechanisms that restores DNA to its original base sequence, or results in such destruction that the DNA strand cannot replicate, no harm is done. When the damage results in a stable change to the DNA strand that can nonetheless withstand replication, the inaccurate replication results in a stable mutation, a heritable alteration in the genome. The incorrect genetic information may be lethal to the cell, but if it is not, and if it occurs at a key location controlling cell replication, the heritable mutation may result in

an irreversible change that resembles a regression to a more primitive state, such as a stem cell. This process is called *initiation*. Its counterpart in the laboratory occurs when an isolated cell is transformed by chemical or viral carcinogenesis and adopts cellular characteristics that are characterized as *preneoplastic*, implying the potential to become cancerous. These include cell surface changes, nuclear changes, and sometimes changes in chromosome organization.

The key interactions that lead to initiation are those that involve oncogenes or tumor suppressor genes. Oncogenes code for cell functions in a manner more appropriate to a primitive, embryolike state, and at least some probably play a physiological role in normal embryonic and fetal growth and development. Their gene products include extracellular growth factors, transcription factors, and factors in intracellular signal transduction pathways that regulate growth. Some oncogenes are derived from viral genomes incorporated in the human genome. Activated in the absence of regulation, the oncogenes trigger malignant transformation of the cell, causing a previously differentiated cell to regress to a more primitive state abnormal for that stage of the life of the organism. The derepressed oncogene comes to life, expressing itself by the production of proteins (many of them enzymes, others messenger molecules or receptors) for which it codes and which transform the cell. These "oncogene products" may serve as very early biomarkers that initiation has occurred.

When the initiated cell divides, the heritable mutation becomes *fixated,* meaning that it perpetuates itself through subsequent cell division. At this juncture, the initiated cell and its daughter cells may remain dormant for some time or may slowly grow. During this dormant stage, the cell may be held in check by host factors or cell-specific factors, such as the need for further DNA reorganization or oncogene activation to take place. The abnormal cell may rest for a very long time, contributing the greater part of the latency period before appearance of the clinically evident tumor.

Tumor suppressor genes are similar in terms of interaction but code for mechanisms that stop cell replication and therefore inhibit tumor growth. The most important gene codes for *p53,* a protein product that acts in the nucleus to stop cells from replicating by blocking a stage in the normal cell cycle when the cell is carrying damaged DNA. This occurs at the transition from stage *G1* to *S* in the cycle, when the initial cell growth following mitosis slows and before DNA is synthesized in preparation for the next round of division. Normally, a cell with damaged DNA would be stopped from dividing by p53 and forced to undergo a form of controlled, programmed cell death called *apoptosis.* When p53 is not present or is present in a mutated, nonfunctional form, the initiated cell proceeds to replicate without restraint. The damaged DNA is perpetuated and the initiated cell survives.

If a critical somatic mutation is present, whether inherited, spontaneous, or induced in the genome by exposure to a genotoxic xenobiotic, the host may be susceptible but will not develop cancer as long as the tumor suppressor mechanisms of the body are intact. A mutation in one tumor suppressor gene is usually not enough to result in a cancer because the gene products of one copy of the gene are enough to suppress the division. A second mutation is required to knock out the other copy, resulting in loss of functionality of both tumor suppressor genes, removing controls on cell division. This is called the *two-hit model* of carcinogenesis. The second hit may occur after an accelerated growth phase related to the first hit, resulting in an increasing number of cells in which the second mutation may occur. In some instances, the first hit may make the second hit more likely. The two-hit model explains much of the observed experimental pattern of chemical carcinogenesis, the observed pattern of radiation-induced carcinogenesis, and the inheritance patterns of many human cancers. There are exceptions, however, and the two-hit model is still being refined.

The initiated cell and its early daughter cells may at some point be stimulated to replicate more rapidly and form a clone. The clone becomes a small focus in situ. Additional exposures may trigger the conversion of the initially abnormal cell into a transformed or preneoplastic cell capable of giving rise to a tumor. This process may be facilitated by exposure to chemicals that also have genotoxic potential, either simultaneously or after the action of the primary carcinogen. This ancillary process is called *cocarcinogenesis,* implying that the second or combination exposure may not be the initiator but participates in the genotoxic cell events, perhaps inducing the second mutation or hit, and either leads to expression of the critical event, resulting in oncogene activation, or overrides mechanisms that would otherwise inhibit oncogene activation and cell transformation. In general, the same chemicals that are complete carcinogens are likely also to be cocarcinogens. The distinguishing feature is not which chemical reaches the DNA first or which exposure preceded which but which chemical actually participated in the critical event that specifically altered the DNA in such a way as to activate the oncogene.

Exposure may occur at this stage to chemicals that are capable of triggering proliferation. This is called *promotion.* Promoters act by removing the inhibitory factors that are suppressing the transformed cell by inducing *hyperplasia* (which is growth by proliferation of cells), and up-regulating gene expression in signal transduction pathways. Promoters are sometimes complete carcinogens themselves and as initiators probably act through genetic mechanisms, as in the case of polycyclic aromatic hydrocarbons. However, others are weakly or not at all carcinogenic and presumably act by nongenetic mechanisms. The most well-known

are the phorbol esters (specifically tetradecanoyl phorbol acetate, TPA), constituents of croton oil that are extremely complex chemically and seem to act at least in part pharmacologically by activating certain specific receptors on the cell surface. Chlorinated hydrocarbon species are often potent promoters, including the PCBs, DDT, PBBs, and certain dioxins. Other promoters include phenobarbital (a drug previously used to induce sleep), cyclosporine (the antirejection drug used in many transplants), hormones (steroid hormones such as estrogen and testosterone and polypeptide growth, or *trophic*, hormones such as growth factor), and the class of xenobiotics called *peroxisome proliferators* (discussed later in the context of nongenotoxic carcinogenesis). They seem to act by nongenetic means and have variable primary carcinogenic activity, depending on the species.

By whatever mechanism, promotion results in loss of suppression and leads to the next stage of carcinogenesis, called *progression*. In the stage of progression, the clone of cells develops into a *neoplasm* (literally, a "new growth") by proliferation of cells into a tumor mass. The tumor is considered to be *well-differentiated* if it bears a recognizable resemblance to the normal tissue of origin and *poorly differentiated* if it more closely resembles a primitive cell type. In general, poorly differentiated cancers grow more rapidly and have a poorer prognosis.

Some oncologists recognize a separate class of chemicals called *progressors*, which accelerate the process of progression and tip the balance in the initiated cell toward malignancy at the time of promotion. Others see these chemicals as promoters.

The transformed cell has now become a cancer cell with the essential features of a malignancy:

1. Unresponsiveness to regulation
2. Loss of contact inhibition
3. Potential for sloughing and migration of cells (*metastasis*)
4. Potential for inducing growth of new nutrient blood vessels (angiogenesis)

To metastasize, malignant cells must digest or displace the matrix binding them, especially basement membranes, migrate through the degraded tissue, gain access to blood or lymphatic vessels for transport, and be deposited in a tissue favorable to growth. This does not occur until most tumors have reached a size of at least 1 cm representing a population of 10^9 cells.

Progression takes time, as the doubling time of a cancer is rarely less than six months and cells are continually killed by the body's natural host factors (espe-

cially by natural killer, NK, lymphocytes) or may be slowed in growth or become necrotic (dead tissue) because parts of the tumor outstrip their local blood vessels and receive inadequate nutrient supply.

Cancers are usually identified either because they cause health problems for the patient or in a screening test. Occasionally, they are found during a workup for other health reasons. Many health problems can be caused by cancer before the cancer itself becomes obvious, such as coughs, bleeding, pain, hormonal abnormalities, skin changes, obstruction of an airway leading to pneumonia, or bowel obstruction. These effects depend on where the cancer is invading or metastasizing and what structures in the body it may be compressing. Many effects that lead to clinical detection are a function of tumor size and therefore are not obvious until the mass of the primary cancer has passed through some number of doubling times. This further contributes to the latency period between initiation and discovery of the cancer.

It is only at this relatively late phase that screening programs for cancers play a role. Cancers that are usually aggressive and metastasize early (such as lung cancer and melanoma) or that are difficult to detect because of their location (such as in the pancreas and ovary) do not lend themselves to effective management by early detection and treatment because it is already too late in the great majority of cases by the time the tumor is detectable. Less aggressive and more accessible malignancies, such as breast and cervical cancer, are more readily treated.

Because each step requires time, there is a delay between the initiation (commonly assumed to be at first exposure) and earliest clinical presentation of a tumor. This is called the *latency period*. For most chemically induced cancers, latency is on the order of twenty to thirty years but may be as long as fifty or more (in the case of mesothelioma and asbestos exposures) or as short as five years (for radiation or radiomimetic exposures and some bladder carcinogens). The latency period is also influenced by the intensity of exposure and can be shortened by intense exposure at initiation or during promotion.

Not all chemically induced cancers act by this genetic mechanism. *Epigenetic* refers to the actions of cancer-inducing agents and exposures that do not necessarily directly interact with DNA by causing somatic mutations. Some act by hypermethylation of cytosine-guanine bases, inactivating tumor suppressor genes. At least some probably act by inducing intracellular free radicals that damage DNA in a nonspecific manner. Others are more obscure in their mechanisms. None are adequately explained by the conventional multistage model of carcinogenesis, but subsequent refinements in theory almost certainly will result in a unitary model demonstrating a final common mechanism for most cancers.

Epigenetic mechanisms are associated with many important occupational exposures (benzene), laboratory reagents (dioxane), consumer products (nitriloacetic acid, NTA), medical devices (foreign bodies), and pharmaceuticals (hormones); epigenetic carcinogens are of particular concern to occupational physicians.

Metal-induced carcinogenesis occurs by a variety of mechanisms and often strongly depends on the chemical composition, redox state, and solubility, for example, arsenic (lung, bladder, and skin), beryllium (lung), cadmium (lung), chromium (hexavalent ion; lung), or nickel (subsulfide; lung). Metal-induced carcinogenesis is genotoxic.

Clastogenesis is a form of relatively gross injury to DNA that is often visible as chromosome damage. It occurs when there is sustained tissue damage and subsequent cell proliferation during the repair process. It is characteristic of intracellular oxidative injury, in which highly reactive, free radical species of oxygen and nitrogen are formed as a result of radiation. Chemicals that act in a similar way are called *radiomimetic.* Examples include alkylating compounds used, ironically, for cancer chemotherapy and related compounds initially used in chemical warfare called mustards (after their characteristic odor, not because of any relationship to the condiment or the mustard plant).

Carcinogens that act by nongenotoxic mechanisms, which are often called *epigenetic* carcinogens, are of particular concern in risk assessment because they do not behave as typically genotoxic agents in the usual in vitro assays and are therefore more difficult to anticipate.

Film and fiber carcinogensis, or *foreign-body tumorigenesis,* is a form of nongenotoxic carcinogenesis that is a response observed when foreign bodies are implanted under the skin of certain rodents. This mechanism yields sarcomas, which are cancers of connective tissue and the middle layer (mesechyme) of embryonic development. In humans this form of carcinogenesis may be important in inducing mesothelioma and lung cancer characteristically associated with fibers, particularly asbestos. Film, and larger foreign-body tumorigenesis, may be important for human beings as a risk following implantation of medical prostheses, but to date this concern is theoretical as there is no clear evidence for the effect in human beings.

Hormonal carcinogenesis occurs when the normal production of hormones is impaired. Often, excessive production of the hormone from a diseased gland or secretory nodule (an "adenoma") produces hormones in excess of physiological need and the stimulation results in unrestrained proliferation of cells and cancer. In other cases, the tight feedback loop that characterizes the endocrine system in the normal body may be impaired so that an otherwise normal gland secretes an excessive amount of hormone because it is not receiving the in-

hibitory stimulus telling it to shut off production. These mechanisms affect hormonally responsive tissues such as the breast, ovary, prostate, testes, uterus, thyroid, adrenal cortex (site of synthesis of many steroid hormones), and pituitary gland (in the brain). Some organic chemicals appear to act by mechanisms that are not genotoxic, including benzene, a very important aromatic hydrocarbon that is a potent carcinogen in human beings. Some of these mechanisms are specific to certain species and may not apply to human risk. It is also often difficult to distinguish the nongenotoxic carcinogenicity of such chemicals from activity associated with promotion, especially because many of these nongenotoxic carcinogens do both. In some cases, the carcinogens may actually act by promoting spontaneously initiated cells, rather than initiating the cells directly. Clofibrate (a drug used to reduce cholesterol levels), 1,4-dioxane (a solvent), saccharine, and 2,4,7,8-TCDD are among the important chemicals that act in this way and are also promoters.

Several important mechanisms of nongenotoxic carcinogenesis have been identified. They have important implications for risk assessment. *Peroxisome proliferating* agents are chemicals, such as phthalates, that induce proliferation of intracellular, hydrogen peroxide–bearing organelles called *peroxisomes* in the livers of rats, leading to liver tumors. Human beings do not generate such an abundance of peroxisomes and therefore are not susceptible to neoplasia by this mechanism. Another such specific mechanism which is specific not only for species but for gender is the induction of excessive amounts of a normal protein called α_{2u}-globulin in the kidneys of male (only) rats, leading to increased cell proliferation in the kidneys and to kidney tumors. Inducers of α_{2u}-globulin include several common chemicals such as d-limonene (a constituent of lemon oil), now considered to present no risk of carcinogenicity to human beings.

Human beings (and female rats) do not produce α_{2u}-globulin and thus are not at risk for cancer through this mechanism.

With respect to new products, the risk of foreign body and hormonal induction of cancer demands particular attention because of, respectively, the development of new biomedical technology and the weakly estrogenic effects of many substituted hydrocarbon compounds, including some pesticides.

Toxicity Testing

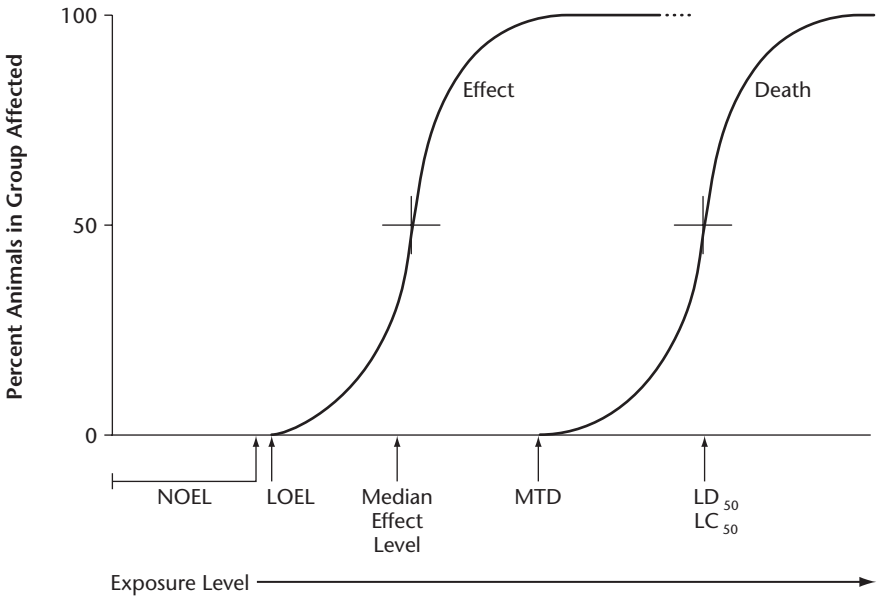
It is possible to predict that some organic compounds are more likely than others to be toxic and especially carcinogenic. For example, all the organophosphate pesticides act by a common mechanism and have a predictable profile of acute toxicity. For example, in carcinogenesis, among the polycyclic aromatic hydrocarbons,

the bay region, a feature of an indented or concave profile in the multiringed structure that is relatively impoverished in electrons, tends to characterize procarcinogens that when activated become genotoxic carcinogens. However, sufficient deviations from toxicity or cancer risk associated with structure-function relationships mean we cannot reliably predict toxicity based on chemical structure and properties alone. For example, delayed neurotoxicity (of the type known as *organophosphate-induced delayed neurotoxicity*) varies greatly among organophosphate pesticides notwithstanding their acute toxicity, and some pesticides, such as methamidophos, are much more likely to induce neurotoxicity than similar compounds of the same potency for acute effects. Likewise, similar polycyclic aromatic hydrocarbons vary in their carcinogenicity: chrysene (with not one but two bay regions) is carcinogenic, and pyrene is not (it is, however, a promoter), although both have four aromatic rings.

Actual testing of the chemical is usually necessary to determine whether it is carcinogenic. When such studies are conducted in the laboratory using preparations of cells or chemical indicators, they are called *in vitro assays.* When they are conducted in the laboratory using animals, they are called *carcinogenesis bioassays.*

A key toxicological measurement, basic to toxicity screening and ranking, is the quantity or concentration of the chemical that kills 50 percent of the test animals, always rats, with the possible addition of one or more other species. This measurement is called the LD_{50} (for lethal dose) as a general term and when cumulative dose is considered, or LC_{50} (for lethal concentration) if exposure over a period of time is considered and specifically for inhalation studies (Figure 4.4). The LD_{50} is remarkably reproducible from study to study, much more stable than minimum toxicity measurements or the LD for 100 percent of the animals. Comparisons of LD_{50} between species and especially between test animals and human beings, taking into account body size and sometimes differences in metabolism, are generally reliable as relative indicators of toxicity, with known exceptions as outlined in the previous section. The LD_{50} itself is an essential measurement in toxicology. The LD_{50} also provides a starting point for designing chronic exposure studies, by providing a benchmark for toxicity so that the investigator can scale down to dosages and exposure levels that are not so toxic that they will be lethal to the animals but that are high enough to result in a high yield of adverse effects, if the chemical induces an effect. This sub-lethal but high level of exposure is called the "maximum tolerated dose" (MTD) and is particularly important in carcinogenesis assays because cancer takes a long time to develop, relative to the life span of the animal, and high levels of exposure are required to produce tumors within the animal's lifetime and in sufficient numbers, in the small population of animals being tested, to be identifiable. The LD_{50} is a calculated measurement, interpolated from a linearized, logarithmic transformation of the sigmoid curve of lethality in a process called *probit analysis.*

FIGURE 4.4. IMPORTANT TOXICOLOGICAL VALUES DERIVED FROM TOXICITY TESTING.



Effects other than lethality can be subjected to the same analysis, in which case the counterpart to the LD_{50} is usually called the "ED_{50}" (for "effective dose"). Like the curve for lethality, the curve for most toxic effects is sigmoid, showing a threshold (when the first animal responds), then rising at an increasing rate to an inflexion point more or less at 50 percent response and then rising at a decreasing rate to a plateau when 100 percent of the animals show a response. The lowest dose at which a response occurs in the study is called the *lowest observed effect level* (LOEL). The LOEL is also an extremely important number because it is the best approximation to the toxicity threshold grounded in the data. However, by definition, it always overestimates the threshold of response. The highest level at which no effect was observed is called the *no observed effect level* (NOEL). The NOEL is also an extremely important number because it provides a lower bound or bracket to the estimate of the threshold. Figure 4.4 describes the relationship among these toxicological values. Within statistical uncertainties and assuming an informative study design, the true threshold will lie somewhere between the LOEL and the NOEL if both are available in a study of sufficient statistical power. These values are also used in risk management, with the application of uncertainty factors, to derive a reference dose or allowable daily intake.

The usual approach to assessing the toxicity, and especially the carcinogenicity, of a new chemical, or one that has recently come under suspicion, is to conduct a sequence of studies starting with short-term assays and leading up to chronic bioassays. Each level of the protocol is called a *tier*, reflecting the idea that toxicity testing moves up through different levels of biological certainty. If a chemical is under consideration to be a drug or to enter common consumer use, a positive result early on almost always results in the chemical being dropped from consideration and no further tests are conducted unless there is research interest. A *tier one* study, for example, may involve the use of in vitro studies, such as the Ames assay (described later) or tissue culture studies. A *tier two* study might involve determination of LD_{50} or LC_{50} in animals. Higher tiers may involve *subchronic* studies (ninety-day exposures, resulting in sacrifice of the animals to examine sublethal effects), *chronic* studies of six months or a year, lifetime studies to evaluate carcinogenicity over two to three years, and special studies to examine teratology, reproductive effects, toxicokinetics and metabolism, allergenicity, phototoxicity, and behavioral effects of exposure. The full panoply of testing is rarely done except for drugs, pesticides, chemicals that have been identified as suspicious under the National Toxicology Program, and chemicals that have attracted research interest.

As the tests become more sophisticated and the outcomes become more difficult to detect, they become much more expensive. Chronic bioassays may easily cost millions of dollars. Scientists would also like to reduce the number of animals involved in bioassays to the minimum required to answer the question. Alternatives to animal studies are becoming available for specific purposes but cannot replace in vivo testing for all needs. Techniques of probit analysis have also been developed that reduce the numbers of animals required to gain a stable estimate of LD_{50}.

A major issue in selecting any kind of animal model is the biological relevance of the model to the application intended. The experiment must be at least comparable to human routes of exposure, metabolic pathways (if applicable), and the potential for expression of the effect. Strain differences within species are as important as species differences. Inbreeding has resulted in considerable differences among rat strains in response to longer-term effects. The longevity of animal species places constraints on what can be studied. Animals such as mice that survive less than two years in confinement are difficult to use for long-term exposure studies. Rats do survive that long but full expression of the effects of exposure may require the animal to live out its life span rather than be sacrificed after an arbitrary time period.

The age and sex of the animals are also important considerations. Although it is difficult to generalize, females are sometimes more susceptible to the effects of toxic exposures involving metabolism of the agent, especially if there is a possible parallel with hormonal effects as in the case of certain aromatic hydrocar-

bons. Young animals may differ from older animals in their degree of resistance to toxic effect: neonate mice are relatively resistant to oxidant gases compared to older animals, for example.

Specialized, species-specific toxicity pathways preclude extrapolating the findings of animal bioassays to human beings unless there is a complete understanding of the biological basis for interspecies differences and knowledge of how the findings translate to the human body. This was a hard lesson in toxicology, learned all over again when it was discovered that unleaded gasoline induces a α_{2u}-globulin in the male rat. The implications for the regulatory process were nightmarish, since gasoline is a chemical mixture currently indispensable to modern society. However, it came to be understood that the mechanism of action, being specific to male rats, did not imply risk to human beings.

Biomonitoring

Estimating a population's potential risk from chemical exposures is based on a function that takes into account the chemical's toxicity, the opportunity for exposure, exposure assessment, and the population likely to be exposed. Exposure assessment is usually the factor of greatest uncertainty, given the paucity of exposure data and incomplete knowledge of exposure mechanisms (especially in the event of mixed exposures) of most chemicals. A number of approaches have been developed to reduce this uncertainty. One approach, often called *molecular epidemiology,* identifies and assesses the relationship between biological markers and health outcomes. Biological markers, or biomarkers, are physiological, cellular, or molecular indicators used to evaluate xenobiotic exposures and potential effects in a population.

Biomarker data can stand alone or augment more traditional risk assessment approaches such as questionnaires. Before conducting an epidemiological study using biomarkers, we need to understand the relationship between the specific biomarker and the toxicokinetics of a specific chemical. This process is defined as *biomarker validation* and includes both laboratory and population components.

Biomarkers are categorized by whether they measure exposure, effect, or susceptibility. In the case of biomarkers of exposure, these biomarkers are better at integrating individual differences than more traditional exposure measures. Biomarkers of exposure identify and measure chemical residues in tissue or body fluids, metabolites of the xenobiotic or physiological outcomes that are effects of exposure, often unrelated to the toxic effect of concern in humans. For example, a biomarker might be the concentration of a chemical in blood, the excretion of a metabolite of the chemical in urine over twenty-four hours, or the degree of inhibition of an enzyme known to be affected by the chemical. These data provide

information on an individual's total exposure from all sources, preceding the time of the analysis. Biomarkers cannot distinguish between the contribution of various absorption pathways to the internal dose that is reflected in the biomarker level. Samples over time are used to identify population trends. Biomarker data can be used to compare exposures in different subpopulations, such as children, adolescents, or the elderly, or residents of different geographical areas. Ultimately, better information about a population's exposure results in better decisions to protect public health and assist in the prioritization of research and intervention programs.

Biomarkers of effect characterize the impact of exposure to chemicals or contaminants on a targeted system such as the blood. As a result, molecular, cellular, or even systemic effects can be observed before clinical symptoms occur. For example, recovery of DNA adducts from blood or urine may reflect the risk of genotoxicity. Not all individuals with a given biomarker of effect will develop the disease, and this distinction is important to communicate to potentially affected groups. Biomarkers of effect can indicate preclinical effects observed between exposure and disease and ultimately serve as surrogates for disease for a population.

Biomarkers of susceptibility can potentially characterize how populations respond to exposures. In addition, biomarkers of susceptibility can identify potentially sensitive population subgroups. For example, studies of genetic polymorphism can identify persons with enzyme types more likely to be affected by a chemical. Susceptibility biomarkers can be used to identify population subgroups potentially at greater risk from a given exposure so that protective measures can be taken. They may also be important in assessing the mechanism of toxicity.

The limitations of using biomarkers in the risk assessment process include characterizing the specificity and sensitivity of the biomarker for the xenobiotic, understanding the metabolism of the xenobiotic, and accounting for individual differences within a population. The primary objective of molecular epidemiology is to identify associations between biomarkers and potential risk. As more biomarkers are developed and data collected, these associations increasingly will be able to provide risk assessors with a better understanding of risk.

Environmental public health *tracking* (EPHT) or surveillance is defined by the Centers for Disease Control and Prevention (CDC) as, "the ongoing collection, integration, analysis, interpretation, and dissemination of data on environmental hazards, exposures to those hazards, and health effects that may be related to the exposures." Public health tracking systems are important in the identification, prevention, and control of diseases in populations. Currently, CDC is leading an effort to build a national EPHT Network in which standardized data provide information on environmental exposures and health effects. Biomonitoring is a vital part to of this effort as biomarkers provide the most potentially relevant method of determining human exposure to environmental hazards. A key difference between EPHT and more traditional surveillance techniques is the integra-

tion of information on the specific hazard, human exposure, and health effects. EHPT builds on other ongoing efforts between public health and environmental sectors to improve hazard monitoring, health surveillance, and response capacity.

Chemical Safety

Chemical safety is a general term for managing the hazards and risk associated with chemicals in order to protect workers and community residents from incidents of uncontrolled release or exposure. The primary concerns associated with particular chemicals may include the risk of explosion, flammability, acute toxicity, release of heat (exothermy), and corrosiveness.

In practice chemical safety involves protecting residents who live and work in communities where chemicals are made, stored, or used or through which chemicals are transported.

About three-quarters of incidents involving chemical releases occur at fixed sites such as factories, storage tanks, and loading facilities, roughly one-third in the chemical and oil industries. The worst chemical disaster from a fixed site was the famous incident in Bhopal, India, in 1984, which killed 3,800 people. Incidents of chemical release are most likely to involve, in diminishing order of frequency, polychlorinated biphenyls, sulfuric acid, anhydrous ammonia, chlorine, hydrochloric acid, sodium hydroxide, methanol (methyl alcohol), nitric acid, toluene, and chloromethane (methyl chloride). However, chlorine is the exposure most likely to cause human fatalities.

Most uncontrolled chemical releases occur during transportation incidents such as derailed railroad tanker cars or trucking accidents. For example, in 2004 a tank car was punctured in a derailment near Graniteville, South Carolina, releasing sixty tons of pressurized chlorine gas, which killed nine people. Many of these incidents involve multiple failures or a sequence of events. For example, on November 10, 1979, 250,000 residents of Mississauga, Ontario, had to be evacuated when a train derailed, triggering a series of "boiling liquid expanding vapor explosions" (commonly called BLEVEs in the field of transportation safety) in three tanks carrying propane, which in turn resulted in a puncture of a tank car containing chlorine; nobody was killed.

In 1985 the chemical industry instituted a program called Responsible Care® requiring participating companies to practice stewardship of chemicals throughout the product life cycle, community participation, planning for emergencies, emissions reduction, occupational safety, and environmental sustainability. Now worldwide, Responsible Care® has addressed community concerns about living next to chemical plants. Since 2001 chemical safety has emphasized prevention of either opportunistic acts of terrorism on-site or the commandeering of hazardous

materials for intentional assaults. This concern has motivated a change to reduce the vulnerability of the entire supply and transportation system as well as increasing security for facilities on-site. This involves technical improvements such as stronger and safer tanks, greater control and monitoring of chemical production, and, particularly, substitution of more hazardous chemicals with less hazardous alternatives. When substitutions are made of less hazardous chemical substances, the supply chain and transportation system carrying the materials also become safer.

The methodological approaches to assessing risk in such situations take two general forms. The first starts with a potential catastrophic release and works backwards to determine the events that may cause it. This approach is called *failure analysis*. The alternative is to consider the probability of each component and control separately and in combination to determine what catastrophic events might occur. This approach is called *hazardous operations analysis*. These methods are well-developed in engineering and management practice.

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CHAPTER FIVE

THE APPLICATION OF PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODELING TO RISK ASSESSMENT

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Learning Objectives

Students who complete this chapter will be able to

1. Understand why PBPK modeling is needed in risk assessment
2. Know what PBPK modeling is
3. Know how PBPK modeling is done, particularly in its application to risk assessment
4. Learn how PBPK modeling of chemical mixtures is done
5. Follow what are some of the latest development in the application of PBPK modeling in risk assessment

The area of science called *physiologically based pharmacokinetic (PBPK) modeling* can be traced back to the 1920s. In June 2005, the first book on PBPK (Reddy, Yang, Clewell, and Andersen, 2005) was published and its contents encompassed over one thousand publications on PBPK modeling. Despite the fact that it is a mature science with almost one hundred years of history, active development is still going on in this area and a later section of this chapter provides a glimpse of some of these latest advances. It is important to emphasize that this chapter, though a learning tool, only provides some of the fundamentals to stimulate your interests. Alone, it will not make you a PBPK modeler. To be proficient, there is no alternative but

to attend specific training workshops, and most important, to get your hands dirty by doing PBPK modeling yourself. Only through repeated practice, reading, and making all the mistakes everyone else has made before you will you then open the window to a very useful and powerful technology.

The Need for PBPK Modeling in Risk Assessment

Conventionally, risk assessment is done based on exposure dose or administered dose. This is neither accurate nor satisfying because an exposure or administered dose will go through absorption, distribution, metabolism, and elimination (ADME) in our bodies before a sufficient amount of the dose reaches the target organ to exert its toxicity. To be able to follow, on a time course basis, the ADME processes of a given chemical in our bodies and, further, to follow an active component (e.g., from a technical formulation) or a reactive species (e.g., from metabolic transformation) require the understanding of pharmacokinetics of that chemical. PBPK modeling is a very useful tool for the integrated computer simulation of pharmacokinetics of a chemical or chemicals. Therefore, the need for PBPK modeling in risk assessment arises when we want to incorporate the state-of-the-science technology to conduct a more accurate risk assessment. Additional arguments in favor of incorporating PBPK modeling into the risk assessment process include deliberations from the following perspectives.

Toxicological Interactions of Multiple Chemicals

Present EPA risk assessment guidelines on chemical mixtures, including the recent effort on cumulative risk assessment of organophosphrous (OP) pesticides (Environmental Protection Agency, 2002a, 2002b), advocate the additivity approach. For instance, in the "Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity" (Environmental Protection Agency, 2002a), it was assumed that at lower levels of exposure typically encountered environmentally no chemical interactions are expected (i.e., simple additivity). For additivity to hold true, a further assumption must be that all the common mechanism chemicals behave the same pharmacokinetically and pharmacodynamically (i.e., having the same PK and PD) (Environmental Protection Agency, 2002a). In reality though, a case study of cumulative risk assessment of thirty-three organophosphorus pesticides provided BMDL (lower bound benchmark dose at ED_{10}) with a range of a 3,977- to 5,528-fold difference between the highest BMDL for malathion and the lowest BMDL for dicrotophos (Environmental Protection Agency, 2002b). These three to four orders-of-magnitude

differences among common mechanism chemicals suggest strongly that the PK and PD are not the same among these chemicals—thus the probability of toxicological interactions at the level of PK and PD. That being the case, PBPK modeling will be a most useful, if not the only, tool available for the integration of PK and PD interactions of multiple chemicals.

Minimizing Animal Experiments

PBPK modeling, as a form of *in silico* toxicology, minimizes animal usage by avoiding unnecessary animal experiments or extremely complex animal experiments. In essence, these complex experiments can be conducted on computer instead. Once a PBPK model is constructed, tested, and validated, an immense number of computer simulations (i.e., *in silico* experiments*)* can be performed by varying exposure scenarios including different routes, doses, species, and the involvement of different chemicals. This is particularly relevant in considering toxicological interactions of chemical mixtures, which is an essential element in cumulative risk assessment.

Food Quality Protection Act (FQPA) and the Subsequent Development of Cumulative Risk Assessment at EPA

In 1996, the U.S. Congress passed the Food Quality Protection Act (FQPA). Among other mandates, FQPA requires that EPA consider *cumulative risk*. As such, EPA is required to evaluate pesticides in light of similar toxic effects that different pesticides may share or involving chemicals with "a common mechanism of toxicity" (Environmental Protection Agency, 1999). Pioneering efforts were provided by the Office of Pesticide Programs (OPP), at EPA. Scientists at OPP took the lead and developed and conducted cumulative risk assessment on organophosphorus (OP) pesticides (Environmental Protection Agency, 2002a, 2002b). Subsequently, an interoffice endeavor on "Physiologically-Based Pharmacokinetic/Pharmacodynamic Modeling: Preliminary Evaluation and Case Study for the *N*-Methyl Carbamate Pesticides: A Consultation" (Environmental Protection Agency, 2003a) at the EPA had been peer-reviewed by the FIFRA Science Advisory Panel in December 2003 (Environmental Protection Agency, 2003b). A further effort, supported by the Office of Drinking Water and National Center for Environmental Assessment (NCEA), Office of Research and Development (ORD), EPA, is a complementary endeavor to earlier development to further advance a framework approach of incorporating PBPK modeling, particularly incorporating credible human tissue studies, into the cumulative risk assessment process (Environmental Protection Agency, 2005b). These scientific activities illustrate the progressive incorporation of PBPK modeling into the cumulative risk assessment process.

Internal Dose

Internal dose, sometimes referred to as *tissue dose* or *target dose*, can be thought of as the integrated dose level over time (i.e., area under the curve [AUC]) of a biologically effective chemical form (the parent compound or a reactive species) in a given tissue. Some consider the maximal concentration (C_{max}) in the blood or plasma versus time curve as a convenient form of internal dose. In either case, the internal dose takes into consideration the ADME processes, and it is therefore a more accurate dose metric, which should be more closely related to the toxic endpoint(s) than the exposure or administered dose. Once again, PBPK modeling is a very useful tool for computer derivation of the internal dose.

Exposure Dose Reconstruction and Human Biomonitoring

One of the missing links of human biomonitoring results such as those published in the Centers of Disease Control and Prevention (CDC) third biannual report (Centers for Disease Control and Prevention, 2005) is that we do not know what exposure conditions and levels were in the environment for those chemicals. When we have a robust and validated PBPK model for one or more chemicals, we can theoretically carry out a large number of computer simulations for numerous hypothetical exposure scenarios to reach the internal dose levels (i.e., human biomonitoring data reported). This is a form of *back-extrapolation* or *back-calculation* to estimate the possible exposure scenarios. It is not that we are trying to emphasize the importance of exposure dose when we have just stressed the importance of internal doses in the last section. We are interested in exposure scenarios leading to human biomonitoring results for a different reason. Possible environmental remedial actions may be taken when we are quite certain how and where the chemicals inside our body (i.e., human biomonitoring results) are coming from.

Systems Biology

The recent emphasis on the application of systems biology to biomedical research frequently traces its origin to cybernetics, as advanced by Norbert Wiener in the mid-twentieth century (Wiener, 1961). Even then, the integration of "computing machines" and biology was already advocated by a handful of visionaries. *Systems biology* integrates computational and experimental sciences in an effort to describe and understand entire biological systems (Kitano, 2002). PBPK modeling is a form of a systems biology approach toward toxicology where the physiology and biochemistry of a given chemical in an organism are integrated with computational modeling. In two of our recent publications (Yang and others, 2006b, 2006c) we

further present a systems biology representation of the integration of different scales of biologically based computer modeling across a number of biological levels of organization. The ADME model, as exemplified by PBPK modeling for whole-body pharmacokinetics, is linked with biochemical reaction network (BRN) modeling, a form of predictive xenobiotic metabolomics (or metabonomics). We can further link these integrated models with the genomic model, which is a general representation of the gene and/or protein expressions related to the toxicological processes being studied. In doing so, we can link a complicated metabolic pathway model with an ADME model and a genomic model to capture the full systems biology of toxicological interactions and effects.

What Is Physiologically Based Pharmacokinetics?

The concept of PBPK had its embryonic development in the 1920s. PBPK modeling blossomed and flourished in the late 1960s and early 1970s in the chemotherapeutic area due mainly to the efforts of investigators with expertise in chemical engineering. In the mid-1980s, work on PBPK modeling of volatile solvents started yet another revolution in the toxicology and risk assessment arena. Today, there are more than one thousand publications directly related to PBPK modeling of industrial chemicals, drugs, environmental pollutants, and simple and complex chemical mixtures. Our laboratory has recently published a book on PBPK modeling in collaboration with others (Reddy, Yang, Clewell, and Andersen, 2005).

Differences Between Classical Pharmacokinetic Models and PBPK Models

Classical pharmacokinetics refers to those empirical noncompartmental or compartmental pharmacokinetic studies routinely practiced in the pharmaceutical industry (van de Waterbeemd and Gifford, 2003). As illustrated later, the compartments of a PBPK model have anatomical and physiological significance. This is a major difference from *empirical* noncompartmental or compartmental pharmacokinetic modeling approaches. PBPK models can be used to describe concentration-time profiles in an individual tissue or organ and in the plasma or blood. When the concentration of a certain target tissue, rather than the plasma concentration, is highly related to a compound's efficacy or toxicity, PBPK modeling is a more useful tool than classical pharmacokinetic models for describing the PK-PD relationship; thus, it better predicts the time course of drug effects resulting from a certain dose regimen for the compound of interests. Furthermore, PBPK models in combination with absorption simulation and quantitative structure-activity relationship (QSAR) approaches bring us closer to a full prediction of drug disposition for new

pharmaceutical entities, and help streamline the selection of the lead drug candidate in the drug discovery process (van de Waterbeemd and Gifford, 2003). Last, unlike empirical noncompartmental and compartmental pharmacokinetics, PBPK modeling is a powerful tool for extrapolation, whether for interspecies, interroutes, interdoses, or interlife stages.

Conceptual Model: Graphic Representation

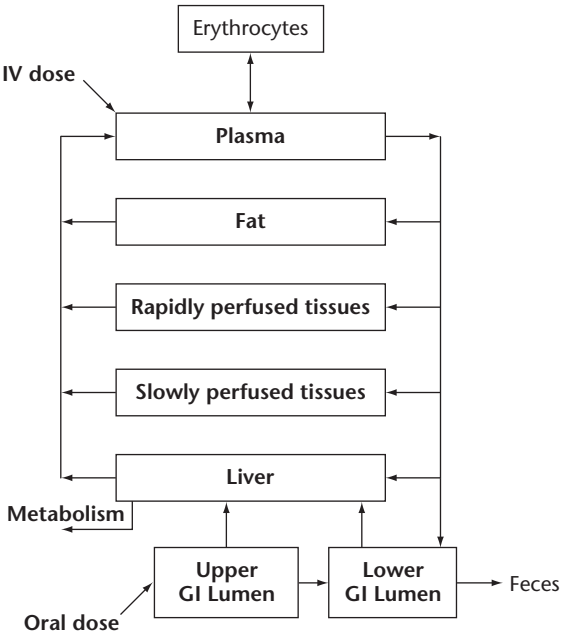
A PBPK model, graphically and conceptually illustrated in Figure 5.1, reflects the incorporation of basic physiology and anatomy. The compartments correspond to anatomic entities, such as the liver and fat, while the blood circulation conforms to basic mammalian physiology. In the specific model in Figure 5.1, a PBPK model for hexachlorobenzene (HCB) in the rat (Lu and others, 2006), the exposure routes of interest are either oral gavage or intravenous (IV) as indicated. Depending on the need, other routes of exposures can be added easily. Some tissues are "lumped" together, such as richly (rapidly) or poorly (slowly) perfused tissues in Figure 5.1, when they are kinetically similar for the specific chemical(s) studied. On the other hand, a given tissue can be split as needed. In this case, HCB is known to bind with erythrocytes and the blood compartment is split into two subcompartments, the erythrocytes and plasma. Similarly, because of the complexity related to the absorption and exsorption (plasma-to-gastrointestinal [GI] lumen passive diffusion) processes of HCB, the GI lumen compartment is split into upper and lower portions. In conceptualizing the PBPK model, the Law of Parsimony should always be applied to keep the model as simple as possible. When the needs arise, complexity can be incorporated as illustrated.

Mathematical Model: Mass-Balance Differential Equations

A mathematical model, regarding PBPK modeling, is computer-code-formulated in such a way that it can be executed by the computer software to simulate the kinetic behavior of a chemical(s) in the body of an organism such as a rat, mouse, fish, or human. A key element of such a mathematical model is a set of mass-balance differential equations representing all of the interlinked compartments such as liver or fat. This set of mass-balance differential equations is formulated to express a mathematical representation, or model, of the biological system. This model can then be used for computer simulation to predict the time course behavior of any given chemical included in the model.

These mass balances are essentially molecular accounting statements that include the rates at which molecules enter and leave the compartment, as well as

FIGURE 5.1. A GRAPHIC OR CONCEPTUAL PBPK MODEL FOR HCB FOLLOWING IV OR ORAL EXPOSURE.



Note: For an IV exposure, the uptake in the upper GI lumen was turned off, and the excretion of metabolites was tracked. For oral exposures, the reverse was true.

Source: Adapted from Lu and others (2006).

the rates of reactions that produce or consume the chemical. For instance, a general equation, for chemical *j* in any tissue or organ, is

$$V_i \frac{dC_{ij}}{dt} = Q_i (CA_j - CV_{ij}) - \text{Metab}_{ij} - \text{Elim}_{ij} + \text{Absorp}_{ij} - \text{Pr}\,Binding_{ij} \qquad (5.1)$$

where V_i represents the volume of tissue group *i*, Q_i is the blood flow rate to tissue group *i*, CA_j is the concentration of chemical *j* in arterial blood, and C_{ij} and CV_{ij} are the concentrations of chemical *j* in tissue group *i* and in the effluent venous blood from tissue *i*, respectively. Please note that C_{ij} here refers to the "free," unbound chemical concentration; in toxicology literature, C_{ij} under similar conditions may mean total chemical concentration (free and bound) and the equation would be different from above (Equation 5.1). A typical example is the TCDD

PBPK model (Leung, Ku, Paustenbach, and Andersen, 1988; Mills and Andersen, 1993). $Metab_{ij}$ is the rate of metabolism for chemical *j* in tissue group *i*; liver, being the principal organ for metabolism, would have significant metabolic rates, while, with some exceptions, $Metab_{ij}$ is usually equal to zero in other tissue groups. $Elim_{ij}$ represents the rate of elimination from tissue group *i* (e.g., biliary excretion from the liver), $Absorp_{ij}$ represents uptake of the chemical from dosing (e.g., oral dosing), and $PrBinding_{ij}$ represents protein binding of the chemical in the tissue. These terms are zero unless there is definitive knowledge that the particular organ-tissue of interest has such processes, and more importantly, that such processes will have significant impact upon the pharmacokinetics of the chemical(s).

A Priori Prediction Versus Curve Fitting

Once a PBPK model is validated (as discussed later in this chapter), it has the predictive capability in carrying out a priori computer simulations given a set of initial conditions such as animal species of interest, dosing route, dosing levels, and regimen. Certain validation experiments under the precise simulation conditions can then be conducted to test the predictive capability of the PBPK model by comparing experimental results with the a priori computer simulation results. Therefore, PBPK modeling should not be considered as curve fitting exercises.

Biological Relevance

As the name *physiologically based* implies, another important consideration in PBPK modeling is that whenever an equation and its related parameter(s) are introduced into the model, they must have biological relevance. In many ways, the mass-balance differential equations in PBPK modeling can be translated into simple English. For instance, the mass-balance equation for the liver compartment in Figure 5.1 is

$$VL \times \frac{dCL}{dt} = QL \times (CA - CVL) - KMET \times CVL + KGILV1 \times AGIUp + KGILV2 \times AGILow \tag{5.2}$$

Equation 5.2 looks like a rather formidably long equation. However, the English translations for both sides of the equation are really quite easy to follow.

Left side: A small change in the amount of chemical (HCB in this case) with respect to a small change in time. We talk about "amount" because when volume of the liver (VL in ml) multiplies the concentration in the liver (CL in mg/ml), it becomes amount (mg). Note the unit on the left side is finally amount/time or more specifically, mg/hr.

*Right s*ide: Amount coming into the liver from general circulation (first term) minus the amount metabolized (second term) plus amount absorbed from the upper GI lumen (third term) plus amount absorbed from the lower GI lumen (fourth term). The first term is derived from blood flow rate (*QL* in ml/hr) to and from the liver times the differential concentration between arterial blood (*CA* in mg/ml) and venous blood (*CVL* in mg/ml). In the second term, *KMET* is metabolic rate constant with a unit of ml/hr. In the third and fourth terms, *KGILV1* and *KGILV2* are absorption rate constants from upper and lower GI lumen with a unit of 1/hr whereas *AGIUp* and *AGILow* are the amounts of HCB in the two GI lumen compartments. Note the unit for each term on the right side is also mg/hr.

The above exercise simply illustrates that all the mass-balance equations and their respective parameters in a PBPK model should be explainable by biologically relevant concepts and terminologies.

How Does a PBPK Model Work?

The fundamental object of PBPK modeling is to identify the principal organs or tissues involved in the disposition of the chemical of interest and to correlate the chemical absorption, distribution, metabolism, and excretion within and among these organs and tissues in an integrated and biologically plausible manner. How individual components of PBPK modeling works has been shown in a previous section. However, we will briefly summarize the process in its entirety.

After a conceptual model is developed as shown in Figure 5.1, time-dependent mass-balance equations are written for a chemical(s) in each compartment. A set of such mass-balance differential equations representing all of the interlinked compartments are formulated to express a mathematical representation, or model, of the biological system. This model can then be used for computer simulation to predict the time-course behavior of any given chemical included in the model. Computer simulations may be developed for any number of desired time-course end points such as the blood levels of the parent compound, liver level of a reactive metabolite, and similar information on different species at lower or higher dose levels and/or via a different route of exposure. The experimental pharmacokinetic data may then be compared with a PBPK model simulation. If the model simulation does not agree with the measurements, the model might be deficient because critical scientific information is missing or certain assumptions are incorrect. The investigator, with knowledge of the chemical and a general understanding of the physiology and biochemistry of the animal species, can design and conduct critical experiments for refining the model to reach consistency with

experimentation. This refinement process may be repeated again and again when necessary; such an iterative process is critically important for the development of a PBPK model. In that sense, PBPK modeling is a very good hypothesis-testing tool in toxicology, and it may be utilized to conduct many different kinds of experiments on the computer, such as *in silico* toxicology. Note that there is always the possibility that a good model may not be obtained at the time because of the limitation of our knowledge about the chemical. Validation of the PBPK model with datasets other than the working set (or training set) to develop the model is necessary. Remember—a model is usually an oversimplification of reality: "all models are wrong; some are useful," as stated by George Box. The more the datasets against which a model is validated, the more robust is that model in its predictive capability. Once validated, the PBPK model is ready for extrapolation to other animal species, including humans.

Data Requirements for PBPK Modeling

What are the specific data needed for building PBPK models? Obviously, well-conducted in vivo pharmacokinetic data are essential and usually the more the datasets (e.g., different doses, routes, species), the better. In each study, time-course blood and tissue concentration data are essential. These time-course data should include at least the following tissues and organs: blood (or plasma if blood cell binding is not an issue), liver (organ of metabolism), kidney (representing rapidly perfused organs/tissues), muscle (representing slowly perfused organs/tissues), and target organ(s)/tissue(s).

Three sets of parameters are needed for PBPK model building: physiological parameters (e.g., ventilation rates, cardiac output, organs as percentage of body weight), thermodynamic parameters (e.g., tissue partition coefficients, protein binding), and biochemical parameters (e.g., Michaelis-Menten metabolism parameters K_m and V_{max}). Most, if not all, of the parameters for laboratory animals are available in the literature (Brown and others, 1997). When information gaps exist, needed data can be obtained via experimentation or through allometric extrapolation, usually based on a power function of the body weight (Lindstedt, 1987).

Datasets Used for Model Building and Model Validation

When building a PBPK model, certain experimental datasets are necessary for comparing with simulation results to see if the theoretical data (computer simulations) are superimposable to the observed data (experimental results). During

this phase of the work, we are trying to (1) test our hypotheses of pharmacokinetic fate of the chemical(s) of interest in the given biological system, (2) assess the appropriateness of the assumptions that we made for the PBPK model, and (3) find appropriate values for those parameters that can neither be derived experimentally nor extrapolated allometrically. The datasets used in this model-building phase should be considered as a *training set* or *working set*. Once a PBPK model is constructed, the next phase is model validation. This is where a priori simulations under a specific exposure scenario can be carried out and the simulation results then compared with available experimental data. Superimposition of the two suggests validity of model prediction under that set of conditions. The more datasets there are against which a model is validated, the more robust is that model in its predictive capability. Validation of the PBPK model with datasets other than the training set (or working set) used to develop the model is essential.

Available Software Comparison

A PBPK model generally is a system of coupled ordinary differential equations, which are solved with the aid of computer tools. The available computer tools for PBPK modeling include programming languages, simulation software, and spreadsheets. An excellent list of these tools, along with their developers/vendors, salient features, and application examples, has been compiled in a recent report on PBPK modeling (Environmental Protection Agency, 2005a). Earlier, Rowland, Balant, and Peck (2004) presented a somewhat different list. Certain commonly known examples in these lists are MATLAB (MathWorks, Natick, Massachusetts), Berkeley Madonna (University of California-Berkeley), SAAM II (University of Washington-Seattle), SCoP (Simulation Control Program, Simulation Resources, Inc., Redlands, California), SimuSolv (Dow Chemical Company, Midland, Michigan), and ACSL, ACSL Tox, and acslXtreme (AEgis Technologies Group, Huntsville, Alabama). The available software for PBPK modeling varies in flexibility and user friendliness. Regardless of the variation in flexibility, PBPK software should at least have proper algorithms for integration, optimization, and sensitivity analysis. Given the diversity in the software in use, concerns have been expressed about standardizing the software for PBPK modeling (Rowland Balant, and Peck, 2004). In the toxicology community, ACSL, ACSL Tox, and acslXtreme, closely related, are the most commonly used software.

Two PBPK simulation programs used in our laboratory, Berkeley Madonna (version 8.3.6) and acslXtreme (version 2.0.1.6), are briefly introduced here. Both programs are general-purpose differential-equation solvers with high flexibility. The modeling process in each program follows the procedure of representing a

model graphically or in equations, compiling model equations into machine code, and reporting results. Berkeley Madonna is more affordable, easier to learn, more user-friendly, and requires less programming knowledge.

The critical components of a model in both Berkeley Madonna and acslXtreme are the equations and statements that represent the parameter settings, model structure, integration method, and other related conditions. In Berkeley Madonna, the equations need not follow a particular order or structure. They will be automatically sorted into a proper order for execution. For readability and ease to debug, however, coding in the following order is recommended: integration method and related conditions, parameters, parameter scaling, exposure conditions, and mass balance for each compartment.

In the following sections, we first provide a general explanation of the blocks for a model written with ACSL. We then provide a detailed explanation of a PBPK model written with Berkeley Madonna. This seemingly preferential treatment of Berkeley Madonna is due to the fact that Berkeley Madonna is more affordable to students and easier to use. We believe that the readers of this book are more likely to be interested in starting their PBPK modeling experience with Berkeley Madonna.

In acslXtreme, the model equations, saved in a CSL (continuous simulation language) file, are organized to a specific structure with several blocks (*acslXtreme Language Reference Guide,* 2005):

```
PROGRAM
    INITIAL
    Statements executed before the run begins.
    State variables do not contain the initial conditions yet.
    END

  DYNAMIC
      DERIVATIVE
      Statements to be integrated continuously.
      END

  DISCRETE
  Statements executed at discrete points in time.
  END
  Statements executed at each communication interval.
  END

  TERMINAL
  Statements executed after the run terminates.
  END

END
```

Equations should be placed in the appropriate blocks; misplacement of equations may prevent the code from running or produce wrong results. In the Derivative block, however, the equations can be grouped in whatever way the modeler likes. Although no acslXtreme code is available in the literature, a reader can refer to Thomas and others (1996a) and Easterling, Evans, and Kenyon (2000) for the codes in ACSL and SimuSolv that are structurally very similar to those in acslXtreme.

After a model code is executed, both Berkeley Madonna and acslXtreme are amenable to *in silico* experimentation, including, but not limited to, tabulating and plotting simulation results, examining the effects of a parameter on model outputs, visual optimization, statistical optimization, sensitivity analysis, and Monte Carlo analysis. In this regard, Berkeley Madonna offers a user-friendly interface so that those manipulations can be achieved by selection of the self-explanatory options from the tool menu. AcslXtreme, however, requires some acquaintance with the specific command language, which is a challenge to a new user.

Explanation of an Example of Computer Code for a PBPK Model in Berkeley Madonna

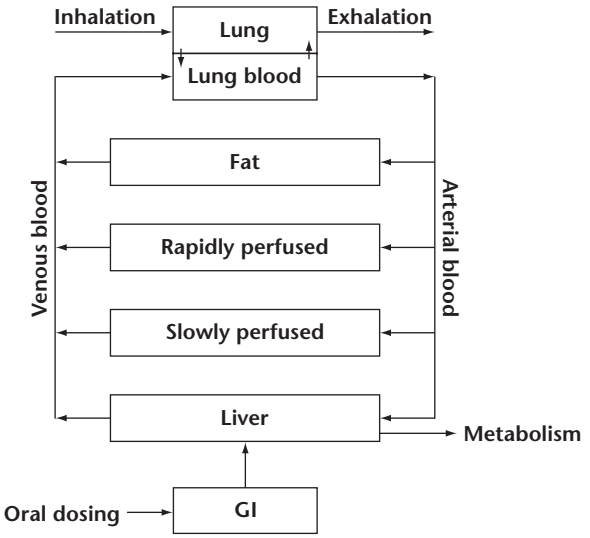
A PBPK model code written in Berkeley Madonna simulates the exposure and pharmacokinetics in the rat of 1,1,1-trichloroethane, a volatile organic chemical, which is lipophilic and slowly metabolized in the liver. Prior to explaining the code, we need to sequentially define the foundations on which the code is based: (1) exposure conditions, (2) PBPK model structure, and (3) necessary assumptions/simplifications and mass-balance differential equations for all compartments.

Exposure conditions: Two exposure pathways, not taking place simultaneously, are involved in this case. At time zero, a rat is orally administered a 1,1,1-trichloroethane water solution at the dose of 14.2 mg/kg body weight; or else it starts inhaling 1,1,1-trichloroethane vapor at 150 ppm continuously for six hours. That determines the time-course concentrations of 1,1,1-trichloroethane in the exhaled air and venous blood.

PBPK model structure: The model structure (Figure 5.2) is determined according to the exposure conditions and the pharmacokinetic characteristics of 1,1,1-trichloroethane. As 1,1,1-trichloroethane is lipophilic and slowly metabolized in the liver, the fat and liver are included in the model structure. The other organs and tissues have no individually distinct impact on the pharmacokinetics, and are thus lumped to a rapidly and slowly perfused compartment. The lung/lung blood and gastrointestine (GI) compartments accommodate the inhalation and oral dosing exposures.

We assume that each of the compartments is homogeneous, that the chemical uptake in each tissue compartment is perfusion-limited, that is the diffusion of

FIGURE 5.2. PBPK MODEL STRUCTURE FOR 1,1,1-TRICHLOROETHANE IN THE RAT.



the chemical into the tissue is rapid and the rate-limiting step is the blood perfusion rate, and that 100 percent of the oral dose in the GI compartment is absorbed. The amount of change of 1,1,1-trichloroethane in a small time interval (*dt*) in the fat (*F*) compartment can be expressed as

$$\frac{dAF}{dt} = QF \times (CA - CVF) = QF \times (CA - \frac{CF}{PF}) \tag{5.3}$$

where *AF* is the amount in fat, *QF* is the blood flow rate into fat, *CA* is the arterial blood concentration, and *CVF* is the concentration in the effluent blood from fat, which is related to the fat concentration (*CF*) divided by the fat partition coefficient (*PF*). Equation 5.3 can be applied to the rapidly (*R*) and slowly (*S*) perfused compartments by replacing the *F* with *R* and *S*, respectively.

The differential equation for the liver is a little more complicated than in Equation 5.3 because the absorption from the GI compartment and the metabolism should be considered therein.

$$\frac{dAL}{dt} = QL \times (CA - CVL) + \frac{dAB}{dt} - \frac{dAM}{dt} \tag{5.4}$$

where *dAB/dt* represents the rate of absorption from the GI compartment into the liver, and *dAM/dt* represents the rate of metabolism that results in a negative change in the chemical amount in the liver.

The differential equation for the GI lumen is

$$\frac{dAGI}{dt} = -\frac{dAB}{dt} = -KAB \times AGI \tag{5.5}$$

where *AGI* stands for the amount in the *GI* compartment, and *KAB* is the rate constant of absorption from *GI* to blood and then to the liver. The minus sign indicates that the amount left in the *GI* compartment decreases with time.

The venous blood concentration, CV, can be expressed using an algebraic equation:

$$CV = (QF \times CVF + QL \times CVL + QR \times CVR + QS \times CVS)/QC \tag{5.6}$$

where *QC* is the cardiac output. For the calculation of arterial blood concentration, *CA,* assumptions are involved that steady state in the lung is quickly reached upon inhalation, that the exhaled concentration is in equilibrium with *CA,* and that the chemical is only absorbed in the alveolar region. In the blood flowing through the lung, the amount of change over time can be expressed as:

$$\frac{dABlood}{dt} = QC \times (CV - CA) + QP \times (CIN - \frac{CA}{PB}) \tag{5.7}$$

where *QP* is pulmonary ventilation rate, *CIN* is the concentration inhaled, *PB* is blood:air partition coefficient, and *CA/PB* is the concentration exhaled. At steady state, *dABlood/dt* = 0. Thus, Equation 5.7 is reduced to

$$QC \times (CV - CA) + QP \times (CIN - \frac{CA}{PB}) = 0 \tag{5.8}$$

Solving Equation 5.8 for *CA,*

$$CA = \frac{QC \times CV + QP \times CIN}{QC + \frac{QP}{PB}} \tag{5.9}$$

Now that the exposure conditions, model structure, and mass-balance equations are clarified, let us turn to the Berkeley Madonna code for this case. Like a

typical PBPK model code, the 1,1,1-trichloroethane includes documentation, integration method, parameters, mass-balance equations, and error-check equations. We will go through it line by line. The code contents are followed by brief explanations; these are not meant to replace a PBPK modeling course or workshop. In a Berkeley Madonna code, documentation is composed of the text strings confined in paired curly brackets or preceded by semicolons.

```
{1,1,1-Trichloroethane code originally supplied by Dr. Reitz. Converted into a Berkeley Madonna form for the 2005 Colorado State University Beginner's PBPK Workshop by Yasong LU and Ray Yang. 7/16/2005. Reference: Reitz RH, McDougal JN, Himmelstein MW, Nolan RJ, Schumann AM. 1988 Physiologically based pharmacokinetic modeling with methylchloroform: Implications for interspecies, high dose/low dose, and dose route extrapolations.

Source: Toxicology and Applied Pharmacology, 95, 185–199}.
```

These sentences are part of the documentation of this code. Different from the other components, documentation is not essential for code execution. However, it records important information pertinent to the code, such as the purpose(s) of the modeling, experimental conditions being simulated, date and author(s) of the code, history of the modifications to the code, rationale of the modeling structure and parameter value selections, and explanation of the terminology in the code. Documentation is critical for model code maintenance. Therefore, it is always good practice to provide documentation as thoroughly as possible.

Method Stiff

The METHOD statement defines the numerical integration method for model calculation. For PBPK modeling, STIFF is a frequently used method that automatically finds the appropriate integration intervals over time. See the next section for more details on numerical integration methods.

```
STARTTIME = 0
STOPTIME = 12
```

The STARTTIME and STOPTIME statements define the starting and ending times of the simulation. The former is usually 0; the latter varies depending on the experimental duration.

```
{Physiological Parameters}
{Constants set for the rat}
BW = 0.233;Mean body weight (kg); Reitz et al. code.
```

```
QCC = 15.;Cardiac output constant [L/(hr*kg^0.74)]; Reitz et al., 1988.
QPC = 15.;Alveolar ventilation constant [L/(hr*kg^0.74)]; Reitz et al., 1988.
{Blood flow fractions}
QLC = 0.24;Fractional blood flow to liver; Reitz et al., 1988.
QFC = 0.05;Fractional blood flow to fat; Reitz et al., 1988.
QSC = 0.18;Fractional blood flow to slowly perfused; Reitz et al., 1988.
QRC = 1.0-(QFC+QSC+QLC);Fractional blood flow to rapidly perfused;
      Reitz et al., 1988.
{Volume fractions}
VLC = 0.04;Fraction liver tissue; Reitz et al., 1988.
VFC = 0.07;Fraction fat tissue; Reitz et al., 1988.
VRC = 0.05;Fraction rapidly perfused tissues; Reitz et al., 1988.
VSC = 0.91-VLC-VFC-VRC;Fraction slowly perfused; Reitz et al., 1988.
```

This block defines the physiological parameters necessary for the modeling. Each parameter statement is followed by a semicolon and text string (documentation) explaining the meaning of the parameter symbol and the source of the parameter value. These statements, either following a semicolon or in between curly brackets, are for our own record or information and they are ignored by Berkeley Madonna.

```
{Chemical specific parameters}
{Partition coefficients}
PB = 5.76;Blood/air; Reitz et al., 1988.
PLA = 8.6;Liver/air; Reitz et al., 1988.
PFA = 263.;Fat/air; Reitz et al., 1988.
PRA = 8.6;Rapidly perfused/air; Reitz et al., 1988.
PSA = 3.15;Slowly perfused/air; Reitz et al., 1988.
PL = PLA/PB
PF = PFA/PB
PR = PRA/PB
PS = PSA/PB
```

The tissue:air partition coefficients were experimentally measured; they are divided by a blood:air partition coefficient to convert to tissue:blood partition coefficients, which govern the distribution of the chemical in each compartment.

```
{Metabolism; saturable; estimated from Schumann et al. data and Reitz et al. drinking
water study}
VMAXC = 0.419;Capacity of saturable metabolism [mg/(hr*kg^0.7)]; Reitz et al., 1988.
KM = 5.75;Affinity of saturable metabolism (mg/L); Reitz et al., 1988.
```

These lines define the Michaelis-Menten kinetic parameters for 1,1,1-trichloroethane metabolism in the liver.

```
{Scaled parameters}
QC = QCC*BW^0.74;Cardiac output (L/hr); Reitz et al., 1988.
QP = QPC*BW^0.74;Alveolar ventilation (L/hr); Reitz et al., 1988.
VF = VFC*BW;Fat volume (L)
VL = VLC*BW;Liver volume (L)
VR = VRC*BW;Rapidly Perfused volume (L)
VS = VSC*BW;Slowly Perfused volume (L)
QL = QLC*QC;Liver blood flow (L/hr)
QF = QFC*QC;Fat blood flow (L/hr)
QR = QRC*QC;Rapidly Perfused blood flow (L/hr)
QS = QSC*QC;Slowly Perfused blood flow (L/hr)
VMAX = VMAXC*BW^0.7;Capacity of saturable metabolism (mg/hr); Reitz et al., 1988.
```

In this block, the physiological parameters and maximum metabolic velocity are scaled by the body weight.

```
{Exposure conditions: oral dosing}
BDOSE = 14.2;Oral bolus dose rate (mg/kg)
KA = 1.25;Rat GI absorption rate constant (/hr); Reitz et al., 1988.
ODOSE = BDOSE*BW;Oral bolus dose (mg)
```

These statements define the oral exposure dose and the GI absorption rate constant.

```
{Exposure conditions: inhalation}
TCHNG = 6.;Length of inhalation exposure (hrs)
;Unit conversion: from ppm to mg/L; often necessary for inhalation exposure scenarios.
MW = 133.5;Molecular weight (g/mol)
CONC = 0.0;Inhaled concentration (ppm)
CIN0 = CONC*MW/24450.;Convert ppm to mg/L
CIN = IF TIME<TCHNG THEN CIN0 ELSE 0;Turn off inhalation after exposure interval
```

The inhalation exposure conditions are defined in this block. Two features here deserve some elaboration:

1. *Unit conversion.* In inhalation experiments, chemical concentrations are frequently expressed in parts per million (ppm), which must be converted to mg/L or something similar for further calculations. The theoretical basis of the unit conversion is the ideal gas law.

2. *The "if-then-else statement."* This statement is used to change a parameter under certain condition(s). In this case, the inhalation exposure is turned off, since the TIME hits six hours. Please note that although this code accommodates both oral and inhalation exposure, they do not coexist. Thus, the inhaled concentration (CONC) is set as zero here to avoid the undesirable double-dosing; when running the code for inhalation, we can turn off the oral dosing and give CONC an appropriate value.

At this point all parameters have been defined in the code. The following sections demonstrate how the chemical amount and/or concentration in each compartment are calculated. For each compartment, there is a mass-balance differential equation coupled with a statement (INIT, which also signifies integration of the parameter that follows) defining the initial value of the amount in the compartment. When necessary, the concentration in a compartment is calculated as the ratio of the amount therein over the compartment volume.

```
{Chemical distribution—mass balances}
;AS = Amount in Slowly Perfused (mg);AS' = dAS/dt
AS' = QS*(CA-CVS);Mass-balance differential equation.
INIT AS = 0.;Initial amount in slowly perfused.
CS = AS/VS;Concentration in slowly perfused, mg/L.
CVS = CS/PS;Effluent blood conc, in equilibrium with tissue conc, mg/L.
```

These lines calculate the amount and concentration in the slowly perfused compartment and the concentration in the venous blood flowing out of that compartment.

```
;AR = Amount in Rapidly Perfused (mg)
AR' = QR*(CA-CVR);Mass balance in rapidly perfused
INIT AR = 0.;Initial amount in rapidly perfused
CR = AR/VR;Conc in rapidly perfused, mg/L
CVR = CR/PR;Effluent blood conc, mg/L
;AF = Amount in fat (mg)
AF' = QF*(CA-CVF);Mass balance in fat
INIT AF = 0.;Initial amount in fat
CF = AF/VF;Conc in fat, mg/L
CVF = CF/PF;Effluent blood conc, mg/L
```

The chemical amount and concentration in the fat and the rapidly perfused compartment are calculated in the same way as for the slowly perfused compartment.

```
;AL = Amount in liver (mg)
AL' = QL*(CA-CVL) – AM' + AO';Mass balance in liver
```

```
INIT AL = 0.;Initial amount in liver
CL = AL/VL;Conc in liver, mg/L
CVL = CL/PL;Effluent blood conc, mg/L
;AM = Amount metabolized (mg)
AM' = VMAX*CVL/(KM+CVL);Rate of metabolism, mg/hr
INIT AM = 0.;Initial amount metabolized, mg
;AO' = Rate of input to liver from stomach after oral bolus (mg/hr)
AO' = KA*MR;Rate of GI absorption, mg/hr
INIT AO = 0.;Initial value of absorbed amount, mg
```

This block shows the calculations for the liver compartment. Different from the fat and the rapidly and slowly perfused compartment, the mass balance in the liver includes metabolism and absorption from the GI compartment.

```
;MR = Amount remaining in stomach after oral bolus (mg)
;First-order absorption
MR' = -KA*MR;Absorption rate, mg/hr
INIT MR = ODOSE;Initial value of the amount in stomach = given dose, mg
```

These lines demonstrate the calculation of the amount in the GI compartment.

```
;Blood concentrations (mg/L)
CV = (QL*CVL+QS*CVS+QF*CVF+QR*CVR)/QC;Venous blood conc, mg/L
CA = (QC*CV+QP*CIN)/(QC+QP/PB);Arterial blood conc, mg/L
CEX = CA/PB;Conc leaving the alveolar region, mg/L
CEXMGL = 0.667*CEX+0.333*CIN;Conc in exhaled air, mg/L
CEXPPM = CEXMGL*24450./MW;mg/L converted to ppm, for comparing with data
```

The venous and arterial blood concentrations are calculated algebraically. By convention, the alveolar respiration has been assumed to account for two-thirds of total respiration (Ramsey and Andersen, 1984); hence the concentration in the exhaled air is a weighted average of the inhaled concentration (CIN) and the concentration leaving the alveolar region (CEX).

```
;Error check
;Total amount of chemical delivered should equal to the amount calculated by the code.
;Amount inhaled
AIN' = QP*CIN
INIT AIN = 0.
;Amount exhaled
AEX' = QP*CEX
INIT AEX = 0.
;TOTAL = Total amount delivered
```

```
TOTAL = ODOSE + AIN – AEX
;Calculated = Total amount calculated
Calculated = AF+AL+AS+AR+AM+MR
ERROR = (TOTAL – Calculated)/(TOTAL+1E-30)*100;ERROR should be close to 0.
```

This final block is set to check the potential error(s) in the code. A small value (1E-30) is added to the denominator in the ERROR equation to avoid a situation where the denominator might end up being zero. If the total amount of chemical delivered experimentally is different from the summed amount in all compartments and eliminated, it would suggest that there is an error(s) in the code. This error-check tool, however, cannot uncover all errors in a code; thorough examination of a code is strongly encouraged.

Numerical Integration

Numerical integration, as opposed to finding an exact solution, is the basis for computer simulation in PBPK modeling. In essence, it is an approach for approximating very closely the true solution of a calculation in much the same way as we approximate an area under the curve (AUC) using the trapezoidal rule. In this latter case, the smaller the trapezoids (i.e., the step size), the more accurate the approximation of the AUC. In Berkeley Madonna, there are five numerical integration methods available for use. They are Euler's Method, Runge-Kutta 2, Runge-Kutta 4, Auto-stepsize, and Rosenbrock (stiff). Detailed explanation of these methods is beyond the scope of this chapter. We will simply point out two things: (1) a very popular method for approximating solutions to first-order initial-value problems is the *fourth-order Runga-Kutta method* (i.e., Runge-Kutta 4 in Berkeley Madonna; Runga-Kutta refers to two German mathematicians); (2) for some differential equations, application of standard numerical integration methods such as the Euler and Runge-Kutta methods exhibit instability in the solutions. This instability or difficult-behavior in the equation is described as *stiffness* and is often caused by the presence of different time scales in the underlying problem. Stiff problems are ubiquitous in many areas of science, including biology. One of the methods in Berkeley Madonna, Rosenbrock (stiff), is specifically to be used for the stiff problems.

Sensitivity and Uncertainty

A PBPK model provides pharmacokinetic profiles of a chemical given physiological, biochemical, and thermodynamic parameters. For various reasons, it is valuable to identify the sensitivity of an output to the model parameters and to

measure the effect of the variability or uncertainty in a parameter on model outputs. These evaluations involve sensitivity analysis and uncertainty analysis.

Sensitivity Analysis

Sensitivity analysis examines the influence of model parameters on outputs. Conceptually, there are two kinds of sensitivity analyses in mathematical modeling: local and global (Blower and Dowlatabadi, 1994; Nestorov, Aarons, and Rowland, 1997; Saltelli, Tarantola, and Chan, 1999). *Local sensitivity* refers to the response of model outputs to the perturbation of a single parameter, whereas *global sensitivity* refers to the response of outputs to the simultaneous alterations in all parameters. Sensitivity analysis in the PBPK community is currently predominantly limited to local sensitivity (Clewell, Lee, and Carpenter, 1994; Easterling, Evans, and Kenyon, 2000; Emond, Birnbaum, and DeVito, 2004; Evans and Andersen, 2000; Evans, Crank, Yang, and Simmons, 1994; Sweeney, Gargas, Strother, and Kedderis, 2003).

The sensitivity of an output to a parameter can be quantitatively reflected by a sensitivity coefficient (SC). Considering an output R is a function of a parameter x, that is, $R = F(x)$, then:

$$SC = \frac{F(x + \Delta x) - F(x)}{\Delta x} \tag{5.10}$$

where Δx is a perturbation in x. When the Δx is sufficiently small, the SC is a partial derivative of R with respect to x. Thus, Equation 5.10 can be reformulated into:

$$SC = \frac{\partial R}{\partial x} \tag{5.11}$$

Since parameters and outputs have distinct units and magnitudes, the SC should be properly normalized for interparameter or interoutput comparisons. Thus:

$$SC = \frac{\dfrac{\partial R}{R}}{\dfrac{\partial x}{x}} = \frac{\partial \ln R}{\partial \ln x} \tag{5.12}$$

where SC can be recognized as the sensitivity of the logarithm of an output R (lnR) to the logarithm of a parameter x (ln$x$), hence it is also known as a *log-normalized sensitivity coefficient* (LSC). An LSC identifies the percentage change in an

output due to a percentage change in a parameter. It has been suggested that LSCs should be in the range of −1 to 1; a value substantially beyond the range indicates that the error in a parameter is greatly amplified in the output, and hence implies undesirable feature(s) in the model (Clewell, Lee, and Carpenter, 1994).

The utilities of sensitivity analysis include

- Identifying the most sensitive parameters for an output, which helps us understand a pharmacokinetic behavior of interest (Emond, Birnbaum, and DeVito, 2004; Evans and Andersen, 2000).
- Evaluating the necessity of carefully measuring unknown parameters. If the output of interest is sensitive to an unknown parameter, precise measurement of this parameter is required.
- Directing targeted experimentation and improving study design. For example, sensitivity analysis may suggest optimal exposure conditions, necessary data to be collected, and the frequency of data collection (Evans, Crank, Yang, and Simmons, 1994; Schlosser, 1994).

Uncertainty Analysis

The term *uncertainty* is often used along with *variability* although they are distinct concepts. *Uncertainty* is defined as the possible error in estimating a true value of a parameter; it is a defect in knowledge and can be reduced by improving experimental methods (Clewell and Andersen, 1996). *Variability,* however, refers to the difference of a parameter among individuals; it is a fact that can be measured but not be changed (Clewell and Andersen, 1996).

For the purpose of risk assessment, average pharmacokinetic information is not very useful because it does not take into account the uncertainty and variability of the parameters (Clewell and Andersen, 1996). Uncertainty analysis measures the effects of uncertainty and variability in model parameters on predicted pharmacokinetics. Monte Carlo simulation is a common technique for uncertainty analysis. Before conducting a PBPK simulation, the statistical distributions of all parameters are determined. A set of the parameters is sampled from those distributions using Monte Carlo simulation. These parameters are then input into a PBPK model, which is executed and generates a set of outputs. Then another set of parameters is sampled, the PBPK model is reexecuted, and the outputs are recorded. This process is repeated many times (e.g., 1,000) until many sets of outputs are generated. The outputs are statistically analyzed to get the means and variances. As such, the effects of the uncertainty and variability of parameters on outputs are measured (Blower and Dowlatabadi, 1994; Clewell and Andersen, 1996; Hetrick, Jarabek, and Travis, 1991; Thomas and others, 1996b). Recently a more advanced statistical approach, *Bayesian analysis,* has been applied in PBPK

modeling to explore the effects of uncertainty and variability in model parameters (Bois 2001; David and others, 2006; Jonsson, 2001; Jonsson and Johanson, 2001a; Marino and others, 2006). This approach can separate uncertainty from variability. More information on the Bayesian approach is introduced in a later section.

PBPK Models for Chemical Interactions (Interactive PBPK Models) in Chemical Mixtures

Since humans are rarely, if ever, exposed to a single chemical, a key feature of PBPK modeling is that it can be used to integrate information on toxicological interactions. The most ideal and scientifically defensible data requirement for establishing an interactive PBPK model is that an established, validated PBPK model is available for each component chemical in the mixture. Furthermore, there are many pharmacokinetic datasets in laboratory animals as well as in humans available for each of these component chemicals. We use the term of *interactive PBPK model* to mean a PBPK model that is capable of simulating interactions between and among chemicals in a mixture. The interactive PBPK model is then built on the basis of known pharmacokinetic interactions. For instance, one chemical may inhibit the biotransformation of other mixture components. The individual PBPK models may then be linked together at the liver compartment by introducing competitive (or other) inhibition terms in the mass-balance differential equation. In our opinion, the application of PBPK modeling to toxicological interactions of chemical mixtures is necessary in cumulative risk assessment. However, this area is very complex, and it is still an emerging field. For a more thorough discussion, see the chapter on PBPK modeling of chemical mixtures in Reddy, Yang, Clewell, and Andersen (2005), as well as the chapter on the application of PBPK modeling in cumulative risk assessment in Yang and others (2006b). It should be emphasized here that PBPK modeling handles only part of the chemical mixture issue in cumulative risk assessment (i.e., the pharmacokinetic interactions at the whole body level). PBPK modeling must be integrated with "biochemical reaction network modeling" in order to go to the molecular interaction reaction network level, and further to the linkage with toxic end points to fully address the chemical mixture issue in cumulative risk assessment (Mayeno, Yang, and Reisfeld, 2005; Yang and others, 2006b, 2006c).

A research group led by Professor Kannan Krishnan, Université de Montréal, Canada, pioneered efforts in the PBPK modeling of more complex chemical mixtures. Earlier work from this group concentrated on interactions and PBPK modeling between two chemicals (Pelekis and Krishnan, 1997; Tardif and others, 1995; Tardif, Lapare, Krishnan, and Brodeur, 1993). As progress was

made, these investigators began to build up the mixtures and devoted their efforts to PBPK modeling of more and more complex chemical mixtures (Haddad, Charest-Tardif, Tardif, and Krishnan, 2000; Haddad, Tardif, Charest-Tardif, and Krishnan, 1999; Tardif, Charest-Tardif, Brodeur, and Krishnan, 1997). So far, these investigators have successfully carried out PBPK modeling on the pharmacokinetic interactions on chemical mixtures involving up to five chemicals (Haddad, Tardif, Charest-Tardif, and Krishnan, 2000; Krishnan, Haddad, Beliveau, and Tardif, 2002); however, they have advanced the hypothesis that pharmacokinetic interactions of complex chemical mixtures, regardless of the number of components, may be predicted based on the PBPK modeling of binary mixtures of the component chemicals (Haddad, Charest-Tardif, Tardif, and Krishnan, 2000; Krishnan, Haddad, Beliveau, and Tardif, 2002). Thus, according to their concept, PBPK models for mixtures of any complexity can be created as long as the quantitative information on the mechanism of interaction for each interacting pair (e.g., competitive inhibition rate constant) is available (Krishnan, Haddad, Beliveau, and Tardif, 2002).

Applying the same approach created by Krishnan and coworkers, investigators in our laboratory have studied PBPK modeling of a ternary mixture of trichloroethylene (TCE), tetrachloroethylene (PERC), and 1,1,1-trichloroethane (methyl chloroform, MC) in rats and humans (Dobrev, Andersen, and Yang, 2001, 2002). Furthermore, Dennison, Andersen, and Yang (2003) in our laboratory characterized the pharmacokinetics of gasoline, a very complex mixture, in rats using an integrated PBPK modeling and lumping approach. The PBPK model tracks selected target components (benzene, toluene, ethylbenzene, *o*-xylene, and *n*-hexane) and a lumped chemical group representing all nontarget components. Competitive inhibition was the principal mechanism of pharmacokinetic interactions among these five selected target single chemicals and a pseudo-chemical from the lumped components. Computer-simulation results from the six-chemical interaction model matched well with gas uptake pharmacokinetic experimental data from single chemicals, a five-chemical mixture, and the two blends of gasoline. The PBPK model analyses indicated that metabolism of individual components was inhibited up to 27 percent during the six-hour gas uptake experiments of gasoline exposures.

The Current Status of PBPK Modeling of Chemical Mixtures

For a more comprehensive discussion of PBPK modeling of chemical mixtures, we refer you to Chapter Thirteen in a recently published book on PBPK (Yang and Andersen, 2005). Currently, the largest number of chemical components incorporated into a PBPK model is five individual chemicals and one lumped pseudo-chemical (Dennison, 2004; Dennison, Andersen, and Yang, 2003). Mechanistically,

competitive enzyme inhibition is still the prevalent toxicological interaction considered. As indicated earlier, K. Krishnan and his colleagues have advanced the idea that predictability of pharmacokinetic and pharmacodynamic consequences of chemicals in more complex chemical mixtures is possible as long as quantitative data in the literature on binary chemical interactions is available (Haddad, Charest-Tardif, Tardif, and Krishnan, 2000; Krishnan, Haddad, Beliveau, and Tardif, 2002). So far their approach has worked for the volatile organic chemicals that they studied. Whether or not this concept has a broader application to mixed classes of chemicals in a mixture remains to be evaluated.

Our current thinking is that PBPK modeling of chemical mixtures is limited in that it would not be possible, at least for the time being, to handle very complex chemical mixtures in a refined and predictive way. We believe that biochemical reaction network (BRN) modeling is a very important tool for helping us break out from such limitation, and we can envision the handling of very complex mixtures with the integration of PBPK and BRN modeling (Liao, 2004; Mayeno, Yang, and Reisfeld, 2005; Yang, Dennison, and Lipscomb, 2006a; Yang and others, 2006b, 2006c. Furthermore, BRN modeling brings us closer to toxic end points, thus, potentially bringing in pharmacodynamics of chemical mixtures into focus.

Predictive Toxicology for Chemical Mixtures: PBPK and Biochemical Reaction Network Modeling

In the last two sections, we introduce the term *biochemical reaction network* (BRN) *modeling*. Integrated with PBPK modeling, this is one approach in attempting to solve the problems of assessing chemical mixture toxicity. What is BRN modeling? How does it work? How is it integrated with PBPK modeling? How does it help to solve the problems of assessing chemical mixture toxicity? Although more detailed answers to these questions are given elsewhere (Klein and others, 2002; Liao and others, 2002; Mayeno, Yang, and Reisfeld, 2005; Reisfeld and Yang, 2004; Yang, Dennison, and Lipscomb, 2006a; Yang and others, 2006b, 2006c), here we provide a brief discussion of these subjects.

BRN modeling had its origin in chemical and petroleum engineering. It was successfully employed in computer modeling and simulation of the complicated processes in oil refineries. In the chemical or petroleum engineering field, a *reaction network* (RN) model is a tool that is used to predict the amounts of reactants, intermediates, and products as a function of time for a series of coupled chemical reactions (potentially numbering in the tens of thousands of reactions). The reaction network itself is the interconnected, time-dependent series of reactions

that occur in the system. In toxicology of chemical mixtures, we transplant the concepts and technology of RN modeling to examine biochemical reaction networks associated with the toxicological processes in an organism upon exposure to toxicants. To bring into focus the role of biochemical reaction networks in relation to the molecular events leading to toxicological changes in the body, the fundamental biological processes involved are as follows: First, mRNA, through the process of transcription, is derived from DNA (genomics). From mRNA, through the process of translation, proteins are formed (proteomics). Enzymes are functional proteins that catalyze reactions, creating biochemical reaction networks (i.e., different pathways). The toxicants, once in the body, can affect any of the steps described above. Furthermore, these toxicants undergo metabolic transformations themselves by the enzymatic pathways existing in the body, and some of their metabolites, being reactive species, become new toxicants. The outcome of the dynamic balance of all these biochemical reaction networks (*metabonomics* for intrinsic chemicals and *xenobiotic metabolomics* for extrinsic toxicants) determines the cellular physiology and toxicology. The term *biochemical reaction network* (BRN) *modeling* was principally derived based on the above description of biological events.

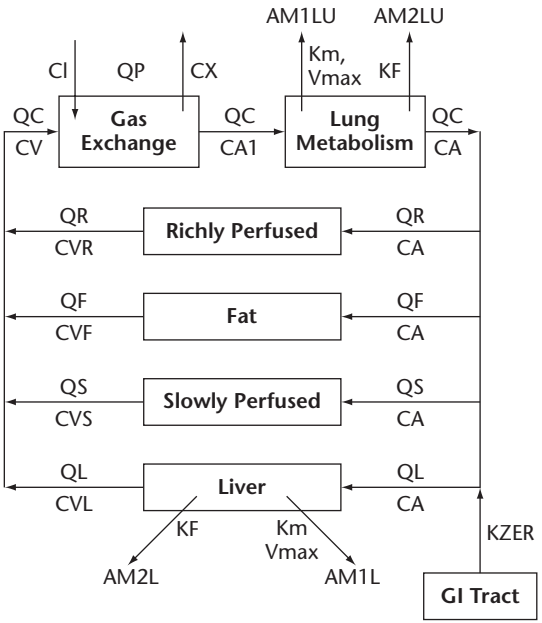
How does the BRN modeling work? How is it integrated with PBPK modeling? How would it solve the problems of assessing or predicting chemical mixture toxicity? The essential idea is that the BRN model software takes, as input, specifications for the reactants (usually in terms of their chemical structures), as well as the enzymes (or other catalysts) involved. Inherent in the virtual enzymes used in the modeling software are certain reaction rules, stipulating the nature of the relevant chemical and biochemical reactions. Algorithms within the software develop the associations between chemical species and create and solve the controlling kinetic equations in the reaction model. Thus, the output from the simulation is formed by the detailed metabolic pathways (biochemical reaction networks) showing the interconnections between the metabolites as well as the concentrations of all of these chemical species over time. As more and more information (e.g., chemical properties, chemical reaction mechanisms) is entered into the databases of the BRN model software, the predictive power of the software increases. At some point, the BRN model grows to the stage where it can accurately predict the biochemical reaction networks of a chemical mixture, be it simple or complex. An investigator can examine the nature and lifetimes of species of interest and, in the context of health risks, easily locate highly reactive species. Moreover, due to its design and flexibility, information can be fed back and forth between the BRN model software and lower-level (e.g., molecular-level such as gene and protein expression) and higher-level (organ/organism-level) modeling tools such as gene network modeling or PBPK modeling to give a more complete picture of the risk.

Application of PBPK Modeling in Dichloromethane Risk Assessment and Its Recent Development in Bayesian Population Approach

Dichloromethane (DCM, methylene chloride) is a volatile organic solvent used in decaffeinating coffee and in the textile and pharmaceutical industries, as well as in paint stripping and metal degreasing. Animal studies in the early to mid-1980s implicated carcinogenic potentials of DCM in mice (National Toxicology Program, 1986; Serota and others, 1986a, 1986b). The initial cancer risk assessment, carried out by the EPA, was based on administered dose from drinking water studies in mice (Serota and others, 1986a, 1986b), and exposure concentrations in inhalation studies (National Toxicology Program, 1986). In 1987, Andersen and others (1987) calculated internal dose (i.e., target tissue dose) using PBPK modeling based on mechanisms of biotransformation and incorporated PBPK modeling into the cancer risk assessment process. Their conceptual PBPK model for DCM is shown in Figure 5.3; it is quite similar to the PBPK models shown in Figures 5.1 and 5.2.

Two metabolic processes were considered for both the liver and the lungs: the oxidative pathway involving cytochrome P450 (CYP) 2E1 (AM1L and AM1LU in Figure 5.3), which follows Michaelis-Menten saturation (nonlinear) kinetics, and a glutathione *S*-transferase (GST) pathway (AM2L and AM2LU in Figure 5.3), which follows first-order (linear) kinetics. Reactive metabolites formed from these respective processes include formyl chloride and chloromethyl glutathione based on mechanistic understanding. The PBPK model was constructed and calibrated using datasets from a series of gas uptake pharmacokinetic studies conducted in their own laboratory (Andersen and others, 1987), and model validation was carried out using four different sets of data under a variety of experimental conditions; these included human experiments, as well as studies published by different investigators (Angelo, Bischoff, Pritchard, and Presser, 1984). Using the resulting DCM PBPK models for mice and humans, Andersen and his colleagues performed extensive computer simulation in mice under the experimental conditions of cancer bioassay studies, as well as extrapolations to humans under similar exposure conditions. Based on their calculated internal dose (target tissue dose) and in comparison with the tumor incidence data from the cancer bioassays (National Toxicology Program, 1986; Serota and others, 1986a, 1986b), they concluded that the GST pathway is the critical one producing carcinogenic metabolites. Furthermore, based on their analyses, they suggested that the conventional linear-extrapolation risk analyses conducted by the EPA greatly overestimated (by about 140- to 170-fold) the risk of DCM in humans. In many ways, the Andersen study (1987) created a scientific revolution in the risk assessment process. The EPA fol-

FIGURE 5.3. A GRAPHIC OR CONCEPTUAL PBPK MODEL FOR DICHLOROMETHANE.



Source: Adapted from Andersen and others (1987).

lowed up on the incorporation of PBPK modeling into the DCM risk assessment; after extensive internal and external deliberations, the EPA adopted the use of PBPK modeling in DCM cancer risk assessment. Subsequently, in 1991 the unit risk factor for DCM in the EPA Integrated Risk Information System (IRIS) was updated to reflect the incorporation of PBPK modeling; that is the first instance of the application of PBPK modeling by the EPA in cancer risk assessment (Marino and others, 2006).

In the meantime, scientific deliberations and advancements were made in the application of PBPK modeling to risk assessment, particularly in the coupling of Monte Carlo simulation with PBPK modeling to address the issue of variability, not only in DCM (Clewell, 1995; Portier and Kaplan, 1989; Thomas and others, 1996b), but also in other chemicals (El-Masri and others, 1996; Thomas and others, 1996a). In these studies, the utilization of Monte Carlo simulation with PBPK modeling produced distributions of internal doses rather than point estimates, thereby reflecting variability in input parameters. In addition, in one study

(Thomas and others, 1996b) where pharmacokinetic studies were conducted in parallel with a two-year chronic toxicity study, PBPK/Monte Carlo analyses provided kinetic changes in mice in relation to age and acute, subchronic, and chronic inhalation exposure.

Two other developments related to DCM risk assessment are notable and both emphasized a population approach (El-Masri, Bell, and Portier, 1999; Sweeney, Kirman, Morgott, and Gargas, 2004). El-Masri and colleagues (1999) considered genetic polymorphism of glutathione-*S*-transferase theta 1 (GSTT1) in human as this is the specific enzyme responsible for the biotransformation of DCM to formaldehyde which, in turn, causes DNA-protein crosslinks (DPX) or formaldehyde RNA adducts in mouse liver (Casanova, Bell, and Heck, 1997). Since the frequency of the GSTT1 homozygous null genotype ranges from 10–60 percent in different ethnic and racial populations around the world, El-Masri, Bell, and Portier (1999) studied how varying GSTT1 genotype frequencies would impact cancer risk assessment using Monte Carlo simulation and PBPK modeling. These investigators carried the internal dose a step further by estimating the DPX as the target tissue dose metric. Their studies revealed that the average and median risk estimates were 23–30 percent higher when GSTT1 polymorphism was not included in the model simulations. Thus, in the specific case of DCM risk, inheritance of a GSTT1 null genotype is protective because the GSTT1 enzyme is necessary for bioactivation of DCM (El-Masri, Bell, and Portier, 1999). In the other development of DCM risk assessment, Sweeney, Kirman, Morgott, and Gargas (2004) revisited the original PBPK model on DCM (Andersen and others, 1987) by re-analyzing a set of previously published (DiVincenzo and Kaplan, 1981) human pharmacokinetic data for DCM. Even with a relatively small sample size of 13 individuals, Sweeney and colleagues were able to detect a bimodal distribution of CYP2E1 with varying V_{maxC} values ranging from 7.1 to 23.6 $mg/hr/kg^{0.7}$. Furthermore, Sweeney and colleagues (2004) indicated that extrahepatic CYP2E1 metabolism is important and should be incorporated into the PBPK model for DCM since CYP2E1 protein and RNA have been detected in human bone marrow, esophageal mucosa, small intestine, blood lymphocytes, bladder, pancreas, brain, and kidney.

The Bayesian population approach to PBPK modeling is another important recent development, which is currently one of the most active scientific activities in PBPK modeling, particularly with respect to DCM risk assessment. Pioneering efforts on Bayesian population approach to toxicology, particularly in PBPK modeling, are from F. Bois and colleagues (Bernillon and Bois, 2000; Bois and others, 1996; Bois, Jackson, Pekari, and Smith, 1996), El-Masri and colleagues (1999), and F. Jonsson and colleagues (Jonsson, 2001; Jonsson and Johanson, 2001a, 2001b, 2003). A dissertation by F. Jonsson at Uppsala University in Sweden pro-

vides a very nice discussion on PBPK modeling in risk assessment and the development of Bayesian population methods (Jonsson 2001). The Bayesian population approach may best be explained by a passage from a 2003 publication by Jonsson and Johanson (Jonsson and Johanson 2003):

> In a Bayesian analysis, the inclusion of previous knowledge is a fundamental and integrated part of the modeling process. The knowledge of model parameters before taking the present experimental data into account is quantified by assigning probability distributions, so-called "priors" to the parameters. These distributions are subsequently updated with regards to the data at hand. The resulting, so-called "posterior probability distributions", or "posteriors" for short, are consistent with both the experimental data and the priors, as the posteriors are derived as the product of the likelihood of the data and the prior probability of the parameters.

Until the early 2000s, Bayesian analyses were hampered by limitation of available methodologies. However, the advent of Markov Chain Monte Carlo (MCMC) methods overcame a number of the difficulties and these powerful methods, along with the availability of MCSim, a software in the public domain, greatly contributed to the recent surge of Bayesian analyses in PBPK modeling (Bois, 2001; Bois and others, 2002).

Marino and others (2006), in their recent revised cancer risk assessment of DCM using Bayesian PBPK modeling, indicated that Bayesian population approach offers a number of advantages. These include: (1) the utilization of data and computer simulations from previous modeling efforts as starting points (priors) for current model calibration; (2) the capability to update multiple variables simultaneously using a hierarchical model, rather than varying one parameter at a time while holding others constant as is typically done in optimization process in PBPK modeling; (3) the ability to separately consider parameter variability and uncertainty in model calibration; and (4) the capacity to account for covariance of PBPK model parameters without the risk of incorrectly assuming all variables are independent. In the Marino and others (2006) paper and the companion publication (David and others, 2006), DCM cancer risk assessment reaches a new height with their Bayesian PBPK modeling approach. These investigators used "priors" from Andersen and others (1987) and the earlier Bayesian modeling of DCM in mice from the U.S. Occupational Safety and Health Administration (OSHA) (1997) and demonstrated the dramatic improvement of Bayesian PBPK modeling results of DCM in mice between using prior values vs. posterior values (Marino and others, 2006). Further dose-response modeling was carried out and the results show that internal doses from the calibrated mouse model are 3- to 4-fold higher than

values used by EPA to derive its current unit risk factor for DCM. David and others (2006), subsequently, extrapolated the DCM PBPK model to human and metabolic data for individual subjects from five human studies were used to derive population values using MCSim. The human PBPK model, calibrated with the population values, was used to perform a cancer risk assessment for DCM. The risks of cancer from exposure to 1 $\mu g/m^3$ DCM over a lifetime (i.e., the unit risks) were estimated using the calibrated model. Taking into consideration of genetic polymorphism for GSTT1 metabolism, the unit risks range from 0 (for GSTT1 −/−) to 2.70×10^{-9} at the 95 percentile. The median (50 percentile) is 9.33×10^{-10}, which David and others (2006) pointed out to be 500 × lower than the current EPA unit risk of 4.7×10^{-7} estimated from an earlier PBPK model.

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CHAPTER SIX

PROBABILISTIC MODELS FOR CHARACTERIZING AGGREGATE AND CUMULATIVE RISK

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Learning Objectives

Students who complete this chapter will be able to:

1. Demonstrate the concept of total exposure from all pathways (*aggregate exposure*) for individual chemicals using deterministic models
2. Explore methods for the assessment of multipathway exposures and chemical mixtures using organophosphate pesticide exposure in children to illustrate the key concepts
3. Explain the rationale for probabilistic assessments, and review the statistics needed to understand the process
4. Explore methods for assessing risks from multiple chemicals (cumulative risk)

One of the thorniest problems in risk assessment is how to characterize the risk from all the different chemical exposures we experience in a day. Common daily activities, such as eating, showering, commuting, working, and recreating, bring everyone in contact with many of the more than eighty thousand chemicals in commerce today. Moreover, all of us have measurable body burdens of many persistent compounds, such as DDT and its breakdown products, which remain in our bodies for years. We are also periodically exposed to many nonpersistent compounds such as herbicides and insecticides, which have relatively short half-lives

in the human body, typically on the order of days. Most of us are periodically exposed to these nonpersistent compounds as a result of their widespread ongoing exposure. We do not know the overall health impact of these compounds and their interaction with other types of chemicals that have varying effects. Although we have developed quantitative and qualitative risk assessment methods to assess their cumulative impact, the process is complex and the risks highly uncertain. It is a useful and necessary exercise to assess cumulative risk, however, because quantitative methods allow us to make informed decisions and discriminate between important and trivial risks, evaluate tradeoffs, set priorities, and allocate resources.

Although effective cumulative risk assessment is a much desired goal, relatively few assessments have been performed to date due to lack of appropriate data and models. In this chapter we use the example of children's exposure to pesticides to demonstrate key concepts and illustrate the complexities of the cumulative risk assessment process.

Pesticides are a good model because there has been increasing concern about their potential effects on children's health and because many pesticides are chemically related compounds that have similar mechanisms of action on the human body. Mounting evidence over the last twenty years from toxicological and epidemiological investigations indicates that children are more likely than adults to suffer adverse effects from pesticide exposure. As a result, it is now widely recognized that health risk assessments should take special account of children because they may be both more exposed and more biologically susceptible than adults. Children may be at greater risk because they have lower body weights, developing organs, higher metabolic rates, and unique behavior patterns. The importance of understanding children's exposure to pesticides was highlighted by the National Research Council (NRC) in its 1993 report, *Pesticides in the Diet of Infants and Children.* One consequence of the report was that the U.S. Congress passed the Food Quality Protection Act (FQPA) of 1996 (P.L. 104-170), which required that children's exposure to pesticides be evaluated for all potential pathways, both dietary (i.e., consumption of food and beverages) and nondietary (i.e., intake of pesticides in air, water, and soil or dust).

The FQPA codified the need for more and better exposure data to help in the process of risk-based decision making, and mandated aggregate (single chemicals via all routes) and cumulative (all chemicals with a common mechanism of action) assessments. The FQPA was one of the first acts to explicitly require a regulatory agency to conduct aggregate assessments of exposure to pesticides from multiple routes, namely, exposures by inhalation of airborne compound, dermal absorption of chemicals in contact with the skin, and ingestion of chemicals in both food and other materials that young children ingest, such as soil and house dust.

In this chapter we review the basic tools needed to conduct aggregate and cumulative exposure and risk assessments, beginning with the governing equations used in cancer and noncancer risk assessment to provide a context for the methods of assessing exposures to pesticides from all sources and pathways. We then present basic deterministic models used to assess exposure for each pathway and methods for aggregating exposures, illustrating these concepts with examples from a children's pesticide exposure study that measured pesticide exposure in multiple environmental media. We then discuss the limitations of measurements and the need for a probabilistic modeling process to perform more complex assessments needed to characterize cumulative risk, and review the statistics needed to conduct a probabilistic analysis risk assessment for both single and multiple chemicals. We apply these methods to the cumulative risk for compounds with a common mechanism of action, organophosphate (OP) pesticides. Finally, we highlight emerging Bayesian methods that provide a systematic way to incorporate expert judgment about uncertainties into the risk assessment process.

Organophosphate Pesticides

Organophosphates (OP) were developed during the nineteenth century, but their effects on insects and mammals were not discovered until 1932. Forty OPs are registered for use in the United States; some are very hazardous, but all are relatively nonpersistent in the environment. OPs affect the nervous system by altering the efficacy of the enzyme cholinesterase, which breaks down the neurotransmitter acetylcholine at nerve synapses. Nerve impulses or neurons remain active if not properly controlled by cholinesterase, which causes overstimulation of the affected nerves and muscles and may result in some of the classic symptoms of OP poisoning such as salivation, muscle weakness, or paralysis.

The OP pesticides are used to kill pests on a variety of crops, ornamental plants, in lawn care, and in residential and commercial buildings. Since 2001, many of their residential uses have been restricted in the United States because of concerns about their potential health effects on children. Under toxicological guidelines determined by the USEPA, all OPs are considered to have *common mechanism of action;* that is, they are toxicologically similar in their mechanism of action on humans. The upshot of this determination for risk assessment purposes is that their doses can be added together once differences in potency between compounds has been adjusted for.

Basic Risk Assessment Equations for Cancer and Noncancer Assessments

At the most fundamental level, human health risk assessments fall into one of two categories: those assessing cancer or those assessing noncancer (or systemic) risks. Today many international (e.g., WHO), federal (e.g., EPA, FDA), and state agencies use quantitative risk assessment as a basis for regulatory decisions about chemical mixtures. Chapters Two and Four present methods of assessing risks to individual compounds, which serve as the necessary first step in these assessments.

Cancer risk is typically estimated by developing estimates of "lifetime excess cancer risk," which is typically presented as the increased probability of developing cancer as a result of the exposure in question. Lifetime excess cancer risk is typically calculated using the following equation:

$$R = LADD \times SF \tag{6.1}$$

where *R* is Risk, a unitless probability (e.g., 10^{-5} = 1 in 100,000), LADD is lifetime average daily dose (typically, mg/kg-body weight per day), and SF is the Slope factor that is an upper bound estimate of carcinogenic potency (typically, in units of $[mg/kg\text{-}bw/day]^{-1}$) developed from human or animal data. The output of this simple model is the upper bound estimate of the increase in cancer risk resulting from this exposure, but includes a number of simplifying assumptions that add uncertainty to the estimate but are intended to be conservative in the public health protective sense, meaning that they are more likely to overestimate than underestimate risk. Excess lifetime cancer risks are often reported as "X in a million." This is the likelihood that up to *X* additional people out of one million equally exposed people would contract cancer if exposed continuously (24 hours per day, 7 days a week, for an assumed lifetime of 70 years) to the specific concentration. This estimated risk is in addition to the baseline cancer cases that would occur more or less spontaneously over a lifetime in an unexposed population of one million people. Lifetime cancer risks are always calculated over the assumed lifetime of 70 years. To obtain an annual cancer risk estimate, one simply divides the lifetime risk estimate by 70.

Noncancer, or systemic, risks are assessed based on the assumption that a threshold exists for each toxicant, which means that there is some level of exposure that is without adverse effect. This level is dependent on the time frame of the question, but for many chemicals it is one day, although health benchmarks for shorter time periods may be necessary for compounds that exert effects over

shorter time periods. For single chemicals, these are typically expressed as a *hazard quotient* (HQ), which is the ratio of a potential exposure to a chemical to the level at which no adverse effects are expected. For a compound that is assessed over a single day, this may be mathematically defined as

$$HQ = ADD/HB \tag{6.2}$$

Where ADD is the *average daily dose,* and HB is a *health benchmark*, such as a *EPA Reference Dose* (RfD), *Concentration* (RfC), or some other point of departure, such as a LED_{10} (lower limit on the effective dose, 10th percentile). A HQ less than 1 means that no adverse health effects are expected as a result of exposure, and a HQ greater than 1 indicates that adverse health effects are possible. Because of the way most health benchmarks are developed, HQs cannot be translated to a probability that adverse health effects will occur. The practical upshot of this is that an HQ exceeding 1 does not necessarily mean that adverse effects will occur, especially if the population of exposed individuals is small or the range of human susceptibility is limited.

Noncancer risks can also be characterized by developing a margin of exposure (MOE), which is essentially the reciprocal of the HQ. A MOE is calculated by dividing an RfD, LED_{10} or some other toxicological point of departure by the actual or projected environmental exposure of interest.

$$MOE = HB/ADD \tag{6.3}$$

The benefit of this approach is that risk assessors can see how far actual or anticipated exposures are from levels thought to have adverse effects. As a rule of thumb, the larger the MOE, the lower the concern about that particular chemical exposure. The limitation of this and the HQ approach is that the result is a single number that does not represent uncertainty or provide information on the probability of an adverse effect.

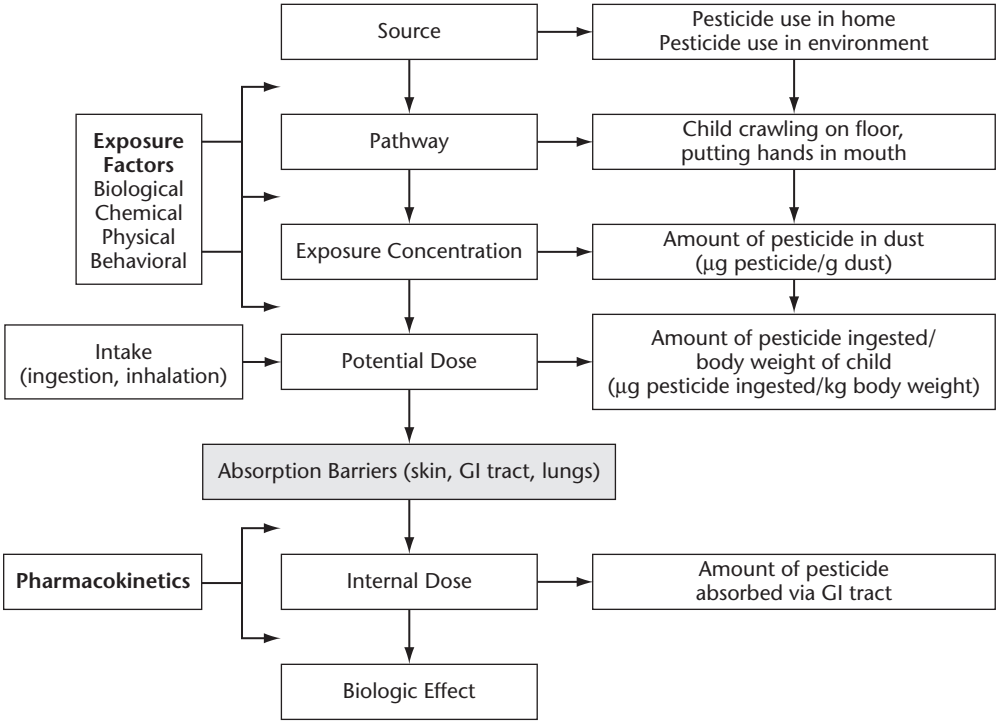
The basic parameters for calculating an HQ or MOE are health benchmarks and average or lifetime daily doses. In practice, these parameters are developed by regulatory agencies such as the USEPA (e.g., RfDs from the Integrated Risk Information System), or transnational bodies such as the World Health Organization. The other parameters, such as ADDs or LADDs, are typically developed on a case-specific basis for each assessment. The exposure assessment process is key to developing aggregate and cumulative risks. The next section reviews the types of information needed to develop ADDs in the context of a noncancer pesticide risk assessment.

Pesticide Exposure Assessment

Exposure is a deceptively simple concept. It is defined as *contact at a body boundary between a person and a chemical or some other environmental agent over time* (see Figure 6.1).

This simple definition masks the fact that a quantitative exposure analysis requires collection and analysis of multiple parameters, such as concentration and duration of exposure, as well as exposure factors that affect contact rates and therefore determine the magnitude of exposure. A description of exposure for a particular route (i.e., inhalation, ingestion, or dermal absorption) must include at least two related attributes: concentration of the pesticide in an environmental medium (e.g., air, soil, water) and the duration of contact. Therefore exposure to

FIGURE 6.1. THE EXPOSURE AND ENVIRONMENTAL HEALTH PARADIGM APPLIED TO PESTICIDE EXPOSURE ASSESSMENT.



Source: Hoppin and others (2006).

pesticides in the environment requires not only the presence of the pesticide, but also an individual to come in contact with the pesticide over a specific period of time. If there is no possibility of contact, there is no exposure. Dose, in contrast, is the amount within a biological boundary and is typically normalized to body weight or surface area.

Concentration is the amount of pesticide measured in a mass of volume of an environmental media. The residential exposure assessment example shown in Figure 6.1 is concerned with contact with residues found in dust and then subsequently ingested as a child goes about his or her age-appropriate activities. In this example, exposure concentration is expressed in units of mass of pesticide/mass of house dust (i.e., μg-pesticide/kg dust). In some cases such as surface-residue sampling, pesticide loading is the exposure metric used. Loading measures the amount of a chemical found over a unit area (e.g., μg-pesticide/cm^2) or per unit measured (e.g., μg/child's hand).

Frequency and duration of exposure are the final elements of a pesticide exposure assessment because these are used to determine the cumulative dose over time. *Frequency* describes the number of contacts over a specific time period (also called *contact rate*), and *duration* describes the lengths of these contacts. Exposures to pesticides typically vary over time with specific events, such as applications indoors or to nearby fields, appearing as spikes in an individual's exposure profile over time above an individual's background rate of exposure. This is an important issue once we begin aggregating exposures and combining compounds exposures over time and within the population, and we address this complexity further in the following sections. The key point to remember is that estimating an average exposure for an individual may underestimate the impact of peak exposure events.

Aggregate Exposure: Combining All Relevant Routes

Multipathway aggregate exposure assessments are performed to estimate exposures through all routes of exposure, i.e., food, drinking water, inhalation, and dermal exposure. This is important because many compounds move between environmental media as they move from their point of release to human contact with them. For example, the OP pesticide chlorpyrifos is semivolatile, meaning that if it is sprayed on a surface indoors, it can remain on the surface where it was applied; or it can volatilize and become airborne and thus be available for inhalation or dermal absorption if it is deposited on a new surface with which a child has frequent contact. To investigate all possible exposures to this compound, one needs to have estimates of the presence of the OP pesticide chlorpyrifos in all

relevant environmental media. To estimate aggregate exposure to any one compound requires information on concentrations in all relevant media, media intake rates, and the frequency and duration of exposure using the following equation:

$$PD = (C \times IR \times EF \times ED)/(BW \times AT \quad (6.4)$$

where PD (potential dose) is the estimated exposure, expressed as a potential intake per unit body weight (μg/kg-bw-d), C is the chemical concentration in the media in question (i.e., μg/kg in food or soil; $\mu g/m^3$ in air, or μg/L in water), IR is the media specific ingestion rate (i.e., kg/day, m^3/day, or L/day), EF is the exposure frequency (e.g., day/yr), ED is exposure duration (e.g., yrs/lifetime), BW is body weight (i.e., kg), and AT is averaging time (e.g., yrs × day/yr). This approach allows us to aggregate across multiple exposure pathways to obtain total exposure. It also serves as the basis for combining across chemicals to estimate cumulative exposure to compounds with similar mechanisms of action if relevant toxicological end points are available.

Developing an aggregate exposure assessment is a data-intensive process, however, and requires media measurements and potential dose data for all relevant pathways. The complexity of this process can best be demonstrated with an example from a large field study of pesticide exposure in children, the Minnesota Children's Pesticide Exposure Study (MNCPES) (Adgate and others, 2000). MNCPES simultaneously collected all the various measurements needed to quantify aggregate exposure to several OP pesticides. In the study investigators and participant families collected samples and other information needed to estimate aggregate exposure from all routes in a representative sample of 102 urban and rural children between ages 3 and 13 over four summer months. Using measurements of the OP chlorpyrifos from air, food, beverages, drinking water, surface dust, and soil, it was possible to aggregate across pathways by developing potential dose rates using the general equation presented above (see Clayton and others, 2003).

The data in Table 6.1 provide a snapshot of exposures to chlorpyrifos over one week in the MNCPES children and can be used to aggregate across the measured pathways. Table 6.1 shows the measurements collected in different environmental media, using different time scales based on available technology. Such studies depend on the willingness of the child participants and their caretakers to perform certain activities (i.e., wear a personal air sampler or provide duplicate diet samples). As with any human observational study, participants could refuse to participate in the collection of any sample type, so the number of measurements is unequal across media: investigators collected a soil sample in each home, but personal air sampling results are available for only sixty children. Table 6.1

TABLE 6.1. NUMBER AND TYPE OF ENVIRONMENTAL AND PERSONAL SAMPLES, MEASUREMENT DURATIONS, AND ANALYTICAL RESULTS FOR CHLORPYRIFOS AGGREGATE EXPOSURE ASSESSMENT.

Medium	Type of Sample	Units	*N*	Percentage Measurable	Median	90th Percentile
Personal air concentration	6-day IA	ng/m	60	95	1.58	11.7
Solid food concentration	4-day IA (duplicate diet)	µg/kg	96	57	0.53	1.26
Beverage concentration	4-day IA (duplicate diet)	µg/kg	101	0	NA	NA
Drinking water concentration	Grab sample	µg/L	55	2	NA	NA
Surface dust loading	Wipe, one time	ng/cm	99	62	1.15	1.33
Soil concentration	Surface soil, grab sample	µg/kg	102	3	NA	NA

Note: IA = integrated average.

also provides clues about the primary pathways of chlorpyrifos exposure. The percent measurable column indicates the media where the collected samples were above the detection or quantification limits, and shows that chlorpyrifos was absent or infrequently found in beverages, drinking water, and soil but was more frequently in soil, solid foods, and indoor and personal air samples. Table 6.1 also provides information on the range of measured values, showing both median (50th percentile) and 90th percentile values for personal exposures and media concentrations or loadings.

To assess the relative importance of all routes of exposure the next step is to convert the exposure measurements to potential dose (see Figure 6.1 and Table 6.2). For example, inhalation potential doses were computed by multiplying the personal air concentrations for the sixty subjects in Table 6.1 by an inhalation rate value from a standard reference source, the *USEPA Exposure Factors Handbook* (Environmental Protection Agency, 1997), and then dividing by the participant's reported body weight. The inhalation rates (m^3/day) used were 8.3 m^3/day for three- to five-year-olds of both sexes, 10 m^3/day for six- to eight-year-olds of both sexes, 13 (females) or 14 (males) m^3/day for nine-to eleven-year-olds, and 12 (females) or 15 (males) m^3/day for twelve- to fourteen-year-olds. Similarly, dietary ingestion potential doses were obtained by multiplying the mass of the duplicate-diet food and beverage samples by their respective concentrations (e.g., kg food × µg pesticide/kg

TABLE 6.2. CHLORPYRIFOS MEASUREMENT DISTRIBUTIONS FOR AGGREGATE ASSESSMENT.

		Distributional Statistics			
Medium	**Units**	***N***	**Percentage Detectable**	**Median**	**90th Percentile**
Food and beverage intake	ng/day	96	57	263	838
Personal air intake	ng/day	60	95	18.3	126
Partial aggregate intake	ng/day	57		304	648
Food and beverage intake	ng/kg-bw/day	95		10.3	29.5
Personal air intake	ng/kg-bw/day	58		0.67	4.95
Partial aggregate intake	ng/kg-bw/day	56		11.7	30.7

Source: Clayton and others, 2003.

food), and then these two masses combined to obtain a chlorpyrifos potential dose estimates for that route. This value was then divided by the number of days (usually four) represented by dietary sample, and then by the participant's reported body weight (BW) to obtain common potential dose units across all both pathways. In this example, the dermal pathway was not assessed because no dermal loading measurements were available to convert the surface-dust-loading values, and it was judged that exposure via this pathway for these children was relatively small compared to ingestion and inhalation sources. Similarly, the low percentage of detectable concentrations in the soil and drinking water samples meant that estimates were not derived for from these potential sources.

Table 6.2 summarizes the results of this aggregation process, with chlorpyrifos intake rates reported in units of ng/day and ng/kg-bw per day. The distribution of aggregate intakes is labeled *partial* because neither dermal nor nondietary ingestion is included, although these pathways are thought to be small relative to the inhalation and food-ingestion pathways. There are several notable trends in these data. First, chlorpyrifos was detectable much less frequently (57 percent) in solid food compared to personal air samples (95 percent). Nonetheless, comparison of the intake rates in Table 6.2 reveals that food ingestion is clearly the more dominant route of exposure. The solid foods are the source of the dietary exposure, as the beverage samples all were nondetects (and only one drinking water sample exhibited a measurable concentration). For the fifty-six participants for whom both an inhalation and an ingestion intake rate for chlorpyrifos were available, the median intakes were 11.7 ng/kg-bw per day and the 90th percentile was

30.7 ng/kg-bw per day. This demonstrates that the vast majority of the intake was from the ingestion route for most individuals.

Limitations of Aggregate Exposure Measurements

The example just shown demonstrates that it is possible to measure most of the relevant pathways and conduct a comprehensive aggregate assessment that provides an estimate of overall aggregate exposure; and valuable information can be gained from conducting such a study to develop ranges of children's exposures. It should also be clear, however, that this approach is data-intensive; while measurements are available for widely used compounds such as chlorpyrifos, the process becomes more difficult and uncertain if assessments consider less frequently used compounds. As there are forty OP compounds in commerce, and thousands of chemicals in use, we can see that it quickly becomes impossible to measure all routes and pathways. Last, the question of how to extrapolate these results to other populations with different behaviors, ages, or living in different climates makes it clear that aggregate assessment models must incorporate this complexity into their exposure estimates as well.

Although these results are uncertain because we lacked information on how to estimate exposure for some routes, they are most likely reliable enough for decision making, and have the advantage of having been collected from a single population that was randomly sampled. Other assessments typically derive aggregate exposure estimates by combining data from different sources to derive point estimate values: the final daily dose estimate is developed by adding together estimated exposures for dermal contact, dietary and nondietary intake, and inhalation. This is typically called a *deterministic model*, meaning that the various exposures added are point estimates and each is added without any distribution or statistical error term and therefore does not reflect any measurement error or underlying uncertainty.

Uncertainty is present in all risk assessments, and it occurs because of a lack of knowledge. For example, a risk assessor can be quite certain that different people breathe at different rates but not know how much rates vary from person to person. The lack of knowledge can be reduced by collecting more and better data, but these uncertainties cannot be eliminated. Gathering data will characterize variability, which reflects heterogeneity and is an inherent property of the population being evaluated. For example, in the MNCEPS population, two individuals may breathe the same concentration of an airborne pesticide at different rates, introducing variability into their pesticide intakes. More data collection can help to characterize variability, but will not reduce or eliminate uncertainty. Efforts to clearly distinguish between variability and uncertainty are important for both risk assessment and risk characterization, and are especially important as we turn to

methods for modeling cumulative risks. This is accomplished most commonly by using stochastic models that employ a large number of trials to develop probabilities of an event such as exceeding a particular risk threshold within a defined population.

Probabilistic Models for Characterizing Uncertainty

The discussion of the various risk models in the previous section has tacitly assumed that the input parameters to the cancer and noncancer risk metrics, such as RfDs, Slope Factors, and Average or Lifetime Average Daily Doses (ADDs or LADDs), are known precisely. Thus, if there is a given set of input parameters, there is one value of the output for the model. Precise knowledge of the values of the multiple-input parameters, however, is impossible, and therefore the output of these models can only be known with some amount of uncertainty. Consequently, selecting one value for each of the input parameters is inadvisable and does not represent uncertainty in a systematic way. It is better to find a way to represent the uncertainty in the input parameters and consider how this uncertainty leads to uncertainty in our risk estimates. To better understand this process, we next review probability theory and statistical distributions and lay the groundwork for a later discussion on propagation of variability and uncertainty in aggregate and cumulative risk models.

Nature of Probability

The *classical* or frequentist view of probability is an empirical one and one you have most likely already encountered in introductory statistics courses. In this view, the probability of an event occurring in any one trial is the frequency with which it occurs in multiple similar trials. For example, if we measure the concentration of an air pollutant every hour, we will have a reasonably good idea of the numerical value of the next measurement or, in probabilistic terms, the probability of the next measurement increasing or decreasing from the observed central tendency.

In many situations, however, there is no such population of trials and/or it is not clear what the relevant population of trials should be. For example, we may want to estimate air, water, or soil concentration of a pesticide in the absence of any previous measurements. In this case, while we may be able to provide a range of values that we think are a likely or even most likely value, they are subjective descriptions of our state of knowledge about media concentrations. This is a subjective, personal view of probability that is often applied as professional judgment in risk assessment but is often not sufficiently acknowledged. It is important to remember that even though such probabilities are somewhat subjective, the proba-

bility assignments are not completely arbitrary. They still need to be consistent with the axioms of probability. For example, if we assign a probability p that an event X will occur, then we must assign a probability $(1 - p)$ that X will not occur.

Sources of Uncertainty

There are three main categories of uncertainty: (1) *environmental or natural variability* or variation in the levels of some quantity, e.g., exposure variability over time and space and between individuals; (2) *sampling and analytical variability* or random errors in the collection and analytical method used to measure some parameter, e.g., an air concentration of a pesticide; and (3) *incomplete scientific or technical knowledge.* The first two kinds of uncertainty can be characterized using sampling statistics. However, in many instances uncertainty arises because "we don't know what we don't know." In most risk assessment scenarios, this third type of uncertainty dominates the overall uncertainty. When classical statistics is unable to cope with such situations, a personalist or *Bayesian view* of uncertainty becomes increasingly important.

Quantifying Uncertainty. Let us assume that we want to measure some parameter x and we have identified all sources of systematic error and reduced them to an insignificant level. We make N measurements of the variable x, and obtain the values $x_1, x_2 \ldots, x_N$. What is the best estimate of the variable x given our measurements? The answer is that the best estimate depends on the nature of the distribution of the parameter values. If the parameter is the concentration of pesticide in air in a given environment obtained from repeated measurements under constant conditions, then the measurement value will be symmetrically spread around a central value and for such measurements the best estimate of x is usually the *arithmetic average* of the N observations.

$$\bar{x} = \frac{x_1 + x_2 + \ldots + x_N}{N} = \frac{\Sigma x_i}{N} \tag{6.5}$$

If the parameter is the exposure of individuals in a neighborhood to the same pesticide in air, then the *median* concentration is likely a better representation, where the median is the middle value when all the measurements are ordered from the least to the highest value.

Instead of summing over all the measurements, we can sum over all different values obtained, multiplying each value by the number of times it occurred, that is,

$$\bar{x} = \frac{\sum_k x_k n_k}{N} \tag{6.6}$$

Further, since n_k/N is the fraction of times that each value occurred, we can express the above as

$$\bar{x} = \sum_k x_k F_k \tag{6.7}$$

where $F_k = n_k/N$. The fraction F_k specifies the *distribution* of the values in our sample.

Table 6.3 is an example of data for one hundred observations of a parameter divided into ten range bins shown in the first column; the second column shows the number of observations in each of the ten ranges, and the third, the fraction of the number of measurements in each bin. For example, 0.26 of the observations (26 percent) are between four and five. Similarly, the cumulative fraction column indicates that 0.99 (or 99 percent) of the values are less than 8.

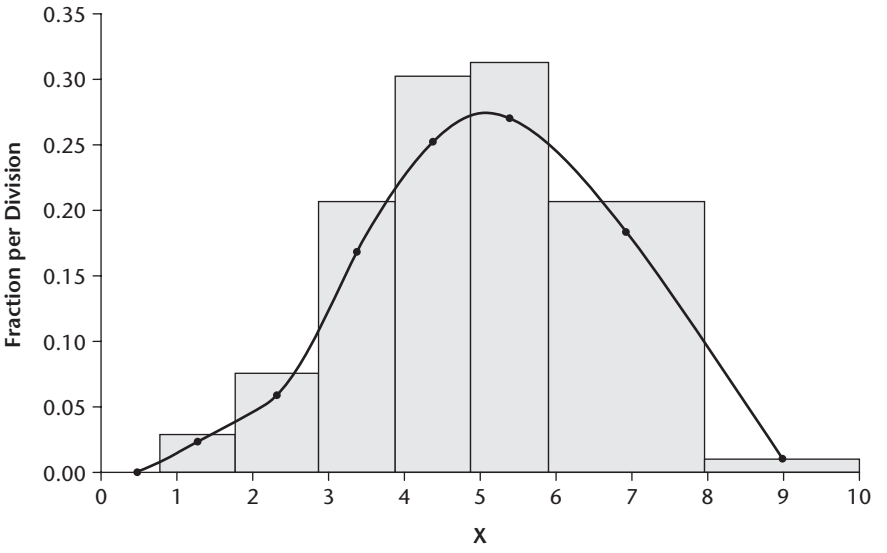
The grouped data can be plotted as a bin histogram as shown in Figure 6.2. Here the fraction of measurements in each interval is equal to the area of the rectangle above the interval. The height f_k is chosen such that the area $f_k \Delta_k$ is equal to the fraction of measurements in the k^{th} interval. Thus, the total area under all the intervals is equal to unity, that is,

$$\sum_k f_k \Delta_k = 1 \tag{6.8}$$

TABLE 6.3. EXAMPLE DATASET WITH 100 OBSERVATIONS OF A RANDOM VARIABLE.

Range	Number	Fraction	Cumulative Fraction
0 to 1	0	0	0
1 to 2	3	0.03	0.03
2 to 3	7	0.07	0.1
3 to 4	18	0.18	0.28
4 to 5	26	0.26	0.54
5 to 6	27	0.27	0.81
6 to 7	13	0.13	0.94
7 to 8	5	0.05	0.99
8 to 9	1	0.01	1
9 to 10	0	0	1
Total =	100		

FIGURE 6.2. BIN HISTOGRAM SHOWING THE DISTRIBUTION OF A RANDOM VARIABLE *X*.



Note: The area of each bin is the fraction of observations in that range.

When the total number of measurements is small, then the bin size must be chosen with care. Too wide a bin width and we might end up with just one bin into which all measurements fall; too narrow a bin width, and the histogram will contain a number of intervals with just one measurement (and therefore the same height). As the number of observations increases, it is possible to choose increasingly narrower interval sizes.

As the number of observations approaches infinity and the bin width approaches zero, the bin histogram becomes a smooth, continuous curve. This is defined by a function $f(x)$ that takes the place of the factor f_k in the bin histogram. For an infinitely large number of observations, the fraction of observations in any small interval between x and $x + dx$ is $f(x)\,dx$.

Similarly, for a large number of measurements, the fraction of observations between $x = a$ and $x =$ b is the shaded area and is equal to the definite integral of $f(x)$, that is,

$$\int_a^b f(x)\,dx = \text{fraction of observations between a and b} \tag{6.9}$$

In other words, $f(x)dx$ is the probability that a single measurement of x will lie between x and $x + dx$. In this case $f(x)$ is called the *probability density function*. Likewise, the definite integral

$$\int_a^b f(x)\,dx$$

yields the probability that a single measurement lies between a and b. Similar to Equation 6.9, $f(x)$ is defined such that

$$\int_{-\infty}^{\infty} f(x)\,dx = 1 \tag{6.10}$$

that is, the probability of a measurement that is between $-\infty$ and $+\infty$ is one.

Suppose X is a random variable, that is, a quantity about whose value we are uncertain. Uncertain belief about the relative likelihood of the variable having different possible values can be represented by a probability distribution. Let x be a possible value that X might have. The probability distribution for X may be represented by its cumulative distribution function (CDF). This function gives the probability that X will be less than or equal to each possible value x:

$$\mathrm{F(X)} \equiv \mathrm{P[X} \le x] \tag{6.11}$$

The median of a random variable is a value such that there is a 0.5 probability that the actual value of the variable is less than that value. If the median is $X_{0.5}$, then

$$\mathrm{P[X} \le \mathrm{X}_{0.5}] \equiv 0.5 \tag{6.12}$$

The median is the fiftieth percentile (or 0.5 fractile) of a distribution. In general, the m fractile $\mathrm{X_m}$, of a distribution is a value such that there is a probability m that the actual value of the variable will be less than that value.

$$\mathrm{P[X} \le \mathrm{X_m}] \equiv m \tag{6.13}$$

The 0.25 and 0.75 fractiles are also called quartiles. The range $[\mathrm{X}_{0.25}, \mathrm{X}_{0.75}]$ is called the interquartile range. The upper tail of an exposure or risk distribution is often of interest for risk assessors, and these are typically the ninetieth or ninety-fifth percentiles of a distribution.

The probability density function (PDF) is the derivative of the CDF.

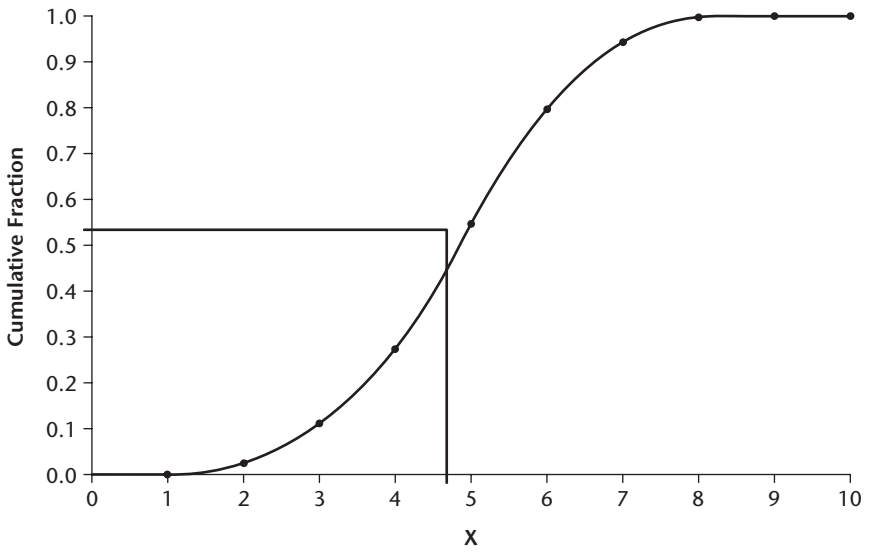
$$f(x) = \frac{dF(x)}{dX} \tag{6.14}$$

The PDF represents the density of probability so that $f(x)\Delta x$ is the probability that X is within the range $x—\Delta x/2$ to $x + \Delta x/2$, for a small increment Δx. The smooth curve in Figure 6.2 connecting the tops of the bins is an approximation to the probability density function representing the data in Table 6.3. The area under curve is unity. The cumulative distribution curve for the data in Table 6.3 is shown in Figure 6.3.

A PDF is often characterized by its summary statistics. The best-known are the mean (or expected value) of the distribution, which is defined as

$$\bar{x} = \int_{-\infty}^{\infty} x f(x)\, dx \tag{6.15}$$

FIGURE 6.3. THE CUMULATIVE DISTRIBUTION OF THE DATASET IN TABLE 6.3.



For the data in Table 6.3, the mean is 4.81. One representation of variability is deviation from the mean, which is defined as the standard deviation of the distribution,

$$\sigma_x = \sqrt{\int_{-\infty}^{\infty} (x - \bar{x})^2 f(x)\,dx} \tag{6.16}$$

where σ_x is the standard deviation. These reflect the amount of spread or dispersion in the distribution. For the data in Table 6.3, the standard deviation is 1.43.

Uniform Distribution. The use of uniform distribution is appropriate when we are able and willing to identify a range of possible values for some variable, but unable to decide which values within this range are more likely to occur than others. In Figure 6.4, the top left figure illustrates the uniform distribution where all values of the parameter between *a* and *b* are equally likely. The PDF and CDF are given, respectively, as:

$$PDF: f(x) = \frac{1}{b - a} \tag{6.17}$$

$$CDF: F(x) = \frac{x - a}{b - a} \tag{6.18}$$

Normal Distribution. If a measurement is subject to many small sources of random error and negligible systematic error, then the distribution of the measured values is described by a symmetric, bell-shaped curve that is centered on the true value of the variable. Random errors are equally likely to result in readings above or below the true value. If we have only random errors, then after many measurements the number of readings above and below the true value will be the same, and our distribution of results will be centered around the true value. The mathematical function that describes this curve is called the *normal distribution* or the *Gaussian distribution*. Two parameters describe the normal distribution—its center value or mean (μ), and its standard deviation (σ):

$$G_{\mu,\sigma}(x) = \frac{1}{\sigma\sqrt{2\pi}}\, e^{-\frac{(x-\mu)^2}{2\sigma^2}} \tag{6.19}$$

We know that the definite integral given by Equation 6.9 represents the probability that a given measurement lies between *a* and *b*. Using the normal function

$G_{\mu,\sigma}(x)$, we can calculate the probability that a measurement lies within Z standard deviations (i.e., $Z\sigma$) of the true center value μ as:

$$\text{Prob}\,(\textit{measurement is within} \pm Z\sigma \textit{ from } \mu) = \int_{\mu - Z\sigma}^{\mu - Z\sigma} G_{\mu,\sigma}(x)dx = \frac{1}{\sigma\sqrt{2\pi}} \int_{\mu - Z\sigma}^{\mu - Z\sigma} e^{-(x-\mu)^2/2\sigma^2}dx \tag{6.20}$$

This integral can be easily calculated using tables found in most books on elementary statistics, and is equal to the area under the curve between the two limits of integration. This distribution arises in many applications and is probably the most well-known distribution. Quantities that are formed by adding several uncertain quantities tend to be normally distributed. The probability density function takes on values over the entire range of real numbers.

Lognormal Distribution. If a random variable is lognormally distributed, then the logarithm of the random variable is described by a normal distribution. Thus, if X is lognormally distributed, then $\ln(X)$ is normally distributed. This distribution is a good representation for quantities that are constrained to being nonnegative, and are positively skewed, such as pollutant concentrations. It is appropriate for representing large uncertainties that are expressed on a multiplicative or order-of-magnitude basis, e.g., when X is known to within an order of magnitude (factor of 10). The lognormal distribution has a mathematical form analogous to the normal distribution.

$$f(x) = \frac{1}{x\ln(\sigma_g)\sqrt{2\pi}} \exp\left(-\frac{\left(\ln(x) - \ln(\mu_g)\right)^2}{2\ln^2(\sigma_g)}\right) \tag{6.21}$$

For a normal distribution, we can calculate the probability that a measurement lies within Z standard deviations (i.e., $Z\sigma_x$) of the true center value μ_x as the area under the curve between $\mu_x \pm Z\sigma_x$. For example, the area under the normal curve between $\mu_x \pm 1.96\sigma_x$ is 0.95. Similarly, for a lognormal distribution the intervals are of the form

$$\frac{\mu_g}{\sigma_g^Z} \text{ to } \mu_g\sigma_g^Z.$$

Thus, 95 percent of the area under a lognormal curve lies between

$$\frac{\mu_g}{\sigma_g^{1.96}} \text{ and } \mu_g \sigma_g^{196},$$

and 68 percent of the area under a lognormal curve lies between

$$\frac{\mu_g}{\sigma_g} \text{ and } \mu_g \sigma_g.$$

In this case 34 percent of the area lies between

$$\frac{\mu_g}{\sigma_g}$$

(the 16th percentile) and μ_g (the 50th percentile) while the other 34 percent lies between μ_g and $\mu_g \sigma_g$ (the 84th percentile). The geometric standard deviation is therefore the ratio of the 84th to the 50th percentile (or the 50th to the 16th percentile).

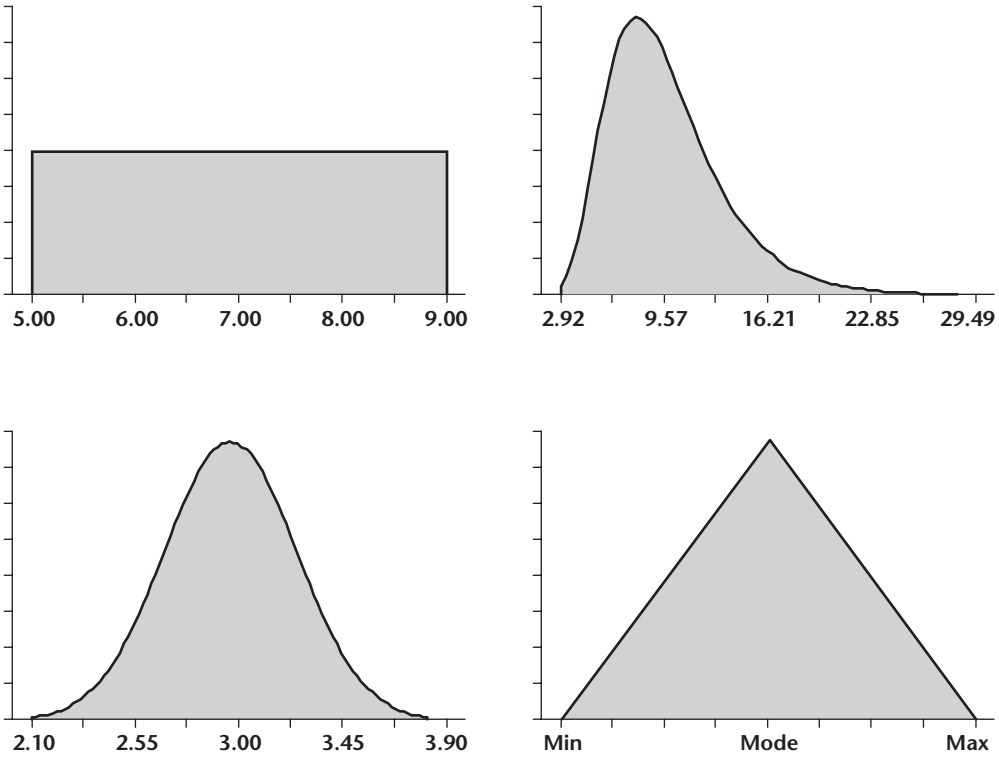
Triangular Distribution. This describes a situation where the minimum, maximum, and values most likely to occur are known. For example, we might describe the distribution of miles driven by a particular type of vehicle during a passenger-year, such as automobiles or SUVs using a triangular distribution. Figure 6.4 shows a pictorial depiction of a triangular distribution.

There are other distributions that are also useful for risk assessment purposes, but these four common distributions are the most useful for most exposure and risk assessments. Information on the mathematical properties of other distributions and their use can be found in the references at the end of this chapter.

Monte Carlo Sampling

Monte Carlo sampling is a powerful technique for propagating the uncertainties in the model inputs to determine the uncertainties in the model outputs. It can provide insights about the relative importance of the various assumptions and uncertainties in the model inputs and their effects on the final model output distribution. Monte Carlo analysis can also help in deciding whether it is worthwhile gathering more information to reduce uncertainty. Assigning distributions also may help avoid disputes over the best value chosen for point estimates, since the full range of pos-

FIGURE 6.4. EXAMPLES OF PROBABILITY DISTRIBUTIONS COMMONLY USED IN EXPOSURE MODELING.



sible results is considered. Most importantly, since it uses random number generation to combine distributions, Monte Carlo analysis produces a final output distribution of exposure or risk values, rather than a single point estimate.

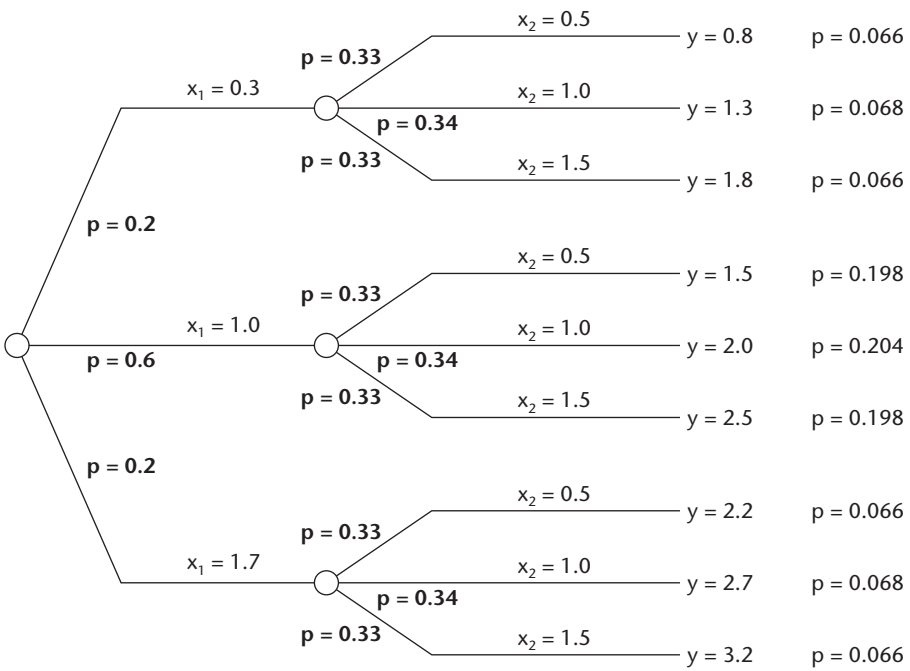
The conceptual basis for the need of error propagation in this process can be illustrated using a simple model where the output is a function of two input parameters. If y is a function of x_1 and x_2:

$$y = x_1 + y_2 \tag{6.22}$$

Both x_1 and x_2 can take only one of three possible values. But these values have different probabilities associated with them. Thus x_1 can only take the values of 0.3, 1.0, and 1.7 with probabilities of 0.2, 0.6, and 0.2 respectively. The

probabilities add up to 1.0. Similarly, x_2 can only take the values of 0.5, 1.0, and 1.5 with probabilities of 0.33, 0.34, and 0.33 respectively (adding up to 1.0). To investigate the possible interactions between the effects of all the inputs at various levels, one has to look at all possible combinations of input values. This is done by constructing a probability tree as shown in Figure 6.5. The uncertainty in the inputs can be expressed as a discrete probability distribution, with probabilities attached to each branch of the tree. Thus, y can take nine possible values. The probability of each value is obtained by the product of the probabilities of the two input variables: for example, y can take a value of 0.8 only if $x_1 = 0.3$ ($p = 0.2$) and $x_2 = 0.5$ ($p = 0.33$). Therefore, the probability associated with $y = 0.8$ is $P = 0.2 \times 0.33 = 0.066$. The probabilities of all the possible values that y can take also add up to 1.0. Figure 6.5 shows the values of the input variables and their associated probabilities. It also shows how the uncertainty in the two input parameters gets reflected in the uncertainty in the model output. While the example is illustrative, it does show the limi-

FIGURE 6.5. PROPAGATION OF UNCERTAINTY THROUGH A MODEL WITH TWO DISCRETE VARIABLES AS INPUT PARAMETERS.



tation in using such an approach when the input variables are continuous, or when there are more than two variables that can make more than three values each, since this is the case for nearly all phenomena, use of a deterministic probability tree comes unwieldy because the probability tree will have an infinite number of nodes and branches.

One way out of this quandary is to select a random sample of scenarios for evaluation, which is what happens in Monte Carlo sampling. Each scenario is generated by selecting each branch at a node according to its assigned probability. The branch values are generated from the underlying continuous probability distribution. The accuracy of Monte Carlo sampling can be improved by increasing the number of trials, but since the process depends on random combinations each trial is unique.

If there are some available measurements for an input parameter, such as pesticide concentrations in food, then we can estimate the mean and standard deviation of these measurements and represent the central tendency and dispersion of the concentrations using a normal or lognormal distribution. If, however, there is very little or no information regarding a parameter, then the probability distribution is a reflection of the subjective state of uncertainty or lack of knowledge on the part of the assessor. For example, if no information is available to estimate the dermal loading of a pesticide on a child's skin after a residential application but an expert tells us that based on its vapor pressure the loading can only vary between X and Y, with each value being equally likely, we can develop a uniform distribution. In this case, however, there is no population of measurements, and the estimate is subjective in the sense that it can vary from expert to expert.

Thus, in a Monte Carlo simulation each input parameter is represented as a probability distribution. A large number of independent sets (e.g., ten thousand) of input parameters are obtained by sampling randomly from their respective probability distributions. For each set of input parameters, a model output is generated by the simulation. Thus, ten thousand values of the output are obtained that can be plotted as a probability distribution (e.g., a histogram, PDF, or CDF). This represents the variability in the model output, and may also be used to reflect uncertainty if multiple trials are compared.

To demonstrate how Monte Carlo works we have created a simple example of a child consuming drinking water with a pesticide in it multiple times over a day. To perform this calculation we use a modified version of Equation 6.4, which reduces to

$$PD = (C \times IR \times EF)/(BW) \tag{6.23}$$

because we are assuming exposure over a single day (i.e., ED and AT are equal to 1 and thus are constants) for a two-year-old child. Table 6.4 assumes that the value of every parameter is equal to 10; that is, the environmental concentration

TABLE 6.4. DESCRIPTION OF VARIABLES USED IN DRINKING WATER EXPOSURE CALCULATION: AN EXAMPLE.

Value	Variable	Distribution	Units
10	Intake rate (IR)	Uniform	ml/hr
10	Concentration (C)	Lognormal	ng/ml
10	Exposure frequency (EF)	Triangular	hr/day
10	Body weight (BW)	Normal	kg-bw
100	Exposure		ng/kg-bw/day

(C) of the pesticide is 10 ng/ml, the child's water intake rate each time she drinks (IR) is 10 ml, that she drinks the water over a 10-hour period each day (EF), and that she weighs 10 kg. Plugging the values into the simple deterministic model above, $E = 10 \times 10 \times 10 / 10$, with a final deterministic value of 100 ng/kg-bw/day.

Now this example shows the intake rate over one day, but we have no representation of the variability in behavior, for example, what if she drinks 20 ml 15 times a day? Furthermore, what about other days or other children's intake rates or body weights, or situations where the pesticide concentration in water varies? To represent this variability and make the assessment more applicable to a larger population of children we can take the above assumptions and assign distributions to each variable, as shown in Figure 6.6. For example, intake rates can be assumed to have a uniform distribution, with each value between 5 and 15 equally likely, and the pesticide concentration to be log normally distributed with a standard deviation of 6.

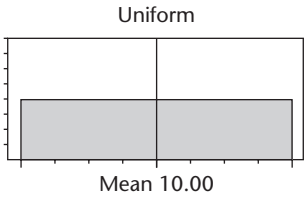
Having assigned these distributions, we can then conduct a Monte Carlo simulation by having a computer package, Crystal Ball®, randomly pick a value from each of these distributions and provide the final distribution based on ten thousand trials as shown in Figure 6.7. In contrast to the deterministic results, the simulation provides a range of values reflecting the variability of the inputs, with descriptive statistics. The mean value of the simulation is 107, with a standard deviation of 91.2 ng/kg-bw/day. As Figure 6.7 shows, the results of this distribution are right skewed with a median value of 83.3 and a range that extends from 5 to 1,354 ng/kg-bw/day. One way to think about these results is that they represent a population of ten thousand similar children with similar behaviors. Although the simple deterministic model gives us a similar answer, results of the simulation suggest that 100 ng/kg-bw/day is a slight overestimate, although one that a risk manager may find acceptable in the context of this specific risk assessment.

FIGURE 6.6. ASSUMPTIONS AND DISTRIBUTIONS FROM MONTE CARLO EXAMPLE.

Assumption: Intake Rate, Uniform Distribution

Uniform distribution with parameters:

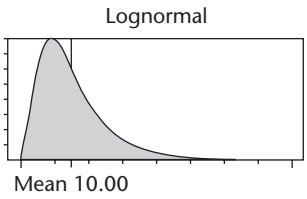
Minimum	5.00
Maximum	15.00



Assumption: Concentration, Lognormal Distribution

Lognormal distribution with parameters:

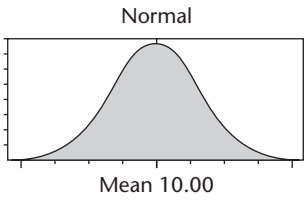
Mean	10.00
Standard Dev.	6.00



Assumption: Body Weight, Normal Distribution

Normal distribution with parameters:

Mean	10.00
Standard Dev.	2.50



Assumption: Exposure Frequency, Triangular Distribution

Triangular distribution with parameters:

Minimum	5.00
Likeliest	10.00
Maximum	15.00

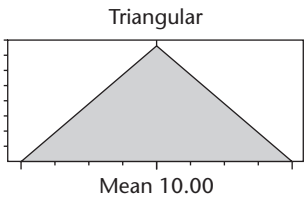
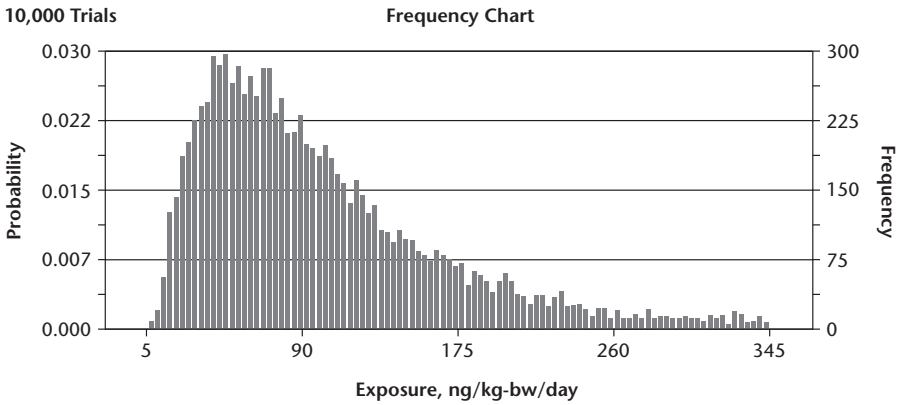


FIGURE 6.7. DISTRIBUTION OF EXPOSURE, IN NG/KG-BW/DAY, RESULTING FROM MONTE CARLO SIMULATION TRIAL.



Cumulative Assessment of Exposure and Risk

Aggregate assessments focus on individual chemicals with the goal to estimate if exposures by all routes are greater than "safe levels" represented by health benchmarks. These assessments typically consider all health endpoints and pathways of exposure. It is a necessary step in developing a cumulative assessment that sums over all pathways and chemicals. Cumulative assessments, in contrast, typically emphasize the most sensitive endpoint or toxic effect shared by a group of compounds with a defined mechanism of action. Chemicals are combined by developing measures that adjust the relative potency of all the chemicals to a common reference point within the group compounds considered. A cumulative assessment must also consider how often exposures to two or more compounds occur, and assign a likelihood to co-occurrence of compounds from the same common mechanism group on the same day. These concurrent exposures have toxicological and exposure related components. From a toxicological standpoint, cumulative assessments must address the issue of baseline exposure to common mechanisms chemicals over time, the critical window of exposure for effects to manifest themselves, and the time course of toxicity before the effect is potentially reversed by the process of detoxification. From an exposure perspective, there are regional differences in pesticide use that are reflected in varying temporal patterns for application in farm fields and outdoors and indoors around residences and other sites of application, all of which affect possible exposures.

The basic equations for cumulative risk are represented by extensions of the equations presented earlier. For example, a cumulative assessment of total lifetime excess cancer risk (R_T) can be calculated by simply summing the calculated risk for each compound:

$$R_T = LADD_1 * SF_1 + LADD_2 * SF_2 + \ldots\ldots + LADD_n * SF_n \quad (6.24)$$

where LADD is lifetime average daily dose, and SF is the slope factor representing compound specific potency. This is a simple summing of risks, however, and does not consider mechanism of action. More refined assessments would consider the target tissues and mechanism of carcinogenic action, as well as the upper-bound nature of many cancer slope factors.

Noncancer hazard quotients are summed in a similar manner, to develop a total Hazard Index (HI_T):

$$HI_T = ADD_1/HB_1 + ADD_2/HB_2 \ldots + \ldots ADD_n/HB_n \quad (6.25)$$

where ADD is average daily dose and HB is a health benchmark (e.g., RfD or LED10). Since different pollutants can cause similar health effects, it may be appropriate to combine hazard quotients for different substances. As a screening exercise HQs may be added to approximate the potential magnitude of a problem, but in a typical situation only compounds that act on the same target organ or organ system (e.g., a group of air pollutants that are all irritants), or by the same mechanisms of action, are included in a refined assessments (e.g., OP pesticides). As with the HQ, an HI of less than 1.0 will likely not result in health effects over a lifetime of exposure, but an HI greater than 1.0 does not necessarily mean that adverse effects will occur but rather indicate an increased probability of adverse effects. It is also possible to develop a total MOE for exposures from different routes or chemicals, based on the following equation:

$$MOE_T = 1 \,/\, (1/MOE_1 + 1/MOE_2 + \ldots 1/MOE_n) \quad (6.26)$$

where MOEs for each route of exposure (inhalation, ingestion, dermal absorption) or chemical are totaled to obtain an overall MOE_T.

These equations can be applied as deterministic point estimates, but numerous decisions go into this process, and expert judgment about various parameters is an important component of this process. A probabilistic approach is needed to reflect both variability and uncertainty inherent in this process, and Monte Carlo processes have been important tools in developing cumulative assessments. In developing a cumulative risk assessment for OP pesticides, EPA actually evaluated

three different models, all of which used stochastic processes to develop their risk estimates. The follow section summarizes some of the decisions that are needed to conduct such as an assessment, and provides examples of some of the key decisions, processes, and model outputs.

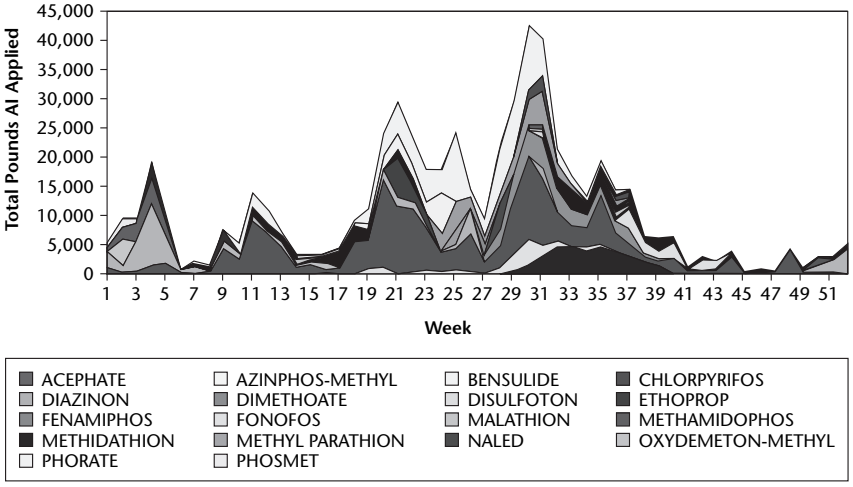
OP Pesticide Cumulative Assessment

The cumulative risk assessment for the group of OP pesticides serves as a good example of methods and decisions that need to be made to develop a risk estimate. There are four basic procedural issues in developing a cumulative risk assessment for a group of compounds that have been determined to have a common mechanisms of action: (1) how to aggregate exposures, (2) how to estimate the probability of concurrent exposure to two or more compounds in a group with a common mechanism of action, (3) how to define a common mechanisms of toxicological potency, and (4) how to combine the risks.

The first step in the process, aggregation of exposures, was described in the previous section and is conceptually summarized by Equations 6.25 and 6.26. The second step, the process of determining concurrent exposure, is complex, but is the general problem depicted by the data in Figure 6.8. This figure shows agricultural releases of OP pesticides in California in 2001, with the *x*-axis depicting time and the *y*-axis depicting pounds of chemicals released, with each OP depicted by a different color. Although this does not depict human exposure, it does show that the use of compounds varies considerably by crop cycle and season. Such data can be used to inform decisions on potential times and locations of exposure, and the impact of these releases will affect concentrations in outdoor air and water and food produced in these regions. The more difficult linkages in this process involve combining information like this with residential exposures, which may be seasonal but are not strictly linked agricultural practices. In the end, this process was governed by expert judgment about pesticide application rates and uses in the home and by a stochastic model applied to develop MOEs for dermal, food, water, inhalation, and nondietary ingestion pathways in different regions of the United States (Figure 6.9).

In the third step, defining a group sharing a common mechanisms of action, the USEPA considered the 40 OP pesticides that were registered for use in 2002 and determine that 29 of them could be compared for cumulative assessment. The remaining chemicals were excluded because the chemicals (1) were being phased out, (2) had no detectable residues on food or other products due to limited use, or (3) were only used in such a way that potential exposure to children was negligible (e.g., to kill mosquito larvae in brackish water or to kill pests on animals).

FIGURE 6.8. ORGANOPHOSPHATE CO-OCCURRENCE BASED ON USE IN CALIFORNIA.

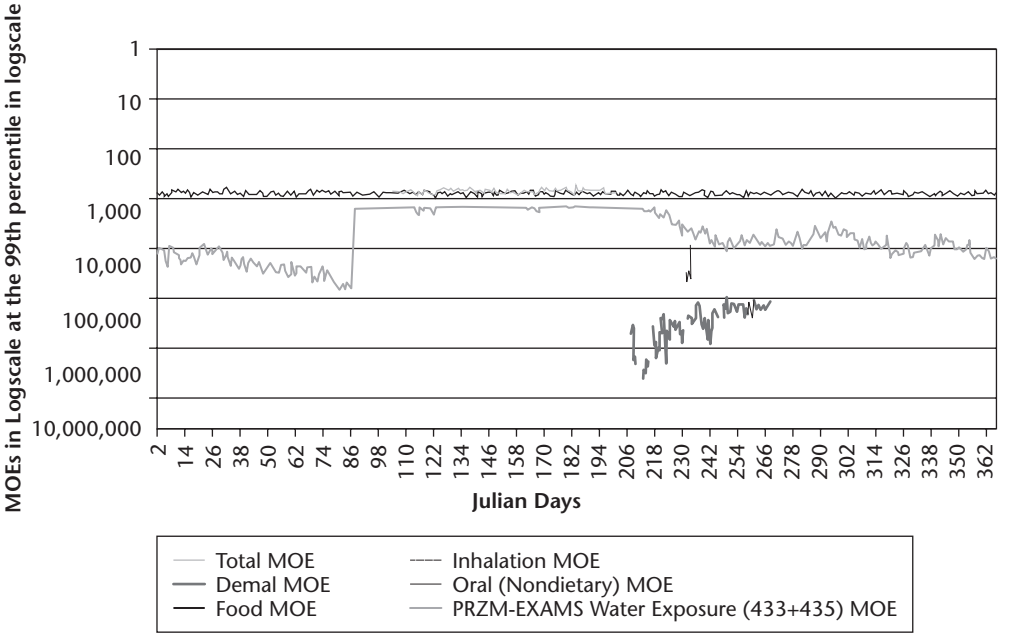


Source: Environmental Protection Agency (2002).

The next step was to determine if these 29 compounds shared a common mechanism of action. This was a lengthy process that is outside the scope of this chapter, but the process was based on a chemical-by-chemical evaluation of individual compounds by a group of experts, and is described in detail elsewhere (Environmental Protection Agency, 2002).

The final step in the process was to develop *relative potency factors* (RPFs) so that different compounds with data on the same toxic end point (cholinesterase inhibition) could be considered on the same scale. This was done by determining the potency of each chemical, selecting an index chemical, and then expressing each chemical's potency relative to the index chemical. In the USEPA OP assessment the compound methamidophos was selected as the index chemical, so its potency value was 1.0 for each exposure route. Chlorpyrifos, for example, was estimated to have only 10 percent of the potency of the index chemical via the oral route, so its RPF for that route was 0.1. After calculating the relative potencies for all 29 chemicals for each exposure route in the assessment, exposure concentrations were multiplied by each exposure of interest, such as residues on foods. This information, coupled with the data on concurrent exposures, allows the assessor to develop estimates of total cumulative exposure in units of the index chemical. Using food exposure for the two chemicals mentioned above as an example, total residues would be calculated by multiplying residue concentrations of methamidophos by 1.0, and residue concentrations of chlorpyrifos by 0.1, then adding these two

FIGURE 6.9. EXAMPLE OF A CUMULATIVE ASSESSMENT FOR OP PESTICIDES OVER ONE YEAR FOR A TWO-YEAR-OLD CHILD.



Source: Environmental Protection Agency (2002).

resulting values together to get total residues of all OP pesticides expressed as index chemical residues. Expanding across all co-occurrences and routes of exposure, the final cumulative assessment is then expressed in terms of a common metric.

Figure 6.9 is an example of the model output of one of the stochastic models that the USEPA used to assess OP risk. This particular assessment was one of many conducted for one- to two-year-old children, a group considered more highly exposed and susceptible, and was grouped by regions of the country to reflect region-specific product uses. Figure 6.9 shows how various pathways vary over the course of a year: drinking water exposures, for example, increase around Julian day 86, reflecting the start of the cropping season when compounds are applied and eventually run off fields and eventually enter the drinking water supply. Similarly, dermal and nondietary exposures are periodic events that add to the totals, but their estimated impact on the overall MOE_T appears to be small relative to food exposure, which has an overall MOE of between 1,000 and 100 and is a large percentage of the overall MOE_T.

Overall, the OP cumulative assessment process is complex and limited by available data and models that can be used to assess both exposure and risk. As a consequence, statistical models and judicious assumptions are necessary for addressing this problem because it is not possible to measure all possible exposure pathways or all parameters necessary to develop a comprehensive risk profile across the affected population(s). Understanding the impact of expert judgment on the selection of parameters is crucial to understanding the uncertainties inherent in the cumulative risk process. One way to assess the impact of expert judgment is through use of a Bayesian framework that makes explicit the incorporation of judgment into risk models.

Bayesian Statistical Framework

While many sources of information may be helpful in quantifying risk, usually no one source by itself will be sufficient. In such cases, it is important to leverage all the relevant information. Risk assessment based solely on sparse or no measurements leads to estimates with such large uncertainties as not to be useful for decision making. Additional inputs are needed to estimate risk from relatively sparse measurements. These additional inputs can take the form of expert judgments from professionals with relevant experience and insights, outputs from risk models, or some combination of the two. A Bayesian probabilistic framework can synthesize expert judgment, historical information, and incomplete or sparse measurements in order to estimate risk. This approach has the advantage of explicitly accounting for the relevant uncertainties and yields a probability distribution of the risk. Such an approach necessarily draws on findings from a wide variety of fields: the technical knowledge underpinning the risk scenario, uncertainty analysis, psychology of expert judgment elicitation, and decision making.

In the Bayesian view, a measurement process serves to refine previous knowledge of physical parameters by adjusting their probability distributions. It is thus based on inductive reasoning. Most risk managers are Bayesian practitioners (even if unknowingly) when they make initial educated guesses about exposures and risks that are subsequently refined by actual measurements. The Bayesian framework formalizes this commonsense approach to risk assessment. If the physical quantity of interest is represented by f and the measured data are represented by m, then the Bayesian expression for the updated probability distribution of f is

$$P_{post}(f/m) = \frac{P_0(f)P_L(m/f)}{P(m)} \tag{6.27}$$

where $P_0(f)$ is the probability distribution of f prior to making any measurements (the *prior*); $P_L(m/f)$ is the likelihood that, given the true value f, the measurement m is observed; $P(m)$ is the probability that the measurement m is observed; and $P_{post}(f/m)$ is the updated probability that the physical quantity of interest is f, given that measurements m are observed (the *posterior*).

The above framework is applicable to a situation where subjective inputs such as expert judgments about the probability distribution of a particular risk model parameter are to be synthesized with objective measurements of the same parameter. The updated probability will provide a better estimate (i.e., narrower probability distribution) of the parameter of interest than either the subjective prior probability provided by the experts or the objective—but sporadic and incomplete—measurements with wide error bars.

An estimate of the prior probability distributions, $P_0(f)$, of the model parameter of interest needs to be obtained using expert judgment coupled with deterministic risk models. The expert prior distributions are then refined using measurements to obtain posterior probability distributions of a model parameter, $P_{post}(f/m)$.

The experts are provided with an information packet that contains all the background information relevant to the risk scenario. Based on this information, the experts provide subjective probability distributions for input parameters to a risk model. This constitutes the prior estimate of risk. The prior distribution of exposure is refined or updated using measurements of some of the input parameters or the output parameter of the model. This is done using Bayes theorem.

Cumulative risk assessments are complex processes that can aid decision making. The use of Bayesian methods represents an emerging method for addressing the challenges inherent in the process and making the assessment and management of risks from multiple chemicals a scientifically defensible process.

Thought Questions

1. The EPA oral reference dose for chlorpyrifos is 3 μg/kg-bw/day, based on decreased plasma cholinesterase inhibition in humans and a NOEL (no observed effect level) of 0.03 mg/kg-bw/day. Based on the data from MNCPES develop an HI and MOE for this population of children.
2. Describe and rank the main uncertainties in developing a risk characterization for chlorpyrifos based on the data from MNCPES.
3. Compare and contrast the results of the Monte Carlo simulation for this particular exposure to the deterministic results for this pesticide.
4. Assuming this distributional output represents an average daily dose (ADD) for a population of two-year-old children, what point on the distribution should

be used to develop an MOE or HQ if the USEPA RfD for this compound is 1 μg/kg/day, based on a NOAEL of 100 and an uncertainty factor of 100?

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CHAPTER SEVEN

MOLECULAR TOOLS FOR RISK ASSESSMENT

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Chisato Mori

Learning Objectives

Students who complete this chapter will be able to

1. Identify genomic and postgenomic approaches to risk
2. Assess gene-environment interaction
3. Identify biomarkers of disease and exposure
4. Understand the role of biomarkers in risk assessment
5. Learn how molecular toxicogenomics is applied to risk assessment

Two of the most significant scientific developments of the latter part of the twentieth century were the elucidation of the double helical structure of DNA and the complete sequence of the human genome (Watson and Crick, 1953; Collins, Morgan, and Patrinos, 2003). Great strides in molecular biology stemmed from the central dogma of biology proposed by Watson and Crick in the early 1950s. The understanding that DNA encoded specific proteins or enzymes allowed for a greater insight into cellular processes at the molecular level. Knowing the sequence of the human genome also gave great promise in environmental medicine and environmental health (see Chapter Two). Editorials in the popular press hinted that now we had a new understanding of life, disease, and prevention. Soon afterwards, it was recognized that the genome sequence was in itself not enough

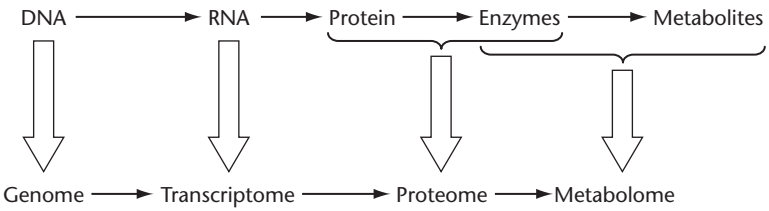
to uncover the secrets of human physiology, but was one important piece of the puzzle. We are now in the postgenomic era. Just as RNA and protein follow DNA in the central dogma of molecular biology proposed by Watson and Crick, the postgenomics era follows a similar pattern (see Figure 7.1). Protein and active enzymes constitute part of the proteome, as do the enzymes, which form metabolites, and the complement of intracellular metabolites constitutes the metabolome.

Transcriptomics focuses on the entire complement of mRNA. *Proteomics* studies the entire cellular complement of proteins, including posttranslational modification processes, which are often associated with active enzymes. *Metabolomics* is the study of the entire cellular complement of metabolites and the enzymes that produce the metabolites as part of the metabolome. The control of metabolites, proteins, and nucleic acid macromolecules are interconnected as networks; thus, these postgenomic sciences anticipated systems biology, which considers the cellular *omes* as a unit.

The systems biology approach recognizes that cells and organisms are different from the sum of their parts. Thus, genes work as interacting networks that regulate one another. That means that systems biology is an integrative approach to understanding organisms. This is different from reductionist approaches, which do not give a complete understanding of human physiology in that they study functions piece by piece in hopes of reconstructing the intricate cellular functions of cellular physiology.

To model the system, systems biology uses mathematics based on accrued knowledge from many sources. These *in silico* models help to predict how alterations in the system affect cells. The models are used to test the actions of changing cellular environment on physiology. The goal is to achieve a greater understanding of health and disease (Hood, Heath, Phelps, and Lin, 2004). The genomic and postgenomic sciences have yielded enormous amounts of new data on se-

FIGURE 7.1. CENTRAL DOGMA AS IT RELATES TO GENOMICS AND POSTGENOMIC SCIENCE.



Note: Protein and active enzymes constitute part of the proteome, as do the enzymes, which form metabolites, and the complement of intracellular metabolites constitutes the metabolome.

quence and expression patterns. Because systems were needed to analyze these datasets, which were stored in computers all over the world, application of the science of bioinformatics is essential to gain the most of genomic and postgenomic data. Bioinformatics methods allow for statistical evaluation and data management and led to the establishment of access to valuable data via the worldwide web. Following are some relevant web sites:

Databases Useful for Toxicogenomic Information

http://www.ncbi.nlm.nih.gov/Genbank (GenBank)

http://www.genome.ad.jp/kegg/pathway.html (KEGG Pathway Data Base)

http://www.ncbi.nlm.nih.gov/Education/BLASTinfo/information3.html (BLAST: Basic Local Alignment Search Tool)

http://genomics.case.edu/links.html (Center for Computational Genomics and Systems Biology)

http://ctd.mdibl.org (Comparative Genomic Data Base)

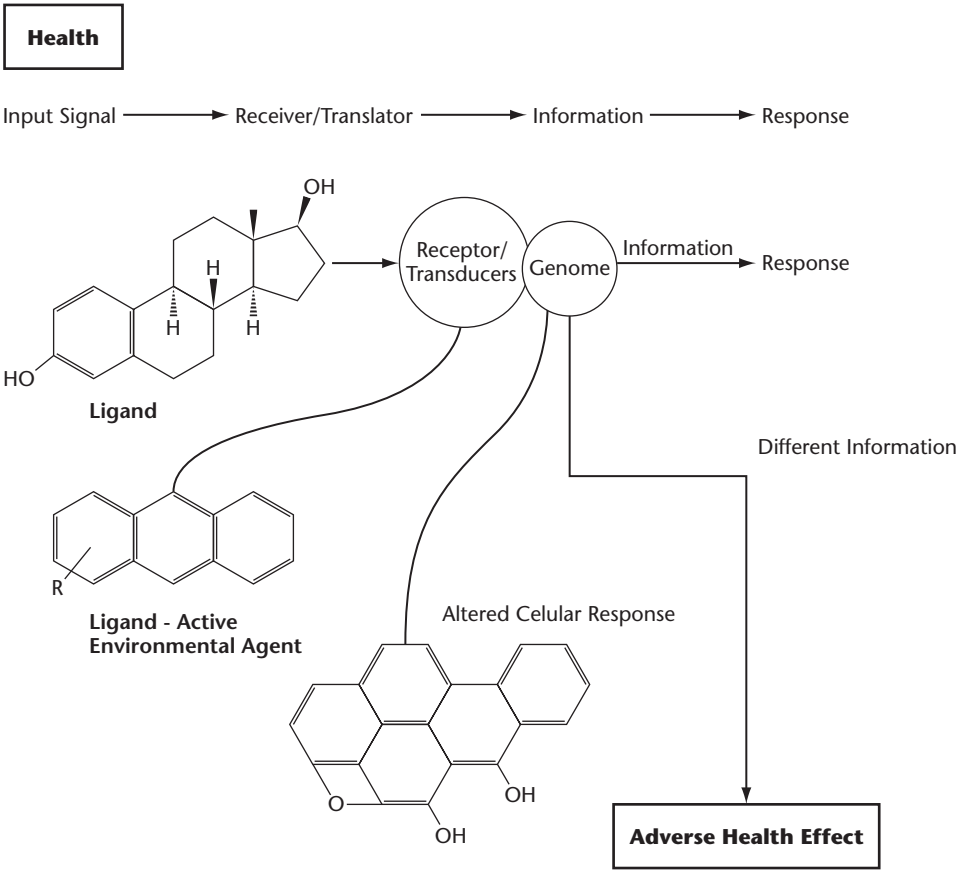
http://toxnet.nlm.nih.gov (Toxnet)

http://www.systemsbiology.org (Institute for Systems Biology)

In the postgenomic era, it has become abundantly clear that genes in themselves do not necessarily lead to disease, but the interaction of genes with their environment is what will determine health or disease. For example, there are "good" environmental components such as vitamins, essential minerals, and other elements that contribute to the healthy state; there are also "bad" environmental agents such as PCBs, dioxins, various pesticides, and metals that interact with genes to cause various diseases. How environmental agents interact with human genomes is an area of intense research. Basically, however, there are at least two different paradigms (see Figure 7.2). The environment affects cells. So-called good environmental factors are essential for health by signaling pathways important to maintain homeostasis. Other environmental agents can adversely affect health by interacting with our genomes, either directly or indirectly to change information that the cells receive, thus causing an adverse health effect.

1. *Direct environment-gene interaction.* Examples include compounds such as carcinogens or mutagens and effectors of epigenetic modification of DNA.
2. *Indirect environment-gene interaction.* Examples include ligand activated transcription factors for hormones, vitamins, dioxins, and endocrine-disrupting agents.

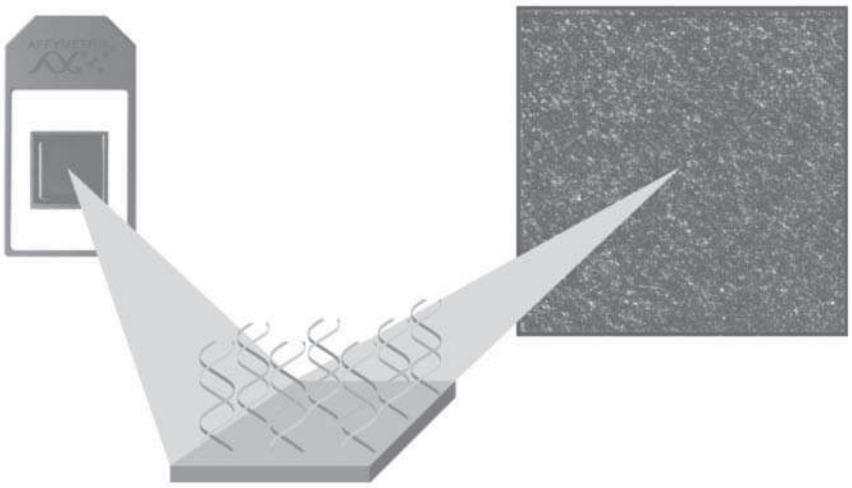
FIGURE 7.2. DIRECT- AND INDIRECT-ACTING GENOME ACTIVE AGENTS.



Because there is similarity among genomes of humans and other species, much insight can be gained from animal data using genomic analysis after exposure to toxicants (Mattingly, Colby, Forrest, and Boyer, 2003; Mattingly and others, 2004). This approach can lead to new biomarkers that can be applied to human studies.

Techniques for examining changes in gene expression in different cellular environments have been developed, which allow for rapid determination of changes in gene expression and mutations. The DNA array, or *Gene Chip*™, technology (Figure 7.3) has found wide use in clinical and research applications.

FIGURE 7.3. MICROARRAY TECHNOLOGY.



Source: From an experiment showing the expression of thousands of genes on a single GeneChip™ probe array. Image courtesy of Affymetrix.

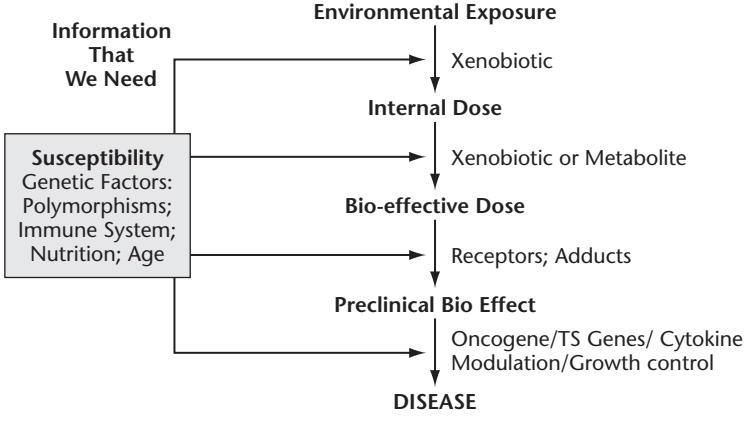
Microarrays are used to quantify mRNA as a measure of gene expression under different conditions. The advantage of this technology is that it enables us to screen hundreds or thousands of genes in a single assay. Basically, the technology used in making microarrays was adapted from the semiconductor industry. Microarrays are prepared on glass or plastic in sections called *fields.* Briefly, synthetic single-stranded DNA probes are deposited and attached to a surface. RNA from cells is enzymatically converted into complementary DNA (cDNA), which can be labeled with a fluorescent tag. The cDNA, containing a sequence that is complementary to one of the single-stranded DNA probes on the microarray, hybridizes to the spot at which complementary reporters have been fixed. The spots hybridized with tagged DNA fluoresce with varying intensity, indicating the level of expression of the genes.

Microarray technology is a potentially powerful tool for determining environmental effects on gene expression. The differences in expression patterns between control and exposed cells can be used to assess gene expression patterns under different environmental exposures. Even though human genome sequences are estimated to be 99.9 percent alike, phenotypic differences among populations are easily recognized. Understanding differences in susceptibility among human populations is one of the most difficult problems in human health risk assessment.

One of the great promises of the human genome project was the hope that molecular biomarkers would yield new information on susceptibility differences among human populations. Advances in the *new biology* will yield new molecular biological markers to allow us to better identify populations susceptible to environmental agents that cause human disease.

Biological markers have been recognized as signs for disease and health for many centuries. For example, ancient physicians understood that the color or smell of urine could be used to determine whether a patient suffered from a specific disease. Biomarkers have been proposed as useful tools in risk assessment since 1983 (National Research Council, 1983; Rodericks, 1994). A biomarker can be defined as any substance, structure, or process that can be measured in a human as a result of a specific exposure or event. Many types of biomarkers are of use in risk assessment. Biochemical biomarkers look at the presence of metabolites or toxicants in the body; enzyme levels may be used as a molecular biomarker, whereas genetic biomarkers could include DNA damage or RNA silencing; immunologic assessment could use cytokine expression; and hormone levels could be useful as physiological markers. Biomarkers are used as indicators of chemical exposure, host susceptibility, early disease, or indicators of health effects. The most useful biomarkers are those that measure what they are supposed to, are specific for the exposure, and are widely applicable, relatively inexpensive, and amenable to high throughput analysis. The rise of biological markers of environmental exposure and early disease together with the sequencing of the human genome has led to the understanding that environment-gene interactions are responsible for many of the chronic diseases about which we are concerned. Figure 7.4 summarizes points in

FIGURE 7.4. BIOMARKERS OF EXPOSURE DOSE AND EFFECT.



the exposure–disease continuum where biomarkers for risk assessment can be developed. There are many places between exposure and disease for which useful molecular biomarkers can be developed and used in human health risk assessment.

Single nucleotide polymorphisms (SNP) play an important role in predicting susceptibility to environmental agents. Polymorphisms are defined as genes for which at least 1 percent of the population has a mutant allele. There is no biological reason to pick the 1 percent level and polymorphisms are not considered to be mutations per se because they are thought to have occurred earlier in human evolution. Polymorphisms in environmental response genes can modify the risk for disease in humans. Cytochrome 1A1 (CYP1A1) is polymorphic in some populations. In some Japanese, change of an isoleucine to valine in exon 7 has been associated with higher induction of CYP1A1, which could result in faster metabolism of some polynuclear aromatic compounds such as benzo [a] pyrene, whose metabolites are known carcinogens. Glutathione S-transferase-M1 (GSHTM1), a phase II metabolism gene that is important in catalyzing the conjugation of carcinogens in humans, is also polymorphic (see Chapter Four). Some populations cannot express GSHTM1. Women who express the CYP1A1 Ile → Val polymorphism in exon 7 have a higher risk of lung cancer than men (see Table 7.1. When they possess the same polymorphism together with the GSHTM1 null phenotype, women exhibit an odds ratio for susceptibility to lung cancer of 6.54 versus men (OR = 2.36) regardless of age or smoking history (Dresler and others, 2000). From these types of data, it could be concluded that the presence of polymorphisms in Phase I and Phase II metabolic pathways together could be used as a predictor of susceptibility to disease in the presence of specific exposures.

Another example of an important polymorphism in an environmental response gene is found in the metabolism of the antihypertensive drug debrisoquin. The rate at which debrisoquin is metabolized has been linked to polymorphisms in the cytochrome P450 2D6 (CYP2D6) monooxygenase. Human populations can be classified as poor metabolizers, extensive metabolizers, and ultra metabolizers.

TABLE 7.1. SUSCEPTIBILITY AND POLYMORPHISM.

Polymorphism		*Odds Ratio*	
CYP1A1	**GSHTM1**	**Male**	**Female**
–	–	1	1
+	–	1.37	4.98
–	+	1	1
+	+	2.36	6.54

Source: Dresler and others (2000).

Poor metabolizers generally express defective CYP2D6 or, in the case of a gene deletion, no enzyme. Poor metabolizers make up about 6 to 10 percent of northern European populations and 15 percent of African populations; and less than 1 percent of Asian populations metabolize debrisoquin very slowly. Extensive metabolizers can metabolize debrisoquin 10 to 40 percent faster than poor metabolizers. A third population expresses multiple copies of CYP2D6 and are classified as ultra metabolizers. Less than 1 percent of northern Europeans are ultra metabolizers, whereas about 21 percent of Saudi Arabians and 29 percent of Ethiopians express this trait; the gene for CYP2D6 is expressed up to thirteen times normal populations. Epidemiological studies have related CYP2D6 polymorphisms to various diseases, including Parkinson's disease and some cancers. Poor metabolizers have a 2.5-fold higher risk of Parkinson's disease. Extensive metabolizers who smoke have shown increased rates of cancer in the bladder, liver, pharynx, and stomach. Having a polymorphism, however, does not guarantee disease. Polymorphisms do not confer risk in the absence of an environmental exposure. The data in Table 7.2 show the relationship between certain polymorphisms and increased odds ratio for susceptibility to various cancers among different populations.

Gene Expression Analysis and Chemical Exposure in Humans: Detection of High-Risk Groups

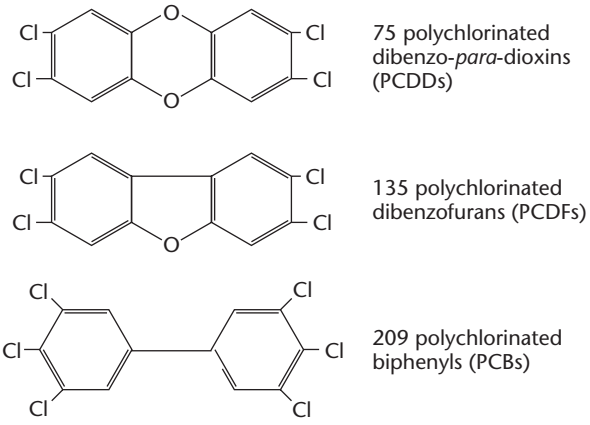
Polychlorinated compounds including dioxins and polychlorinated biphenyls (PCBs) are persistent organic pollutants (POPs) that are widespread in the environment. PCBs were used because of their heat-transferring ability and were commonly used in transformers. PCBs are no longer manufactured in the United States since they were banned in 1977, but they are common environmental pollutants. There are approximately 209 related PCB compounds, or congeners (see Figure 7.5). 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is the archetype of the

TABLE 7.2. EXAMPLES OF POLYMORPHISMS AND CANCER.

Gene	Cancer	Subgroup	Odds Ratio
NAT2 + GSTM1	Bladder	Male	4.4
GSTM1 + GSTT1	Breast	Premenopausal + alcohol	5.3
CYP1A1	Breast	African American	9.7
NAT1 + NAT2	Bladder	White smokers	6.3

Source: Garte (2001).

FIGURE 7.5. FAMILIES OF POLYCHLORINATED ORGANIC COMPOUNDS.



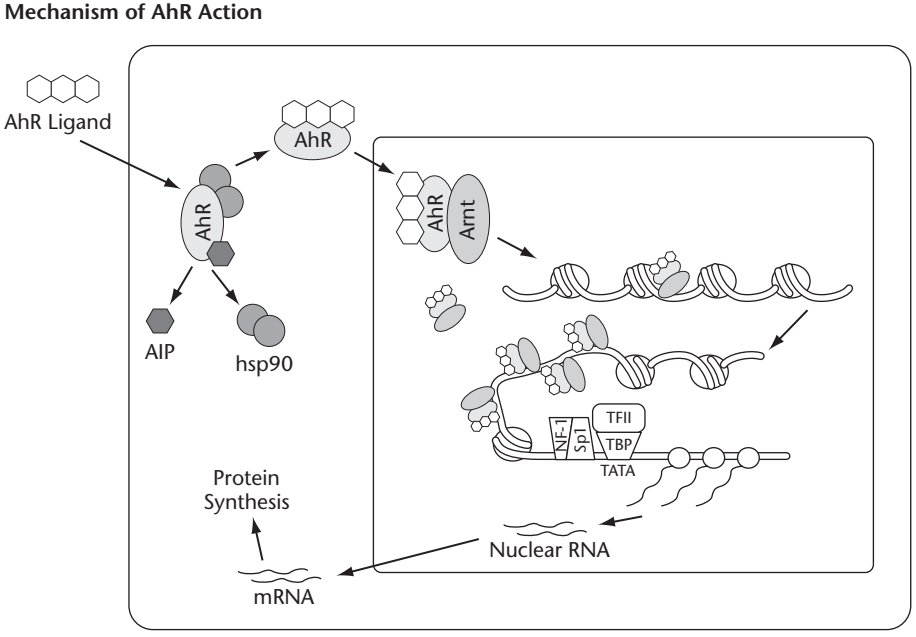
family of related polychlorinated compounds known as *dioxins*. Prominent members of the dioxin family include dibenzofurans, biphenyls, azoxybenzenes, and dibenzo-*para*-dioxins. Based on studies in animals, TCDD is considered one of the most toxic compounds ever released into the environment (Gough, 1991). Humans have been exposed to TCDD as a result of industrial accidents, improper handling of incinerators and hazardous waste, as well as spraying of the citizenry and American servicemen in Vietnam with Agent Orange, a herbicide mixture that contained TCDD as a contaminant (Gough, 1991; Bogen, 1979; Reggiani, 1980). Recently, attention has been drawn to possible dioxin exposures to the general population through the use of paper products, including coffee filters and feminine hygiene products (Beck and others, 1989; Holloway, 1994). Examination of epidemiological evidence has led some investigators to conclude that human exposure to dioxins is linked to various forms of cancer (Fingerhut and others, 1991; Bertazzi and others, 1989; Bertazzi, 1993), but it has been difficult to derive a mechanism for the role low-dose exposures to dioxins play in the etiology of human disease. Dioxins are persistent in the environment, with a half-life of approximately 10 years (Gough, 1988). Whether the general population is at risk of dioxin-induced disease is not known. A recent study of human adipose tissue collected by the National Human Adipose Tissue Survey demonstrated an average concentration of TCDD in the U.S. population of 5.38 pg/g, and that the average body burden levels of dioxins increase with age (Orban,

Stanley, Schwemberger, and Remmers, 1994). Some estimates state that humans in industrial countries eat an average of 133 pg dioxin per day.

Dioxins are interesting because their actions are regulated by an intracellular receptor. It is known as the *Ah receptor* (Figure 7.6), because it was shown to regulate the induction of cytochrome P450s that catalyzed aryl hydrocarbon hydroxylase activity (Nebert, Puga, and Vasiliou, 1993; Poland and Glover, 1977). Because dioxins, PCBs, and other polyhalogenated compounds are so prevalent and persistent in the environment, they have many biological actions, including being implicated in immune response effects, various cancers, endometriosis, and endocrine disruption, and are of particular interest as agents of possible risk to human health.

TCDD or a related AhR ligand enters the cell by diffusion and binds to the AhR-Hsp-90 complex. The ancillary proteins are released from the ligand binding AhR, which forms a heterodimer with the aryl hydrocarbon translocator protein (ARNT); this binds to the Ah receptor responsive element (AhRE) in DNA,

FIGURE 7.6. PROPOSED MECHANISM OF AH RECEPTOR ACTION.



Source: Adapted from Whitlock (1999).

resulting in mRNA synthesis, protein synthesis, and cellular effects. A number of coactivators are also involved in the action of AhR.

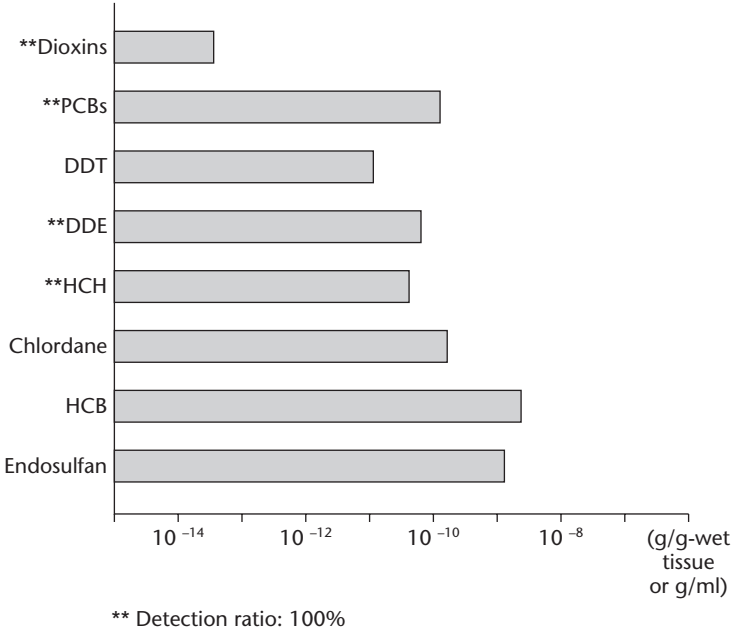
Increasing evidence demonstrates that human fetuses are contaminated by exposure to multiple persistent chemicals (Miller and others, 2004). There is genuine concern that these multiple persistent organic chemical exposures at a high-risk life stage may cause delayed long-term effects to humans. This concept has been called *fetal programming*, which results from imprinting in utero of the child for future disease (Nathanielsz, 2000; Nathanielsz and Thornburg, 2003). Early studies focused on nutritional problems, but the same concept can be applied to exposure to toxicants in utero (Newbold, Banks, Bullock, and Jefferson, 2002). Organochlorine pollutants have been detected in maternal serum, cord serum, and the umbilical cord (Fukata and others, 2005). Organochlorine pollutants cross the placenta and reach the fetus, thereby providing a fetal exposure route. It has been suggested that fetal exposure to organochlorine pollutants has adverse effects on development (Needham and Sexton, 2000). Some studies suggest that fetal exposure to organochlorine pollutants also have an adverse effect on the reproductive system later in life (Anas and others, 2005). Other studies suggest that fetal exposure to PCBs has an adverse effect on the neuropsychological development (Needham and others, 2005). Hence, we believe that if we are to assess health risk later in life, it is important to correctly understand the effects of fetal exposure to organochlorine pollutants and to identify high-risk groups of organochlorine pollutants contamination in the early stages of life.

In human studies on effects of exposure to multiple environmental agents, it is important to pay attention to two key issues. First is the presence of a high-risk group in a human population. Both high exposure and genetic high susceptibility to multiple environmental agents should be regarded as higher health risk to individuals. Second is the high-risk life stage at which the exposure occurs, such as embryonic/fetal periods (see Chapters Twelve and Thirteen). Genomic technology is a powerful tool that has the potential to determine environmental actions of chemicals at various life stages. Human embryos, fetuses, and infants are thought to be significantly more sensitive to a variety of environmental toxicants than adults. Thus, it would be expected that differences in gene expression patterns in developing humans, neonates, infants, adolescents, and adults would differ considerably. Genomic technology also is a valuable tool in assessing the actions of mixtures in human disease. In human health risk assessment we currently target the adult and evaluate the risk of single chemicals. Traditional risk assessment methods lack consideration of multiple chemical exposure, susceptibility, and sensitive windows. Thus, establishing a new evaluation method of health risk assessment derived from fetal exposure to multiple chemicals has great promise in understanding environmental disease etiology.

A Technological Approach to Risk Assessment Using Toxicogenomics, Exposure Level, and Susceptibility

Human fetal exposure to multiple environmental agents has been studied by analyzing umbilical cords and cord blood (Mori and others, 2003; Mori, Sakurai, and Iguchi, 2001; Todaka and Mori, 2002). Figure 7.7 shows results from over 300 human umbilical cords collected from normal newborns at Chiba University Hospital in Japan and analyzed for levels of POPs. When human umbilical cords, a part of the fetal tissue, were collected from normal newborns, human fetal exposure assessment revealed that at least twenty environmental chemicals and toxicants were transplacentally transferred from mothers to their fetuses. The detected chemicals and toxicants were as follows: dioxins (PCDDs + PCDFs + co-PCBs), PCBs, DDTs, DDEs, aldrin, chlordanes, hexachlorobenzen (HCB), hexachlorocyclohexane (BHC), and heavy metals (Cd, Pb) (Mori, Sakurai, and Iguchi, 2001;

FIGURE 7.7. CONCENTRATIONS OF POPs IN UMBILICAL CORDS.



Source: Mori, Sakurai, and Iguchi (2001).

Todaka and Mori, 2002). All of these chemicals and toxicants were detected in more than 50 percent of the umbilical cords investigated. Some interesting observations on birth order and exposure to the toxicants were made. The concentrations of dioxins, PCBs, and DDEs (persistent chemicals) in first-born infants were higher than those in second or third babies (Mori and others, 2003). A large difference of the sum of the concentration level of several persistent chemicals was also found among individuals. Fetuses that accumulated PCBs at high levels had a tendency to also accumulate other chemicals at high levels (Fukata and others, 2005). Our exposure assessment suggests that certain fetuses are highly exposed to multiple persistent chemicals. This suggests the presence of potential high-risk groups of human fetuses exposed to multiple environmental agents, which could be important in risk of disease in later life.

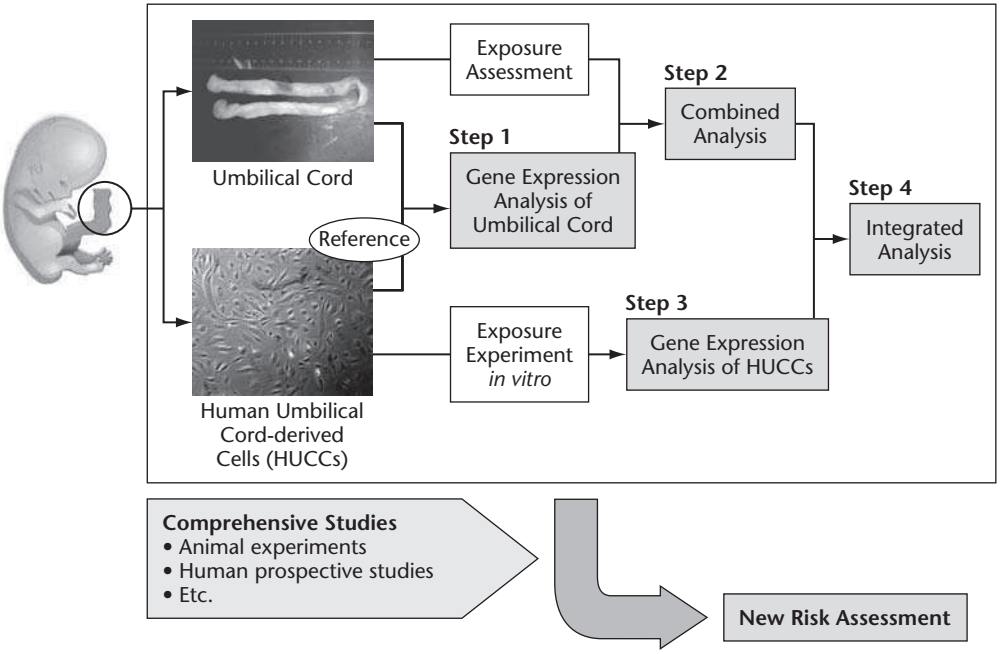
In the current risk assessment paradigms, we mainly target the adult and the risk of single chemicals. We do not consider multiple chemical exposure, susceptibility, and sensitive window because conventional methods lack the power to investigate multiple interactions. Thus, the establishment of new evaluation methods of health risk assessment derived from fetal exposure to multiple chemicals is an important tool in developing appropriate biological markers to assess risk of disease after environmental exposures. Such a framework of risk assessment using toxicogenomics is illustrated in Figure 7.8. In this framework two approaches are taken: (1) exposure assessment and toxicogenomic studies of gene expression in an integrated format and (2) a combination of laboratory studies in animals and epidemiologic perspectives to gain a comprehensive perspective of risk.

Current risk assessment often does not consider susceptibility. Application of genomic and postgenomic technology allows us to consider susceptibility, together with exposure level. Adverse health effects might be imprinted in babies exposed to chemicals even at low doses. The key issue of a new health risk assessment is to find the potential high-risk group in the next generation who is exposed to multiple chemicals at high-risk life stages. Both the actual exposure and genetic susceptibility to multiple chemicals should be regarded as higher health risk to the individual.

We are now proposing a strategy for establishing new methods of health risk assessment based on fetal tissue using umbilical cords as bioindicators. This approach starts with transcriptome studies using DNA microarray, biomarker, and toxicogenomic analysis (Mori and others, 2003). Figure 7.9 shows how the molecular tools of genomics, transcriptomics, and proteomics use DNA microarrays and protein chips to examine molecular biomarkers and assess susceptibility and exposures in human embryos with samples collected from umbilical cords and cord blood.

Since the umbilical cord is a readily obtainable part of the fetal tissue, it is possible to estimate the effects of environmental agents on the fetus by analyzing

FIGURE 7.8. FRAMEWORK FOR ESTABLISHING A NEW RISK ASSESSMENT OF HUMAN FETAL EXPOSURE USING TOXICOGENOMICS.

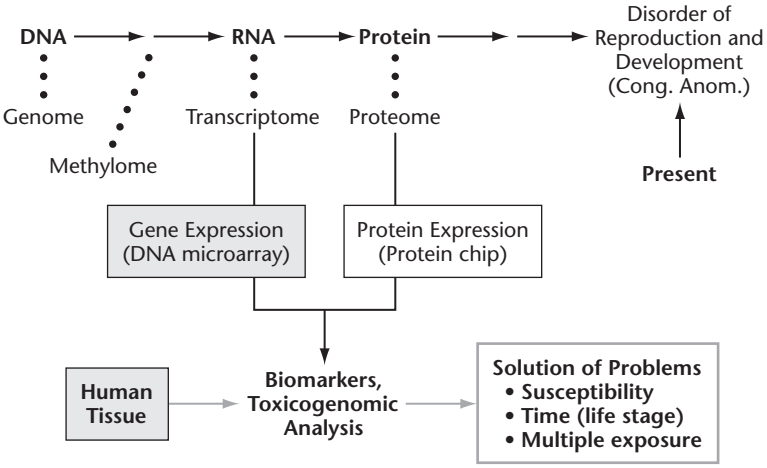


Source: Mori and others (2003).

alteration of gene expression using microarray technology. *Toxicogenomics* has been rapidly developing in recent years. It is the study of the genes and their products, which show adaptive response to toxicants. The definition of toxicogenomics is "an emerging scientific field that combines studies of genetics, genome-wide mRNA expression, cell and tissue-wide protein expression, bioinformatics and toxicology to understand the roles of genes-environment interactions in disease." Microarray technology has been applied to toxicology using animal experiments, and will be applied to the field of risk assessment of human exposure to several environmental toxicants. A recent study using cDNA microarray reported the identification of lead-sensitive genes in immortalized human fetal astrocytes (Hossain, Bouton, Pevsner, and Laterra, 2000). This report indicates the potential of DNA microarray for the discovery of novel toxicant-induced gene-expression alterations, and the understanding of the mechanisms underlying lead neuro-toxicity.

In the process of our establishing toxicogenomic analysis for risk assessment, we propose four steps as outlined in Figure 7.8.

FIGURE 7.9. STRATEGY FOR ESTABLISHING A TOXICOGENOMIC EVALUATION METHOD FOR HEALTH RISK ASSESSMENT.



Step 1 is global gene expression analysis of exposed tissue by DNA microarray.

Step 2 is a combined analysis of data generated in Step 1 together with exposure-assessment data in each sample. In this combined (Step-2) analysis, a global gene-expression profile with chemical exposure levels allows analysis of tissue exposed to multiple chemicals.

Step 3 uses an in vitro experiment in which DNA microarray analysis of the alteration of gene expression is examined in cultured cells after exposure to chemicals.

Step 4 employs an integrated analysis of a comparison between Step 2 and Step 3. In this integrated analysis, the biological reactions at the molecular level after exposure to chemicals in tissues can be detected.

In order to extend the toxicogenomic analysis method to develop a new risk assessment, comprehensive studies are required to clarify the correlation between data from toxicogenomic analysis, from animal experiments observing the adverse effects of chemical exposure, and from study of the human prospective. By establishing the toxicogenomic analysis, with the *in silico* integrated analysis of human umbilical cords, the new risk assessment for multiple chemical exposures will be practical.

As mentioned, there are many steps for establishing an accurate toxicogenomic analysis method using umbilical cords, and there are still technical problems and socioethical issues to be surmounted. However, when these problems are resolved, we hope the new risk assessment with toxicogenomic analysis can be applied to prevent the long-term effects of multiple chemical exposure. Furthermore, if the new risk assessment involves cooperation from current environmental genome projects, it could possibly lead to the development of new tailor-made preventive interventions or medications.

In addition to the establishment of new risk assessments using molecular techniques it is necessary to develop a risk reduction method to avoid multiple chemical exposure and at the same time reduce the concentration level of persistent chemicals in the human body. To reduce the risk for future generations, worldwide cooperation is urgently required regarding high-risk group and high-risk life stage. Exposures to chemicals are not confined to geographic boundaries. Thus, people all over the world are exposed to similar or even worse conditions of environmental contamination, which reinforces the need for more powerful tools in the arsenal of human health risk assessment and management.

Thought Questions

1. What is the predictive value of using fetal umbilical cords to assess risk of disease from environmental exposure?
2. What can be deduced from biological markers using polymorphisms of xenobiotic metabolic enzymes?
3. What are some of the ethical issues of analyzing umbilical cord DNA expression patterns as predictors of future disease?
4. Discuss the reason that polymorphism does not predict disease in the absence of exposure. How does this compare with the concept people have about diseases "running in families"?

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CHAPTER EIGHT

COMPARATIVE RISK ASSESSMENT

Michele Morrone

Learning Objectives

Students who complete this chapter will be able to

1. Define comparative risk
2. Identify three to five key circumstances that led to the widespread use of comparative risk in the 1980s and 1990s
3. Explain the comparative risk process, including the way a comparative risk project is organized and managed
4. Debate the impact of comparative risk on public health policy

Risk assessment has been used since the early 1980s to examine the human health and ecological effects of specific chemicals. The four-step risk assessment process of hazard identification, dose-response evaluation, exposure assessment, and risk characterization was published by the federal government in 1983 in the *Red Book* (National Research Council, 1983). Since then, the *Red Book* has become the paradigm for assessing human health risks and providing quantitative information to policy makers who decide how to manage these risks.

In 1986, the United States Environmental Protection Agency (USEPA) published five guidelines for risk assessment in the *Federal Register.* These guidelines addressed (1) carcinogenic risk assessment, (2) estimating exposures, (3) mutagenicity

risk assessment, (4) health assessment of suspect developmental toxicants, and (5) health risk assessment of chemical mixtures (Environmental Protection Agency, 1986). The guidelines were based on the National Research Council process and most have been updated as additional information became available.

One major recommendation in the *Red Book* was that policy choices for managing risks should be separate from scientific assessment of risk.

> We recommend that regulatory agencies take steps to establish and maintain a clear conceptual distinction between assessment of risks and consideration of risk management alternatives; that is, the scientific findings and policy judgments embodied in risk assessments should be explicitly distinguished from the political, economic, and technical considerations that influence the design and choice of regulatory strategies [p. 7].

While the risk assessment paradigm strives to provide information in a quantitative and objective way, there is always some scientific judgment in the process (National Research Council, 1994). In risk assessment, judgment is needed because of uncertainties that exist in gathering data and using models to estimate risk. The results of the risk assessment are typically characterized as the probability of cancer or noncancer health effects. Decision makers use the risk characterization to decide policy approaches to address the risk. The risk assessment paradigm does not allow for the comparison of risks from different chemicals or sites, a situation that forces decision makers to make one-dimensional decisions based on the results of a risk assessment that may include much scientific uncertainty.

The role of uncertainty has been a major issue in the debate about the usefulness of risk assessment. How to deal with uncertainty is a policy issue that has been handled with specific default assumptions that are incorporated into the risk assessment process. The use of these assumptions has been one of the most controversial aspects of risk assessment. For example, Ricci, Cox, and MacDonald (2006) argue that there are quantitative tools available to minimize the need for default assumptions and that employing these tools would reduce the amount of uncertainty in risk characterization. One major issue having to do with uncertainty is that it influences the perception that risk assessment is an objective scientific method. Using assumptions implies using judgment, and critics of risk assessment argue that there is a need to reduce the need for judgment so that the process can be truly objective and unbiased.

The federal government has taken steps to minimize the use of judgment and enhance objectivity in agency decision making. As an example of one measure to accomplish this, the Federal Data Quality Act (DQA) was passed by Congress as a rider to the 2001 appropriations bill. As mandated by DQA, the Office of Man-

agement and Budget (OMB) developed *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies* for agencies to use in complying with the goals of the Act. The guidelines finalized by OMB in February 2002 require agencies to: (1) develop their own guidelines to ensure information quality by October 1, 2002, (2) provide a mechanism for stakeholders to request corrections to information, and (3) prepare an annual report summarizing corrections requests and agency responses.

More recently the OMB released a "Proposed Risk Assessment Bulletin" (Office of Management and Budget, 2006) that explicitly targets uncertainty in risk assessment. This bulletin (still in draft form at the time of this writing) calls for increased transparency in risk assessments. In addition, the bulletin advocates an enhanced role of the public throughout the process. In the risk assessment paradigm outlined in the *Red Book,* there is no opportunity for public involvement; risk assessment is a scientific process completed by scientists; the public can be involved once the risk management phase begins. The new OMB bulletin suggests that the public be involved in risk assessments as early as practicable.

One result of the lack of public access and involvement during the risk assessment process may be enhanced mistrust of scientists. Risks are often characterized as being one in a million, which may not be significant to scientists but is too great for a public that will not accept any risk. The public is ignorant of the steps in the risk assessment paradigm and their lack of empowerment in the process creates suspicion.

Comparative risk goes well beyond traditional public involvement in environmental decision making in that it invites the public to contribute to setting environmental priorities based, at least in part, on how they perceive those risks. A major premise of comparative risk is awareness that there are differences between the way the public perceives risk and how scientists evaluate it, so the best way to address these differences is to bring scientists and the public together to discuss risk.

Straying even further from the risk assessment paradigm, comparative risk analysis offers the opportunity to examine risk from many dimensions, including human health, ecological health, and quality of life. The multidimensional nature of comparative risk analysis is its greatest strength as well as its greatest challenge as a decision-making tool (Andrews, 2004). It is a challenge that has been met with transparency on the part of those participating in the process. That is, all of the comparative risk projects completed to date have been open and explicit about the role of judgment in prioritizing environmental issues. There have been no claims of pure objectivity in the ranking process, a major component of comparative risk, and uncertainty about the quality and quantity of data used in the process is well-accepted and openly discussed.

Comparative risk analysis takes the risk assessment paradigm to new levels because it is a tool that decision makers can use to prioritize a wide range of risks in order to decide which should be managed first. It can be argued that comparative risk was devised as a tool to make subjectivity explicit in the risk assessment process.

Defining Comparative Risk

That there is no generally accepted definition of comparative risk is indicative that each comparative risk project is different. There is a framework that most projects have used, but the spirit of comparative risk is that it is a grassroots, nonprescriptive way to examine local environmental conditions. An excellent overview of some working definitions of comparative risk has been offered by Cura, Bridges, and McArdle (2004). In particular, they argue that comparative risk is different from risk comparison, which they view as a hard version of comparing risks using statistical methods. In explaining how comparative risk can contribute to making decisions about managing dredged materials, Cura and coworkers offered the following definition of comparative risk as a method that

> separately ranks either ecological or human health risks associated with a small set of technological options; recognizes that the development of categories for ranking and the criteria against which to score the categories involves judgment; attempts to employ a rational and iterative process in developing both; ties the ranking or prioritization to the opportunity to address the risk [p. 489].

Although comparative risk has been used in a variety of ways, for the purpose of this chapter comparative risk is discussed in the realm of environmental policy making. In this arena, comparative risk is basically a process for setting priorities. The process attempts to combine qualitative with quantitative data to prioritize issues through ranking, rating, or some combination of the two. The major result of the process is usually a list of risk-based priorities with some recommendations for addressing the priorities.

Unfinished Business

The first comparative risk project was conducted by the federal government in 1987 and resulted in a report referred to as *Unfinished Business* (Environmental Protection Agency, 1987). This report was commissioned by USEPA Administrator

Lee Thomas, who charged agency scientists with evaluating and ranking more than thirty environmental issues on the basis of their risk to human health, ecological systems, and public welfare. The result of this effort, which used only scientific information and expertise, was a ranking of threats based on available scientific evidence. Exhibit 8.1 depicts the ranking of risks that was published in the "Unfinished Business" report.

EXHIBIT 8.1. USEPA RANKING OF CANCER RISK FROM ENVIRONMENTAL ISSUES.

Overall High-Medium Risk

- "Criteria" air pollution from mobile and stationary sources (includes acid precipitation)
- Stratospheric ozone depletion
- Pesticide residues in or on foods
- Runoff and air deposition of pesticides

High Health, Low Ecological and Welfare Risk

- Hazardous or toxic air pollutants
- Indoor radon
- Indoor air pollution other than radon
- Drinking water as it arrives at the tap
- Exposure to consumer products
- Worker exposure to chemicals

Low Health, High Ecological and Welfare Risk

- Global warming
- Point and nonpoint sources of surface water pollution
- Physical alteration of aquatic habitat (including estuaries and wetlands) and mining waste

Overall Medium-Low Risk (Groundwater-Related Problems)

- Active hazardous waste sites
- Inactive hazardous waste sites (Superfund)
- Other municipal and industrial waste sites
- Underground storage tanks

Mixed and Medium-Low Risk

- Contaminated sludge
- Accidental releases of toxic chemicals
- Accidental oil spills
- Biotechnology (environmental releases of genetically altered materials)

Source: Environmental Protection Agency (1987).

The report alarmed many policy makers because those issues that the scientists ranked high were clearly not the priorities of government spending. For example, indoor air quality was evaluated as a high risk to human health by the panel of scientists, while accidental releases and hazardous waste sites were ranked as of significantly lower risk. At this time, indoor air quality issues such as radon were not part of the policy-making agenda because the public was more concerned with seemingly catastrophic risks.

In the ten years prior to the release of *Unfinished Business,* people were evacuated from Love Canal, New York, and Times Beach, Missouri; methyl isocyanate was released in Bhopal, India; radiation was released in Chernobyl, Ukraine; and there was a serious accident at the Three-Mile Island nuclear power plant in Pennsylvania. These events led to great public attention to and fear about exposure to chemicals and radiation. One major result of this concern was environmental legislation, which was passed by Congress at lightning speed, addressing hazardous waste and creating a Superfund to clean up abandoned hazardous waste sites. The Superfund law was enacted in 1980—three years prior to the publication of the *Red Book,* so there were no scientific risk assessments that provided data to policy makers. Decision makers reacted to public perception and created one of the most extensive regulatory programs in the face of a significant level of uncertainty.

When examining budget allocations for environmental health issues during the time *Unfinished Business* was released, dealing with hazardous waste appeared as a major governmental priority, adding fuel to the fire of reformers who argued that government was spending money on the wrong environmental problems (Landy, Roberts, and Thomas, 1990). Furthermore, there was a clear difference between how the experts in the EPA ranked environmental issues and how members of the public perceived risk from the same issues; not surprisingly, the views of the public were more closely aligned with budgetary priorities.

Even though the *Unfinished Business* report caused a stir among environmental policy makers and scientists, it had relatively little immediate impact on operations at the USEPA. After Lee Thomas left the EPA in 1989, William Reilly took over as administrator and charged the agency's Science Advisory Board (SAB) with completing a similar process that led to the *Unfinished Business* report. The major difference between what Reilly asked the SAB to do and the EPA's earlier work is that the SAB was a group of experts external to the agency.

Reilly released the report entitled *Reducing Risk: Setting Priorities and Strategies for Environmental Protection* on September 26, 1990 (EPA Science Advisory Board, 1990). During his speech introducing the report, Reilly's support of priority-setting processes using relative risk was explicit and seemingly unconditional. He believed that environmental priorities should be based on reducing the risks of the most

serious environmental issues as identified by scientific data (Reilly, 1990). He was also concerned that the EPA was spending money and resources addressing environmental issues that were not necessarily of greatest risk to people and the environment (Reilly, 1991).

In 1996, the SAB was asked to update the *Reducing Risk* report. They were specifically asked to revisit the report and create new rankings of environmental issues based on risk. The SAB established the Integrated Risk Project coordinated by a steering committee with several subcommittees. In their 2000 report the chair of the steering committee explained that as they began their work, they realized that a more useful project would result in one that assisted the agency in understanding how to take a more integrated approach to making decisions (EPA Science Advisory Board, 2000). To this end, the highlight of their work is a "Framework for Integrated Environmental Decision Making." This framework incorporates all of the major tools for decision making currently used by the EPA, including comparative risk, goal setting, performance analysis, risk assessment, and monitoring for results.

While the SAB was preparing their report on integrating risks, the EPA's National Center for Environmental Assessment (NCEA) was conducting a case study using a comparative risk framework. The case study compared the risks from microbial contamination in drinking water to the risks from disinfection by-products from chlorinating water. This was the agency's first attempt to integrate the 1983 risk assessment paradigm with cost-effective analysis. The Science Advisory Board reviewed their work and noted that this approach had promise, but additional research was needed to address some weaknesses with the methodology (EPA Science Advisory Board, 1999).

Carol Browner, who was the EPA administrator during most of the Clinton presidency, continued agency support of comparative risk analysis. During her tenure federal funds became available to state and local governments for conducting comparative risk projects. In addition, staff at USEPA were specifically identified to assist states with coordinating and conducting comparative risk. USEPA also funded two centers for comparative risk, the Northeast Center for Comparative Risk in Vermont and the Western Center for Comparative Risk in Colorado.

Comparative Risk and Politics

As with all agency funding decisions, it is necessary to discuss the role that Congress played in the comparative risk movement in the 1990s. During this time, there was increasing interest in the role of science in decision making. The "Contract

With America," which was a cornerstone of the 104th Congress under Newt Gingrich, included elements of comparative risk. Specifically H.R. 9, the Job Creation and Wage Enhancement Act of 1995, included the following language:

> To the extent feasible, the Federal agency shall provide a statement that places the nature and magnitude of risks to human health in context. Such statement shall include appropriate comparisons with estimates of risks that are familiar to and routinely encountered by the general public as well as other risks. The statement shall identify relevant distinctions among categories of risk and limitations to comparisons.

There was additional language in this bill about comparing risks prior to making agency decisions. This led to an outcry from the environmental community, who perceived comparative risk as being a way to weaken environmental health and safety regulations. The Job Creation and Wage Enhancement Act never made it past the Senate Committee on Governmental Affairs.

In 1997, new legislation emerged in the Senate that incorporated comparative risk. The bill, known as the Regulatory Improvement Act of 1997, would require agencies to conduct a regulatory analysis for any major regulation that was being considered. The regulatory analysis as laid out in the bill included cost-benefit analysis and risk assessment. In addition, this bill included a requirement for the director of the Office of Management and Budget to conduct a comparative risk analysis according to the following:

1. A systematic comparison of the extent and severity of significant risks to human health, safety, or the environment (hereafter referred to as a comparative risk analysis)
2. A study of methodologies for using comparative risk analysis to compare dissimilar risks to human health, safety, or the environment
3. Technical guidance and recommendations on the use of comparative risk analysis to assist in allocating resources within and across agencies to set priorities for the reduction of risks to human health, safety, or the environment

Even though the Regulatory Reform Act of 1997 died in the Senate, it highlighted the role of politics in comparative risk. Indeed, the link between conservative Republicans and comparative risk created some credibility problems as state and local governments embarked on their own plans to prioritize environmental issues. For example, in Ohio, the environmental activist community was reluctant to be involved in the project, and at least one statewide environmental organization called the Ohio Comparative Risk Project a hoax. Nevertheless, comparative

risk projects did proceed across the country in a wide array of political climates, and most projects used similar methods.

The Comparative Risk Process

The process of comparative risk can be compared to an environmental planning endeavor that seeks to make recommendations to focus resources on solving problems that pose the greatest risk. The process offers opportunities for debate and discussion among diverse stakeholders rather than the more traditional approach to decision making that involves structured public comment either in writing or in the form of testimony.

Committee Structure

While the comparative risk process at the federal level has mainly involved technical experts and environmental agency personnel, state and local governments have expanded participation to explicitly include public perception. Comparative risk projects have been structured to include a decision-making group, committees of scientists and other experts, and the public. The outcome of most processes is a ranking of risk and a compilation of available data about environmental conditions. Not all comparative risk projects result in policy recommendations, but several of them have.

Coordinating Committee. Sometimes referred to as the Public Advisory Group (PAG) or the Steering Committee, this group is critical to project management. In most projects this group includes diverse viewpoints such as business and industry, environmental organizations, members of the public, academics, and agency personnel. It plans and implements the project, usually with the assistance of staff members from the sponsoring organization. In most projects, this is also the group that ranks environmental risks based on the information gathered by other groups.

The composition of this group is extremely important because it will be the most scrutinized in the project. When the risk ranking is released, those who disagree with the priorities will look at who is on the coordinating group and challenge the credibility of the entire project based on its participants.

Scientific and Expert Involvement. One of the most astounding components of comparative risk projects has been the universal involvement of high-quality scientists and other experts as volunteers in the effort. This is astounding because

these scientists volunteer their time and expertise to the effort. Typically, work groups have been formed around gathering data about environmental issues that affect human health, ecosystems, and quality of life in the area of concern. The work groups have gathered data, identified data gaps, and contributed to the production of some of the most comprehensive documents detailing current environmental conditions.

Public Involvement. Perhaps the most critical element of comparative risk is involving the public in meaningful dialogue about environmental issues that affect them. The purpose of involving the public is to gather data about risk perceptions that will be incorporated into ranking environmental threats to the area. Public involvement methods include surveys, interviews, focus groups, and direct participation in project committees.

Relying on surveys to incorporate concerns of the public is one way to gather data from people who might not participate in the project in any other way. However, it has been argued that most comparative risk projects are operating with limited technical and scientific data, so it may be better to offer opportunities for more direct involvement from the public (Darnall and Jolley, 2004).

Project Methods and Outcomes

Comparative projects usually proceed in multiple phases. The first phase includes identifying issues, gathering data, and ranking risk. The second phase includes developing recommendations for policy and determining priorities for action based on the ranked list of issues.

Risk Ranking. Regardless of deviations in project structure, most projects result in a list of issues either ranked or rated on the basis of risk to the environment, human health, and quality of life. Every project starts with environmental problems that are unique to their state or local area and ranks these problems using different approaches. Some projects have attempted to be quantitative and objective in their approaches,; others have embraced subjectivity. Examples of how some projects have ranked risk can be found in Exhibit 8.1.

Environmental Indicators. One of the most important contributions of comparative risk projects has been the development of and attention to indicators of environmental quality. As project participants have researched environmental conditions in their respective locales, they have uncovered and compiled a wide array of data. In some instances these data have been labeled *benchmarks* owing to the

fact that comparative risk projects use currently available data on which to base risk ranking.

Recognizing the contribution of comparative risk to developing comprehensive environmental data, the USEPA focused resources on environmental indicators. In 1994, USEPA provided funding to the Florida Center for Public Management, at Florida State University, to conduct and coordinate a State Environmental Goals and Indicators Project (SEGIP). One purpose of SEGIP was to compile environmental indicators to help state government enhance its use in decision making. Comparative risk projects provided critical information for SEGIP (see http://www.pepps.fsu.edu/segip for further information).

The Impact of Comparative Risk on Policy Making

Comparative risk projects have had very little impact on policy making, a situation that is somewhat perplexing considering the fact that most projects are supported by policy makers who want better information on which to base their decisions. One explanation for the limited impact might be that in the course of the project, limitations of technical information and environmental data are uncovered, which minimizes the credibility of the risk rankings.

While there have been some minimal adjustments in some state and local environmental programs based on comparative risk results, overall there has been no significant effect (Jones and Klein, 1999). State and local governments generally develop their environmental policy priorities around federal government mandates and available resources, so there is often little local control over which environmental problems to tackle first. With this in mind, it is easy to see that state and local comparative risk projects have the potential for being highly controversial.

A major controversy arises when project participants promise that the results of the effort will lead to changes in environmental policy. As Jones and Klein note, comparative risk ranking "cannot replace the decades of democratic policy development" (1999). In the case of the Ohio Comparative Risk Project discussed in Chapter Twenty-Six of this book, there was a great deal of media attention to the project. Generally the media portrayed the project in a positive light, but several media accounts elevated the project to a panacea for solving the most important problems with limited resources. Interestingly, when the policy suggestions were released from the project, there was very little media attention.

In addition to the need to address federal mandates, there are other factors that contribute to the relative failure of comparative risk to deliver changes in environmental decision making at the state and local levels. One key factor is a lack of

continuity in governance during a project. Most comparative risk projects take several years, during which time governors are reelected or not, heads of key environmental agencies rotate in and out, and other elected officials are distracted by more pressing issues than setting environmental priorities. This lack of leadership continuity at the state and local levels mirrors the situation at the federal level, in which support for comparative risk waned when the administration changed. It is clear that a key factor in the ability to change policy lies in the sustained support from political operatives, a condition that has been lacking in most situations.

One other factor contributing to the lack of policy change is dissent among project participants while developing policy strategies. Consider the diversity of viewpoints involved in a comparative risk project and the intention of reaching consensus on recommendations; it should be clear that there is potential for contentious results. When participants are politically savvy they can take their dissent to the media, which can undermine many years of work in a few short quotes in the newspaper. With the credibility of the project in question, policy makers are less likely to make any policy changes for fear of public outcry.

Conclusion

Comparative risk and environmental priority setting reached a climax in the mid- to late-1990s with numerous projects being completed all across the country and at all geographic levels. Although government agencies coordinated many projects, some local projects were coordinated by grassroots groups and nonprofit organizations. The success of comparative risk may have led to its downfall as an influential tool in environmental decision making. In the course of ranking risk and producing environmental indicators, data gaps were uncovered that made explicit the difficulties of incorporating science into environmental decision making.

When comparative risk projects first began, they were promoted as a rational way of improving environmental decision making. Now, more than a decade later, the impact of comparative risk has been largely local and minor. The federal government, including Congress, has moved on to other priorities.

Thought Questions

1. Discuss the history of risk assessment and how the accepted risk assessment paradigm applies to the comparative risk framework.
2. What was the motivation behind the first comparative risk projects in the early 1990s? Discuss the role of politics in the influence of comparative risk.

3. How is comparative risk different from risk assessment?
4. Why did comparative risk have almost no effect on environmental decision making?

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CHAPTER NINE

RISK IN THE WORKPLACE

Where Analysis Began and Problems Remain Unsolved

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P. Barry Ryan

Learning Objectives

Students who complete this chapter will be able to

1. Understand the scope, magnitude, distribution, and temporal changes in the major safety and health hazards workers face on the job, both in absolute terms and relative to analogous risks in the community or ambient environment.
2. Become familiar with the institutions (primarily OSHA and NIOSH) set up in the United States to evaluate and control these hazards, and with the major legal, scientific, and political challenges these agencies have faced over the past 35 years.
3. Understand how quantitative risk assessment (QRA) for occupational hazards has developed, how it differs from QRA as applied to similar hazards in the general environment, and which aspects of methodology remain the least well-developed.
4. Appreciate the complex interplay of science and policy involved in controlling occupational risks—in particular, the limited role of formal cost-benefit balancing in managing workplace risks—and be able to discuss some of the innovative approaches government, industry, and labor are contemplating to reduce risks through means other than command-and-control regulation.

Background

More than 60 percent of U.S. citizens ages 18 and over work full-time, totaling more than 130 million persons in more than 8 million separate establishments. These people face many of the same hazards on the job as those who do not work full-time face in their daily lives, including hazards in the ambient environment, the community, the home, and in transportation. As we will see, however, workers almost invariably are exposed to these hazards at a much higher frequency, intensity, or concentration. In addition, of course, workers are exposed to various unique hazards that are not found outside the occupational setting. A central irony in considering occupational risk assessment in context of the broad field of risk assessment is that most environmental health standards were motivated by discoveries of human disease in the workplace (see Table 9.1) and are

TABLE 9.1. DISEASES FIRST NOTED IN OCCUPATIONAL SETTINGS THAT IMPELLED ENVIRONMENTAL STANDARDS.

Disease	Cause	References
Asbestosis	Asbestos exposure	Selikoff and others (1965); Selikoff and others (1967); Selikoff and Greenberg (1991).
Silicosis	Exposure to silica-containing rock dust	For a historical overview, see Bufton and Melling (2005).
Black lung	Exposure to coal dust	Black lung disease was recognized in the early part of the 20th century. For an overview of the subject, see Smith (1981).
Byssinosis	Exposure to cotton dust	Corn (1981).
Various malignant and other diseases	Radiation exposure, including radon in mines	For an overview, see Upton (1987).
Lead poisoning	Lead dust exposure	Lead poisoning was known to the ancients; several more recent papers review effects. See Baker and others (1979); Winegar and others (1977).
Neurological symptoms	Pesticide exposure, solvent exposure	Landrigan and others (1980); Baker and others (1985).
Dermatitis, hyper-pigmentation, keratoses, black-foot disease	Arsenic exposure	Landrigan and others (1980).
Leukemia	Benzene exposure	Landrigan (1987).

based quantitatively on scientific studies of worker populations. For that matter, quantitative estimates of the value of averting a "statistical fatality" are also derived from economic studies in the workplace—but the protections that have resulted from these inquiries have either failed to include the workers themselves or have been applied in a disparate fashion. Whether measured by public and private expenditures on control, monetary penalties levied against individuals and companies who defy regulatory standards, or the level of public and media concern, hazards in the ambient environment capture much greater attention than similar or identical hazards faced to a greater degree by blue-collar and white-collar workers.

This chapter focuses on occupational illness, where risk assessment methods have of necessity become relatively well developed, but we need to recognize at the outset that occupational injury was the first workplace problem area to gain national attention. Events such as the Triangle Shirtwaist Fire of 1911, which claimed 146 victims in New York City (Von Drehle, 2003), the 1947 explosion in Texas City, in which at least 580 workers and others died when a docked ship carrying ammonium nitrate exploded (Pandanell, 2005), and landmark books such as Upton Sinclair's *The Jungle* ([1906] 1985, detailing working conditions in the meatpacking plants around Chicago) focused some attention on occupational injury events and led finally to the creation of the Occupational Safety and Health Administration (OSHA) in 1970, the same year as the United States Environmental Protection Agency (EPA) was established. Indeed, although perhaps as many as 10 times more workers die prematurely from occupational disease than from acute occupational injury (see below), and although there were galvanizing examples of worker disease in the past (e.g., Hawk's Nest, black lung, brown lung, and vinyl chloride; see Cherniack, 1986; Young and Rachal, 1996; Annas, 1981; Jones, 1981), OSHA continues to devote a very large and arguably a growing percentage of its staff, budget, and enforcement resources to the problem of worker injury.

Acute Fatal and Nonfatal Injuries

The most fundamental measure of the risk of occupational accidents, of course, is the national death toll and the related measure of death rate. Table 9.2 shows the number of workplace fatalities since OSHA was created 35 years ago, along with the number of U.S. civilian employees in each year and the crude death rate (in fatalities per 100,000 workers). The most striking aspect of these statistics is the rather steady decline in total deaths and the (almost) inevitable decrease in death rate over the 35-year period—although some critics of OSHA (Kniesner and Leeth, 1995) assert that the slope of the downward trend was actually steeper before 1970 than after (which, if true, would not necessarily be an indication of

TABLE 9.2. WORKPLACE FATALITIES SINCE THE PASSAGE OF OSHA.

Year	Employment Work Deaths	Fatality Rate (x 1,000)[a]	(Per 100,000 Workers)
1970	13,800	77,700	18
1971	13,700	78,500	17
1972	14,000	81,300	17
1973	14,300	84,300	17
1974	13,500	86,200	16
1975	13,000	85,200	15
1976	12,500	88,100	14
1977	12,900	91,500	14
1978	13,100	95,500	14
1979	13,000	98,300	13
1980	13,200	98,800	13
1981	12,500	99,800	13
1982	11,900	98,800	12
1983	11,700	100,100	12
1984	11,500	104,300	11
1985	11,500	106,400	11
1986	11,100	108,900	10
1987	11,300	111,700	10
1988	10,800	114,300	9
1989	10,400	116,700	9
1990	10,500	117,400	9
1991	9,900	116,400	9
1992[b]	6,217	117,000	7
1993	6,331	118,700	6
1994	6,632	122,400	5
1995	6,275	126,200	5
1996	6,202	127,997	4.6
1997	6,238	130,810	4.7
1998	6,055	132,684	4.5
1999	6,054	134,666	4.5
2000	5,920	136,377	4.3
2001	5,915[b]	136,252	4.3
2002	5,534	137,700	4.0
2003	5,575	138,928	4.0
2004	5,703	140,411	4.0

[a]Employment is an annual average of employed civilians 16 years of age and older from the Current Population Survey, adjusted to include data for resident and armed forces from the Department of Defense.

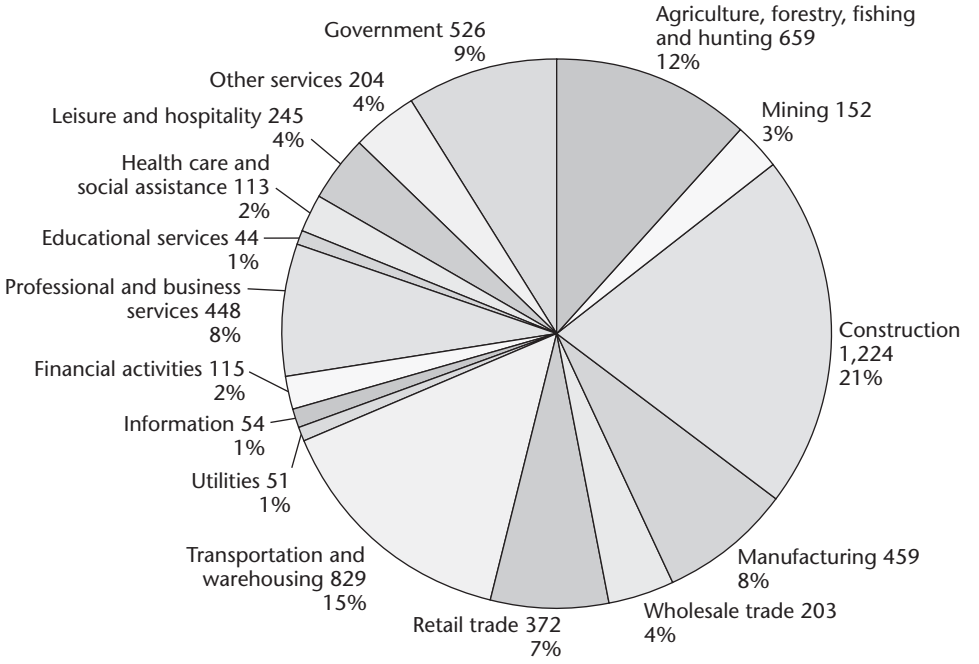
[b]Excludes fatalities from the events of September 11, 2001.

Sources: Fatality information for 1971 to 1991 is from National Safety Council Accident Facts, 1994. Fatality information for 1992 to 2004 is from the Bureau of Labor Statistics, Census of Fatal Occupational Injuries. (In 1994 the National Safety Council [NSC] changed their reporting method for workplace fatalities and adopted the BLS count. The earlier NSC numbers are based on an estimate; the BLS numbers are based on an actual census.)

OSHA's ineffectiveness, since we might expect continued decrements in the fatality rate to be harder and harder to achieve as the absolute rate decreased). Perhaps more ominous is the increasing number of accidental deaths in each of the past two years for which there are data (2003–2004), the first sustained increase since 1993–1994 and the only period since 1970 in which the fatality rate has actually increased. Also note that the current population fatality rate of 4.1 per 100,000 per year yields a working-lifetime risk of roughly 1.8×10^{-3}, or more than one thousand times higher than the 10^{-6} benchmark EPA often uses to define the lower limit of acceptable risk.

Figure 9.1 shows that most of the 5,713 fatalities in 2004 occurred in the construction, transportation, and agricultural sectors of the economy. Figure 9.2 shows that in recent years, the total number of work-related homicides has decreased significantly, but the causes more squarely within OSHA's regulatory and enforcement purview (fatal falls, deaths caused by objects striking or crushing

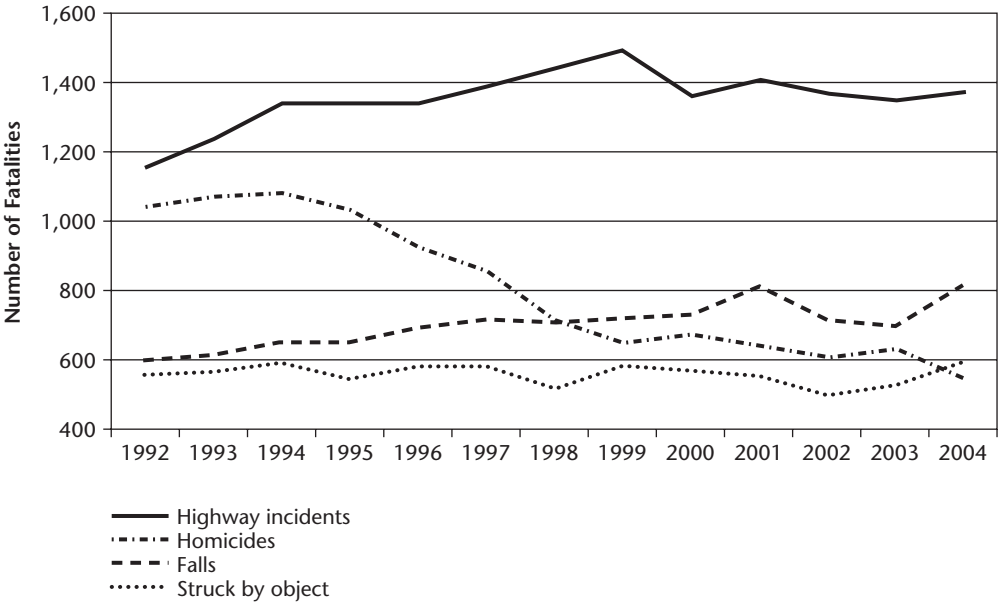
FIGURE 9.1. OCCUPATIONAL FATALITIES BY INDUSTRY, 2004: PRIVATE SECTOR, GOVERNMENT, AND SELF-EMPLOYED (5,703 TOTAL FATALITIES).



Note: Percentages may not add up to totals because of rounding.

Source: Bureau of Labor Statistics (2004).

FIGURE 9.2. THE FOUR MOST FREQUENT WORK-RELATED FATAL EVENTS, 1992–2004.



Note: Data from 2001 exclude fatalities from September 11, 2001, terrorist attacks.

Source: Bureau of Labor Statistics (2004).

workers, acute exposures to electric current or hazardous substances) have remained steady or increased in number.

Table 9.3 provides further detail on the racial composition of workers killed on the job, showing most notably that over the past 10 years, the death toll in all other racial groups has dropped while the number of deaths among Hispanic workers has increased by roughly 40 percent.

For every fatal injury in the United States, nearly one thousand other nonfatal injuries also occur. In 2004, the Bureau of Labor Statistics reported a total of 4.3 million workplace injuries and illnesses; all but roughly 200,000 of these were injuries; of the illnesses recorded, nearly half were skin conditions or occupational hearing loss, and it is unclear to what extent *any* chronic work-related illnesses such as cancer, heart disease, or neurological damage are recorded. The injury rate for the entire population was roughly 4.8 cases per 100 workers in 2004, with rates of 10 per 100 or more (that is, one chance in 10 of being injured during the year) in especially risky occupations such as primary metal manufacturing, wood

TABLE 9.3. FATAL WORK INJURIES BY RACE, 1992–2004.

	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001[a]	2002	2003	2004
Total Fatalities	6,217	6,331	6,632	6,275	6,202	6,238	6,055	6,054	5,920	5,900	5,534	5,559	5,703
White	4,711	4,665	4,954	4,599	4,586	4,576	4,478	5,019	4,244	4,175	3,926	3,976	4,030
Black or African American	618	649	695	684	615	661	583	627	575	565	491	542	542
Hispanic	533	634	624	619	638	658	707	730	815	895	841	791	883
Asian or Pacific Islander	169	190	179	161	170	195	148	192	185	182	140	158	177
American Indian Alaskan Native	36	46	39	27	35	34	28	57	33	48	40	42	26
Other Races/ Not Reported	150	147	141	185	158	114	111	146	68	50	96	50	41

[a]Data from 2001 exclude fatalities from September 11, 2001, terrorist attacks.

Source: Bureau of Labor Statistics (2004).

products manufacturing, air transportation, courier services, and nursing home care. More than half of the injuries in 2004 were serious enough to involve one or more days away from work and/or a change of working conditions (i.e., transfer to a different job or restrictions placed on work activities) dictated by the injury; nearly 25 percent of these lost-workday injuries were serious enough to result in one month or more of an absence from work.

Work-related fatalities can be enumerated rather precisely, with the annual number of deaths attributable to occupational injuries in the United States placed in the 5,000 to 8,000 range (Pratt, Kisner, and Helmkamp, 1996; Stout and Linn, 2002). The national recording systems doubtless fail to count some fatal injuries occurring at work, either because of exemptions to the required reporting or the failure of some employers to file reports. A recent article (Rosenman and others, 2006) found that the Bureau of Labor Statistics (BLS) data accounted for only about 32 percent of work-related injuries (fatal and nonfatal) that occurred in Michigan during 1999–2001, suggesting a substantial underestimate.

Occupational Disease

The total number of deaths attributed to occupational exposures is more difficult to quantify. Inspection of Table 9.1 reveals the potential for numerous occupationally related diseases. Research in this area often focuses on a single disease or a single industry; compendia of data are not available. However, the number is certainly much greater than the numbers for injury fatalities. Neurodegenerative diseases, lung diseases, and various forms of cancer suggest a much higher total likely in the 50,000 to 75,000 deaths-per-year range. The true numbers may be even higher, since the effects of occupational exposures to physical and chemical stressors are not completely understood. Perhaps the most sophisticated estimates of the number of occupational diseases in the United States were derived by Leigh and colleagues (1997), who developed an estimate of "the incidence, the mortality, and direct and indirect costs associated with occupational injuries and illnesses in the United States" for the year 1992 using a complex methodology. They took data from several government agencies and made use of an attributable risk proportion argument whereby the fraction of risk directly attributable to occupational exposures is applied to general morbidity and mortality statistics. They estimated that roughly 60,000 deaths and 850,000 illnesses annually can be attributed to chronic diseases caused by workplace exposures.

Occupational Exposures

Unfortunately, it is virtually impossible to produce a predictive (as opposed to the epidemiology-based estimates discussed above) estimate of the aggregate risk of occupational exposures to toxic substances, due to decades of national inatten-

tion to the task of measuring workplace exposures. There has never been a comprehensive survey of what substances U.S. workers are exposed to, and at what concentrations; the last attempt to survey a representative sample of workplaces for certain substances was in 1983, when the National Institute of Occupational Safety and Health (NIOSH) made exposure measurements in approximately 4,500 workplaces. For comparison, since 1983 there have been at least five separate national surveys to gauge the nutritional status of U.S. residents, several of which have included extensive survey questions to estimate exposures to chemicals in the home and extensive measurements of the body burdens of various substances in residents.

The largest database of nonrandom samples of contaminant concentrations in U.S. workplaces is the result of OSHA compliance inspections. Since 1979, when the agency began collecting inspection information in a single database, OSHA inspectors have collected more than two million air, wipe, and bulk samples. OSHA has never published reports analyzing trends in these data, and only a handful of journal articles have done so for various single substances (Gomez, 1991; Yassin, Yebesi, and Tingle, 2005). Hence, even the most basic questions about the average contaminant levels workers are exposed to can only be roughly estimated. Simply starting from the premise (see below) that because EPA often strives for an acceptable risk target of 10^{-6}, and OSHA often finds it difficult to reduce workplace risks to below 10^{-3}, we might conclude that workers generally face concentrations roughly one thousand times higher than those citizens face in the ambient environment. A preliminary investigation of this rule of thumb (Finkel, 2005), however, suggests that it may hold for substances like benzene, where an OSHA standard has been in effect for nearly 20 years, but that the average ratio of workplace to ambient concentration is closer to one *millionfold* for substances like methylene chloride (where a new OSHA regulation has been in effect for fewer than 10 years) or perchloroethylene (where OSHA still enforces a threshold limit value [TLV®] from the late 1960s).

With regard to *criteria pollutants* (see Chapter 13), occupational settings typically display higher concentrations of airborne pollutants than are allowed in community, or ambient, air, but perhaps not on the order of 3 to 6 orders of magnitude, as seen in the case of toxic air pollutants. Table 9.4 compares the allowable values for several air contaminants. *Permissible exposure limits* (PELs) are occupational standards that supply a degree of protection for workers exposed to such compounds in their work environment. They represent time-weighted, eight-hour exposure levels. For example, in the case of nitrogen dioxide, a worker could be exposed to 5 ppm of NO_2 for an entire eight-hour shift without a violation of the PEL. Similarly a worker could be exposed to 10 ppm for four hours and there would be no violation of the standard if no further exposure were experienced during the eight-hour shift. National ambient air quality standards are generally much lower, as

TABLE 9.4. A COMPARISON OF OCCUPATIONAL STANDARDS AND AMBIENT AIR QUALITY STANDARDS.

Compound	PEL[a]	NAAQS[b]	Notes[c]
NO_2	5 ppm	0.053 ppm	Annual average
SO_2	5 ppm	0.03 and 0.14 ppm	24-hour and 1-hour averages
O_3	0.1 ppm	0.08 and 0.12 ppm	8-hour and 1-hour averages
CO	50 ppm	9 and 35 ppm	8-hour and 1-hour averages
Lead	0.05mg/m^3	0.0015 mg/m^3	Quarterly average[d]
Dust	15 mg/m^3	0.050 and 0.150 mg/m^3	24-hour and 1-hour averages

[a]*Permissible exposure limit:* eight-hour time-weighted average allowed values in occupational settings.

[b]*National ambient air quality standards:* allowable outdoor concentrations; designed to protect health and supply a margin of safety.

[c]NAAQS often have multiple standards with different averaging times for the same contaminant. The longer the averaging time, the lower the allowed concentration.

[d]Rarely violated since the removal of lead from gasoline.

they are required to protect the general population (including sensitive subpopulations) and supply an adequate margin of safety for such individuals. Note that Table 9.4 involves a comparison of regulatory limits, whereas the preceding discussion of toxic air pollutants involves a comparison of measured or modeled concentration values—therefore, the ratios of occupational to environmental values must be interpreted separately in light of the different sorts of comparisons being made here.

Note the large differences in allowable concentrations in the work environment. Typically, regulations permit workers to be exposed to a factor of ten or more higher concentrations. In part, this reflects differences in how OSHA and EPA set standards, and in part it reflects differences in the feasibility of reaching particular limits (both "objective" constraints on feasibility involving economic and technological limits, and also political constraints on feasibility driven by the generally much greater public and interest-group concern with environmental than with workplace exposures). To some extent, workers are viewed as generally healthier than the general population and as having chosen to face certain risks and be compensated for this risk through payment of wages, but neither assumption is necessarily correct.

An exception to this general statement is found for ozone exposure. Allowable ozone exposure in the occupational environment does not differ substantially from that allowable in the community, since health effects are found at only modestly elevated concentrations of this irritating air contaminant.

Together, all these injuries (fatal and nonfatal) and illnesses exact a huge cost on the nation, albeit one that is hard to estimate or even to define precisely. In particular, less severe impairment—ranging from minor hearing loss to full disability—increases the social cost of occupational disease substantially (Leigh and others, 2004). Considering only some of these costs (e.g., medical expenses and lost earnings) and explicitly ignoring other costs that are even harder to quantify (e.g., pain and suffering and effects on the families of the victims), Leigh and others (1997) estimated nearly 10 years ago that occupational injuries and illnesses cost approximately $171 billion annually (roughly 2 percent of the entire U.S. gross domestic product). A recent report (Islam and Anderson, 2006) estimated the cost of work-related injuries and disease to be $176 billion annually in the United States.

Controlling exposures to workplace hazards also involves substantial costs, although the amount already spent on the controls that currently exist may bear no relationship to the amount that would be needed to avert the injuries and illnesses that still occur. One such retrospective cost estimate comes from Johnson (2001), who estimated that OSHA regulations cost the economy roughly $40 billion annually. However, regulatory cost estimates are notoriously unreliable, and many observers believe that common errors and biases therein tend to exaggerate rather than to underplay the true cost of controls; in the workplace, the most comprehensive study (OTA, 1995) suggested that costs predicted before regulations are implemented often exceed actual costs by a factor of two or more.

U.S. Federal Apparatus to Assess and Manage Workplace Risks: OSHA

Congress established two agencies, OSHA and NIOSH (now part of the Centers for Disease Control and Prevention), when it enacted the Occupational Safety and Health Act in 1970, in the first wave of environmental and health legislation that also created the EPA and (two years later) the Consumer Product Safety Commission. As a rough rule of thumb, OSHA commands about one-twentieth of the resources of EPA; it has roughly 2,200 employees (down from a high of 2,950 employees in 1980), and a budget of roughly $470 million annually (as compared with EPA's budget of roughly $8 billion). OSHA uses its resources to undertake three fundamentally different and complementary activities: enforcement, standard-setting, and education/outreach/partnership programs.

Enforcement. OSHA employs roughly 1,200 inspectors, who visit worksites and look for violations of specific OSHA safety and health standards or breaches of the "general duty clause" of the OSH Act, which allows OSHA to issue citations against employers who knowingly fail to abate "recognized hazards that are causing or are likely to cause death or serious physical harm" (even in the absence of

a specific standard). In 2004, OSHA conducted 39,400 inspections: roughly half of these were programmed inspections of companies whose injury rate the previous year was among the highest in the nation. Roughly one-quarter of the inspections were in response to complaints filed by employees or to accidents that caused fatalities or multiple hospitalizations, and roughly one-quarter were in response to referrals from other local, state, or federal organizations or follow-up inspections to verify satisfactory abatement of hazards previously identified. Nearly 60 percent of all inspections now involve construction sites, although that percentage is artificially inflated because OSHA records multiple inspections at the same construction site when it examines the work of different contractors. When OSHA inspectors find violations at the worksite, they can recommend various different levels of monetary penalty; about 70 percent of all violations are deemed *serious,* meaning that they cause a substantial probability of death or serious physical harm, with an average penalty of roughly $900 per violation. Another 3 percent are repeat violations of the same standard by the same employer (roughly $4,000 average penalty), and about 0.5 percent are *willful*, meaning that they are committed knowingly by an employer who either intentionally disregards the standard or is "plainly indifferent to its requirements," with an average penalty of $30,000. A Pulitzer prize-winning series in the *New York Times* (Barstow, 2003) documented that although over 1,200 cases between 1982 and 2002 involved willful violations that had led to worker deaths, OSHA sought criminal charges against the employers in only about 80 of those cases (7 percent). Finally, unlike EPA, which relies on state personnel to enforce many of its regulatory programs, OSHA uses federal personnel to enforce its programs in only 24 of the 50 states. The other 26 states employ their own inspectors, and together these "state plan programs" conducted over 57,000 inspections in 2004, with a very similar pattern to the federal program of planned/unplanned inspections, types of citations issued, and industrial sectors emphasized. Because OSHA has jurisdiction over more than 8 million separate U.S. establishments, even at a rate of 100,000 federal and state inspections per year, it would theoretically take more than 80 years for inspectors to visit each worksite even once.

Regulation. The OSH Act empowers OSHA to set mandatory standards to govern specific safety and health risks. Congress gave OSHA special authority during the first two years of the agency's existence (1970–1972) to "inherit" existing national consensus standards such as those developed by the American Society for Testing and Materials, the National Fire Protection Association, and other organizations, and adopt them as mandatory regulations. Also during this period OSHA adopted roughly 400 TLVs® that had been recommended before 1968 by the American Conference of Governmental Industrial Hygienists (ACGIH),

establishing them as mandatory permissible exposure limits (PELs). Since 1972, however, OSHA has had to promulgate standards under a lengthy (and increasingly complex) process involving public, scientific, White House, and judicial review. Perhaps the most significant aspect of this process from the point of view of controversies in risk assessment is that unlike most other agencies, OSHA by law must receive public comment on its regulatory proposals during public hearings, rather than via a "notice and comment" process that allows interested parties to submit their comments in writing only. The OSHA rulemaking hearings resemble civil trials in some ways, with a judge presiding and the key parties (OSHA staff and public questioners) subject to cross-examination by the other party. Some observers believe that this process amounts to a more rigorous (as well as more open) form of scientific peer review than occurs in the traditional academic peer review process. Due in part to the procedural hurdles the agency must surmount, and in part to the perhaps surprisingly small number of staff assigned to develop standards (of OSHA's 2000 employees, roughly 60 of them work on rulemaking and only about 5 of these have doctoral degrees in the relevant scientific or economic disciplines), OSHA has only promulgated about 40 safety standards and 25 health standards since 1972. Some of the health standards cover generic issues (e.g., respiratory protection, employee access to medical and exposure records, and material safety data sheets and other hazard communication issues), while others (notably an early standard governing 14 carcinogens not in widespread use) specify work practices but do not set exposure limits. Thus, for only 16 substances (see Table 9.5) has OSHA established any mandatory exposure limits other than the several hundred TLVs® inherited in 1970, many of which are now outdated; almost all of the changes that ACGIH has made to TLVs® since 1968 have been in the direction of lowering rather than increasing the recommended exposures.

In the past eight years, OSHA has issued only two health standards; one, protection against accidental needlesticks in health-care settings, was written by Congress, and the other, a revised standard for hexavalent chromium, was produced in response to a court order. Two of OSHA's most far-reaching standards were promulgated but never took effect. In 1989, OSHA attempted to modernize its list of over 400 PELs to keep up with changes (almost exclusively more stringent changes) to the TLVs® between 1970 and that date. A federal judge invalidated the new list, however, on the grounds that OSHA had failed to undertake any of the quantitative risk assessment the Supreme Court had deemed essential in the 1980 *Benzene* decision (see below). On the day before the January 2001 inauguration of President George W. Bush, OSHA's new ergonomics standard was to take effect (all new regulations were subject to a temporary moratorium imposed a week after the inauguration), but both houses of Congress passed bills in March 2001 revoking the standard. Although musculoskeletal disorders (MSDs)—ergonomic

TABLE 9.5. SUBSTANCES WITH A PERMISSIBLE EXPOSURE LIMIT SET BY OSHA SINCE 1971.

Substance	Year Final Standard Issued (After Subsequent Revisions, If Any)
Vinyl chloride	1974
Coke oven emissions	1976
Dibromochloropropane	1978
Arsenic	1978
Cotton dust	1978
Acrylonitrile	1978
Lead	1978 (general industry); 1993 (construction)
Ethylene oxide	1984
Benzene	1987
4,4′-Methylenedianiline	1992
Cadmium	1992
Formaldehyde	1992
Asbestos	1992
1,3-Butadiene	1996
Methylene chloride	1997
Chromium (hexavalent)	2006

injuries—account for roughly one-third of all workplace injuries that involve one or more lost workdays, industry groups vociferously opposed OSHA's attempt to require companies to correct conditions that had led to diagnosed MSDs.

Education and Partnership. OSHA also produces a wide variety of guidance documents to help interpret standards, or to substitute for regulations in areas where it feels that lack of knowledge rather than willingness to comply is a major impediment to safer workplaces. It provides most of the funding for consultation projects in each U.S. state, under which employers can request on-site visits by safety and health experts (housed generally at state universities or state government agencies), who provide free advice on hazard abatement, with no connection to the enforcement program; in 2004 over 31,000 such visits were conducted. In recent years OSHA has established a program of over 200 partnerships with trade associations and individual companies, generally involving a trial of more

streamlined inspections if the parties meet specified targets for improved safety and health results. More recently, OSHA has also set up several hundred "alliances" with industry and nongovernmental organizations, which generally commit OSHA and the participating organization to specific outreach or training activities but do not generally envision changes in workplace conditions, affect enforcement, or track safety and health results.

Role of the EPA in Occupational Risk Management

While the primary role of the EPA has focused on the protection of the health of individuals in the community setting, the agency has also been involved with certain aspects of occupational health protection.

Development of Acute Exposure Guidelines. EPA has an ongoing program designed to assess appropriate guidelines for short-term or *acute* exposure to environmental contaminants. These Acute Exposure Guideline Levels (Environmental Protection Agency, 2006a) focus on exposures that occur very infrequently, perhaps only once in a lifetime and that might be caused by a spill, a train crash, or other catastrophic event. While following EPA's general charge of protecting the public from exposure to toxic compounds, these guidelines have their greatest utility in protecting workers who are more commonly exposed to the highest levels of chemicals in the air that they breathe.

According to EPA (2006a), AEGLs are threshold exposure limits for airborne contaminants applicable to the general public that occur over acute time scales, usually defined as ten minutes to eight hours. Such exposures are likely to produce toxic effects. Airborne concentrations below the AEGL-1 represent exposure levels that can produce mild and progressively increasing, but transient and nondisabling, effects. AEGL-1 levels are airborne concentrations above which most individuals, including sensitive individuals, are likely to experience discomfort but which are transient and not likely to disable the individual. The next level, AEGL-2, may result in long-lasting or permanent effects and may result in impairing the individual's ability to escape from the exposure. Like AEGL-1 levels, these apply to airborne concentrations. The highest AEGL is AEGL-3, a level that, if exceeded, is likely to cause life-threatening effects, or even death. While AEGLs are written to apply to all members of the public, workers are most likely to experience such exposures and are at higher risk because of this.

It is of interest to examine how such standards are developed. In developing AEGLs, EPA works with both national authorities such as OSHA and local authorities, including county public health offices. Typically, EPA makes use of a Federal Advisory Committee (2006) that consists of scientists, physicians, and

stakeholders drawn from the community at large and who act as special government employees in developing these standards for exposure. The process is iterative, with reviews by two different external committees before the final AEGL is finalized. As can be seen from this development, the AEGL process is designed to afford input from many different groups of scientists and stakeholders in developing these important standards. Further, the iterative process ensures that up-to-date information from the published literature as well as ancillary information from other sources is used to afford protections to those likely to be exposed.

Toxic Substances Control Act, Section 8(e). Section 8(e) of the 1976 Toxic Substances Control Act (TSCA) states that

> Any person who manufactures, imports, processes or distributes in commerce a chemical substance or mixture and who obtains information which reasonably supports the conclusion that such substance or mixture presents a substantial risk of injury to health or the environment shall immediately inform the (EPA) Administrator of such information unless such person has actual knowledge that the (EPA) Administrator has been adequately informed of such information [Environmental Protection Agency, 2004].

According to the EPA guidelines for TSCA Section 8(e):

> The term "person" includes the following: any natural person, corporation, firm, company, sole-proprietorship, joint-venture, partnership, association, or any other business entity, any State or political subdivision of a State, any municipality, any interstate body, and any department or agency of the Federal Government.

This implies that workers are protected by this Act in that all workplaces are required to report the use of any chemical or mixture of chemicals deemed hazardous. From an occupational risk assessment point of view, this is beneficial to the worker. Although no risk assessments are required through this Act, the process of reporting the use of hazardous material in the workplace is a matter of public record and thus accessible to the worker, the union, or any other entity acting in the interest of the worker. In a recent example of interagency cooperation using TSCA 8(e) authority, EPA and OSHA jointly issued a hazard advisory warning users of 2,4-dichlorophenol (a chemical feedstock used in herbicide production) that the substance in its molten form can cause death if even a relatively small amount contacts the skin and is not immediately removed (EPA, 2000). EPA learned of the hazards of this exposure route through a report of a worker fatality submitted under TSCA 8(e) by the major producer of 2,4-dichlorophenol.

Agriculture. The impact of agricultural chemicals, including pesticides and fertilizers, is controlled by EPA through the Safe Drinking Water Act and the Clean Air Act and its 1990 amendments. EPA's role is to ensure that the air we breathe and the water available for public consumption are safe and unlikely to produce harm. EPA also takes a secondary role in ensuring that our food supply is safe by enforcing regulations on pesticide application and registration; only certain pesticides may be used on agricultural products destined for the food supply, and only specified amounts may be used.

The risks experienced by farmers and farm workers are affected by these regulations. Control of the kinds and amounts of pesticides used on agricultural crops reduces the exposure experienced by workers. Further, EPA regulates the *reentry time,* the time workers must wait before returning to a field onto which pesticides can be applied. In conjunction with controls placed by other agencies (e.g., OSHA, on work practices), such control reduces the adverse health impact on the worker. Although worker exposure to pesticides would seem to be squarely within OSHA's purview, a federal court decision in 1974 ruled that EPA's initial reentry rules preempted OSHA. Since then, Congress has forbidden OSHA from conducting inspections at farms that employ 10 or fewer persons, leaving EPA as the only agency with meaningful enforcement authority in many situations.

Case Study: The Libby, Montana, Superfund Site. The Libby, Montana, Superfund site (Environmental Protection Agency, 2006b) offers an example of secondary protection offered to workers through the auspices of EPA's interest in community air pollution. In the late 1800s the northwest corner of Montana was the site of numerous mining operations, most notably gold. Miners discovered a large deposit of vermiculite in the Libby area in 1881, and by 1920 the Zonolite Company began mining this substance, which has multiple uses in the construction industry, primarily as an insulating material. W. R. Grace purchased the Zonolite mining operations in 1963; by 1990, mining operations ceased in Libby. During the peak of the mining operations, the Libby site produced as much as 80 percent of the vermiculite used worldwide.

The site came to the attention of EPA in 1999 due to local news reports alleging asbestos contamination of vermiculite and associated widespread exposure to both former workers at the facility and the townspeople in general. Asbestos is a known carcinogen, and individuals exposed to asbestos are at risk for developing lung and pleural cancer. The risk is dependent upon the exposure received and is likely to be higher in workers in the vermiculite processing facility. EPA sent an emergency response team to the town and began collecting environmental samples in an effort to assess the public health risk. Elevated levels of asbestos were noted in the community, and the site was placed on the Superfund National Priorities List in 2002. Eventually, over 12,000 soil samples were taken. EPA estimated that between

1,200 and 1,400 properties will have to be remediated. Further, medical follow-up of individuals exposed in the occupational setting and in the community will be done.

"Risk Transfer" from the Environment to the Workplace. EPA and OSHA, and a few visionaries in the academic community (see especially Lowell Center for Sustainable Production, 2006), have begun to explore the intriguing (and daunting) possibility that compliance with environmental regulations tends to exacerbate worker exposures. In theory, this problem was recognized decades ago, in special cases such as the attempts to protect ecosystems from lead by encapsulating bridge-repainting projects in large enclosures, which increased lead inhalation hazards to the workers within them. In 1999, EPA and OSHA cosponsored a conference (Environmental Protection Agency, 1999) to examine whether "risk transfer" was a more general phenomenon, especially as EPA continued to promulgate "maximum available control technology" (MACT) standards for industrial processes under the Clean Air Act. One obvious way to comply with emission limitations from point sources is simply to increase the fraction of a toxic air pollution that remains within the workplace, as apparently has happened in several of the cases detailed in this conference. Also in 1999, EPA and OSHA signed a Memorandum of Understanding (MOU) that gave OSHA a review role in proposed MACT standards, to flag instances where EPA requirements might encourage companies to increase worker exposures rather than to install control technology that reduced both workplace and ambient concentrations, or make fundamental process changes. This MOU has lapsed and OSHA appears not to be seeking to review MACT standards currently.

Overview of Occupational Risk Assessment Methodology and Policy

Because quantitative risk assessment (QRA) for environmental exposures is much more prominent in the academic literature, in controversial science-policy reports, and in media commentaries, perhaps the best way to introduce occupational risk assessment is to summarize the similarities and differences between these two arenas. Some of the commonalities and divergences may simply mirror aspects of the risks themselves; some obvious differences between the two types of risk include

- *Population size.* Whereas many environmental contaminants (e.g., ground-level ozone, fine particulate matter) expose nearly all U.S. citizens to some degree, most of the health hazards OSHA considers affect less than 1 percent of the national population, and some (see Table 9.6) affect as few as several thousand workers.

TABLE 9.6. LIFETIME EXCESS CANCER RISKS ASSOCIATED WITH ALL THE OSHA SUBSTANCE-SPECIFIC PELs (SET SUBSEQUENT TO THE 1980 *BENZENE* DECISION).

Substance (Year)	Species Used for Extrapolation	Number of Workers Exposed	Risk at Old PEL	Risk at Average Exposure Level (at Time of Promulgation)	Risk at New PEL
Ethylene Oxide (1984)	Rat	71,000(directly exposed) 69,000(indirectly exposed)	(50 ppm) $63 – 109 \times 10^{-3}$	??	(1 ppm) $1.2 – 2.3 \times 10^{-3}$
Benzene (1987)	Rat/Mouse/ Human	238,000	(10 ppm) 95×10^{-3}	??	(1 ppm) 10×10^{-3}
4,4′-Methylene-dianiline (1992)	Mouse	4,000	(no prior PEL)	(70 ppb) 6×10^{-3}	(10 ppb) 8×10^{-4}* 9×10^{-4}**
Asbestos (1992)	Human	1,316,000	(2 fibers/cm^3) 64×10^{-3}	??	(0.2 fibers/cm^3) 6.7×10^{-3}
Formaldehyde (1992)	Rat	2,160,000 (at > 0.1 ppm)	(3 ppm) 8.3×10^{-3}** 0.07×10^{-3}*	??	(0.75 ppm) 0.006×10^{-3}* 2.6×10^{-3}**
Cadmium (1992)	Rat/Human	525,000	(100 µg/m^3) 58×10^{-3} 157×10^{-3}	??	(5 µg/m^3) $3 \times 10^{-3} – 15 \times 10^{-3}$
1,3-Butadiene (1996)	Mouse	9,700	(1000 ppm) ?? (note: 60 ppm ≈ 99th percentile of exposure)	(1.25 ppm)	(1 ppm) 1.3×10^{-3} to 8.1×10^{-3} (multiple assessments)
Methylene Chloride (1997)	Mouse	240,000	(500 ppm) 126×10^{-3}	(43 ppm) 6.2×10^{-3}** 2.1×10^{-3}*	(25 ppm) 3.6×10^{-3}** 1.2×10^{-3}*
Chromium (VI) (2006)	Human	558,000	(52 µg/m^3) $100 – 350 \times 10^{-3}$	(2.75 µg/m^3) $\approx 5.5 – 25 \times 10^{-3}$	(5 µg/m^3) $10 – 45 \times 10^{-3}$

* = maximum likelihood estimate

** = 95th percentile upper confidence limit

Therefore, this disparity of a factor of 10^2 to 10^4 in affected population size may counteract or exceed the disparity in average concentration (see above), which of course cuts in the opposite direction (occupational exceeding environmental).

• *Population characteristics.* By and large the general population exposed to environmental hazards is more diverse than the working population. Workers, especially those exposed to chronic health hazards, are generally between ages 18 and 65 and so do not exhibit those special sensitivities to exposures that are peculiar to infants, children, or the very old. Workers are also healthier than many in the general population simply by virtue of being fit enough to perform moderate or strenuous physical labor; hence, epidemiologists are well aware of the "healthy worker effect" that complicates the interpretation of disease rates in occupational cohorts when background rates from the general population are the basis for comparison (McMichael, 1976). On the other hand, the fact that workers may have a longer-then-average life expectancy in the absence of additional risk factors does not necessarily mean they are any less susceptible than the general population to these incremental stresses. Although no studies to date have resolved this issue, first principles suggest that many important genetic and other determinants of risk (e.g., variation in enzymes that activate or detoxify carcinogens and other substances) bear no relationship to age or the ability to do work; that makes the occupational population on average no less susceptible than the general population, to say nothing of individuals within either population whose sensitivities may fall anywhere along the spectrum.

• *Exposure patterns.* Occupational exposures are generally confined to 40 of the 168 hours in a week, and rarely extend for more than 45 years, whereas some environmental exposures approach the theoretical maximum of continuous lifetime exposure. Depending on the mode of action of the substance(s) involved, the intermittent nature of occupational exposures can call for a quantitative adjustment (as when bioassay data are adjusted by 5/7 and 8/24 to account for the workweek), or a qualitatively different assessment. Sporadic high exposures can be risky when continuous lower exposures are not if they exceed a biological threshold; the converse pattern can apply, as when the intermittent exposures allow for physiologic recovery and hence have zero chronic effect.

Despite these differences, however, the fact is that most of the agents of particular concern in environmental risk management emerge from workplaces, or stem from choices that citizens make both in the workplace and the general environment (e.g., environmental tobacco smoke, which for some people is a fairly constant exposure during the workday and then at home). To the extent that residents and white-collar workers may suffer health effects from exposures to contaminants at and around the World Trade Center site, for example, it will be because they essentially experienced occupational levels and patterns of exposure not much different from those encountered by the responders (especially to the

extent that some in the latter group, but not the former, availed themselves of respiratory protective devices).

Several more dramatic and persistent differences separate the methods and orientation that EPA and OSHA bring to the *assessment* of the related risks within their own domains. In some important ways, occupational risk assessment should be less controversial than its environmental analog, particularly because it often concerns human exposures within a factor of 10 or less (rather than a factor of 10,000 or more) of exposures that cause statistically significant increases in adverse health effects in populations of laboratory animals and humans. Nevertheless, this most basic generalization is not seriously in dispute; OSHA has lagged behind EPA in developing and implementing methods for QRA, out of proportion to the differences in resources across the two agencies.

For more than 20 of its 35 years, OSHA deliberately *resisted* the impulse to perform QRA at all, whether by developing its own preferred methods or adopting those of other agencies. OSHA memorialized its concerns about QRA in a massive undertaking (roughly 1,500 pages of text) published in January 1980, in which it codified procedures for hazard identification while declaring that it would stop after this first phase of the four-step NAS risk assessment process (Occupational Safety and Health Administration, 1980). Table 9.7 shows some of the major science-policy default assumptions OSHA codified in this Cancer Policy document, many of which it and other agencies still rely on for cancer hazard identification two decades later. OSHA's verdict on proceeding from hazard identification to QRA was unequivocal:

> The uncertainties involved in extrapolating from high-dose animal experiments to predict low-dose risks to humans are far too large at present to justify using the estimates as the basis for quantitative risk/benefit analysis. This conclusion is well illustrated by the more than million-fold variation in the estimates of risk derived by different authors for risks to persons exposed to vinyl chloride at the OSHA standard of 1 ppm [p. 5200]. . . . OSHA's estimates of possible risk will not be used to justify the establishment of any particular permissible exposure level, or to imply that any level of risk is judged to be "acceptable" [p. 5256].

For risk management purposes, therefore, OSHA's 1980 Cancer Policy rejected the idea of computing a *de minimis* or acceptable concentration based on risk estimation, but instead concluded that chemicals it deemed potentially carcinogenic to humans [Category I] should be regulated to the lowest feasible limit (and also that exposures to chemicals with suggestive evidence of human carcinogenicity [Category II] should be "reduced as appropriate"). This policy mirrored the approach NIOSH held at the time; in developing recommended exposure limits

for carcinogens, NIOSH determined that zero was the only acceptable recommendation it could make.

Six months after the Cancer Policy was published, the Supreme Court's *Benzene* decision (*Industrial Union Department, AFL-CIO* v. *American Petroleum Institute;* see Vig and Faure, 2004) made OSHA's key risk management policy obsolete by requiring OSHA to quantify risk rather than assert that only the lowest feasible limit was acceptable. OSHA, therefore, never actually used the cancer policy to classify chemicals as potential or *suggestive* carcinogens, although it has used many of the science-policy defaults for hazard identification in subsequent rule makings. OSHA was slow to adopt QRA in the first decade after the *Benzene* decision: it only issued four risk-based health standards (including a revised benzene standard to comport with the Court decision) during that time, and declined to participate in the interagency committee (EPA, FDA, and Consumer Product Safety Commission) to develop a consensus position supporting the use of $(\text{body weight})^{3/4}$ as the default for converting doses used in animal bioassays to human-equivalent doses (Environmental Protection Agency, 1992). OSHA also attempted to eschew risk assessment in its most ambitious health standard of all, the 1989 rule making that sought to change over 420 PELs to track changes in the TLVs® between 1970 and 1989. A federal court struck down all of these limits in 1992 on the grounds that OSHA had not assessed the risk of any of the substances at the old or new PELs (and so OSHA can now enforce only the TLVs® as they existed in 1970). Although OSHA issued four more risk-based health standards in the 1990s, and in at least one case pioneered some computational methods and codified evidentiary criteria for replacing a default assumption with a more sophisticated biologic model (see the methylene chloride case study below), it has never developed any written risk assessment guidelines of the types that have figured so prominently in EPA rule making. Because OSHA regulations are generally constrained by technological and economic feasibility, however, it makes sense for the agency to present multiple risk assessment models in order to show that the exposure limit chosen does not run afoul of the significant risk test in the *Benzene* decision, no matter what model might actually be the most appropriate. So in this respect, guidelines for choosing among competing models and for quantifying uncertainties may not be as important for OSHA as they are for EPA. OSHA also has not yet promulgated any risk-based exposure limits since the *Benzene* decision to protect against health effects other than cancer (although this may in part be due to the opinion from the court in the PELs case, which arguably misinterpreted the use of tenfold safety factors for noncancer risk assessment as a policy judgment rather than as a scientifically sound way to interpret animal toxicity data).

To the extent that observers can infer what OSHA standard risk assessment procedures are by examining its track record in its assessments subsequent to the *Benzene* decision, one pattern does emerge: OSHA's risk estimates are less conser-

TABLE 9.7. EXAMPLES OF DIFFERENCES BETWEEN EPA AND OSHA DEFAULT RISK ASSESSMENT ASSUMPTIONS.

EPA Standard Practice	OSHA Standard Practice
Potency estimated from UCL of multistage dose-response function	Potency estimated from MLE of multistage dose-response function
Interspecies scaling by (body weight)$^{3/4}$	Interspecies scaling by body weight
"Response" defined as any animal with a tumor (regardless of tumor site)	"Response" defined (usually) as any animal with a tumor at a specific site
Exposure assumed to occur 24 hours/day, 365 days/year, 70 years	Exposure assumed to occur 8 hours/day, 250 days/year, 45 years
Acceptable exposure sometimes (e.g., pesticide regulation) depends on concurrent exposures to other substances acting by common mechanism	Acceptable exposure set independently for every substance, not considering concurrent exposures
Long-term exposure can be inferred (without adjustment) from shorter-term measurement(s)	If sampling time is < 8 hours, assume zero exposure during remainder of 8-hour period

vative then EPA's (or more likely to underestimate risk, if one accepts the premise that EPA's procedures are not necessarily conservative to begin with), as can be seen in Table 9.7. For a comprehensive review of the differences between OSHA and EPA risk assessment assumptions and methods, see Rhomberg (1997).

Court Decisions Affecting Risk Assessment

Unique among the federal agencies, OSHA now operates under specific instructions from the nation's highest court that govern when—and to some extent, how—it can or must perform quantitative risk assessment and cost-benefit analysis. In two landmark decisions reached less than one year apart, the U.S. Supreme Court essentially concluded first that OSHA must perform QRA and abide by its results when it regulates health hazards, and then concluded that OSHA is not permitted to base its regulations on a quantitative comparison of the monetary value of these risk-reduction benefits to the cost of reducing the risks. Both decisions hinged on the interpretation of one (long) sentence in Section 6(b)(5) of the Occupational Safety and Health Act of 1970—that in regulating "toxic materials or harmful physical agents," OSHA must

> Set the standard which most adequately assures, to the extent feasible, on the basis of the best available evidence, that no employee will suffer material

> impairment of health or functional capacity even if such employee has regular exposure to the hazard dealt with by such standard for the period of his working life.

In its 1980 *Benzene* decision, the Supreme Court (by a narrow 5-to-4 vote, with the five justices in the majority issuing four separate opinions explaining their decision) made quantitative risk assessment the cornerstone of OSHA regulation of occupational health hazards, and issued the most detailed language to date about the high court's interpretation of several fundamental and controversial aspects of risk assessment and management. OSHA had issued a final standard governing worker exposure to benzene in April 1977, lowering the PEL from 10 ppm to 1 ppm. At 10 ppm or slightly above, workers exposed to benzene can experience central nervous system effects and diseases of the blood-forming organs (including aplastic anemia, an often-fatal disease); even in the 1970s, there was substantial evidence from human studies that levels of benzene exposure at or below 10 ppm increase the risk of various forms of leukemia. OSHA, however, in line with its Cancer Policy (which it had published in proposed form in 1976), declined to quantify the possible cancer risk either at 10 ppm or 1 ppm; rather, it set the PEL at the lower number on the grounds that while an exposure limit of zero was appropriate for a carcinogen, 1 ppm was the lowest feasible level. OSHA acknowledged that various industrial sectors that use benzene could achieve levels lower than 1 ppm, but made a policy judgment that a uniform limit was appropriate. Both the AFL-CIO and the American Petroleum Institute filed petitions seeking to strengthen or weaken the 1977 standard, respectively.

The five justices who voted to invalidate the benzene standard objected on two basic grounds to the central precept of OSHA's Cancer Policy—that carcinogens should be controlled to the lowest feasible level, irrespective of the extent of exposure, the strength of the dose-response relationship, or other factors. First, the Court concluded that Congress did not intend terms such as "a safe and healthful workplace" to mean absolutely risk-free, a condition that literally could only apply if workplaces were shut down. Second, it concluded that a federal agency like OSHA has the responsibility to demonstrate the need for a regulation, and cannot shift the burden to the regulated industry to show that the rule is not needed—that in setting the benzene standard, OSHA had "relied squarely upon a special policy [the Cancer Policy] for carcinogens that imposed a burden on industry of proving the existence of a safe level of exposure."

Together, the Court's requirements that OSHA not seek to eliminate all risk (however trivial its magnitude) and that it must marshal evidence to determine a regulation are necessary to "assure that no employee will suffer material impairment of health" and add up to a recipe for QRA, as expressed in the heart of the

Benzene decision: "the burden [is] on the Agency to show that long-term exposure to 10 ppm of benzene presents a *significant risk* of material health impairment" (emphasis added). This conclusion, as the case studies below will demonstrate, immediately changed OSHA from an agency that repudiated QRA to one that (however reluctantly) had to embrace it as the primary tool for justifying new regulations and for setting the all-important level of stringency.

The *Benzene* decision was much more than a statement that risk must be quantified, however. The Court delved into some of the details about *how* QRA could be undertaken and used, and generally gave with one hand what it had taken with the other, providing OSHA with its blessing to fashion agency risk assessments according to its own policy judgments and scientific interpretations, with the explicit goal of avoiding putting the agency into a "mathematical straitjacket." First, the Court made clear that OSHA could decide for itself what level of risk was large enough to be "significant" and what level was so small it had to be deemed "insignificant." In the Supreme Court's only numerical foray into the "acceptable risk" issue to date, it provided specific (but extremely broad) guidance as to what risks it thought were "plainly acceptable" and which ones were "plainly unacceptable" by stating that an individual risk of one in a billion (10^{-9}) "could not be considered significant," while "a reasonable person might well consider" a risk of one in a thousand (10^{-3}) to be significant. *As Congress has generally instructed EPA to regulate risks down to a level of one in a million (10^{-6}), OSHA has thus for the past 25 years been permitted either to set standards one thousand times more strict than this reference point, an unprecedented amount of discretion that OSHA has rarely even begun to make use of (see below).* Not only did it give OSHA the authority to declare a risk within that broad range "acceptable," but the Court also allowed OSHA to choose a numerical estimate of risk according to its own science-policy judgments, and even signaled that it understood that those judgments might be intentionally precautionary: "So long as they are supported by a body of reputable scientific thought, the Agency is free to use conservative assumptions in interpreting the data with respect to carcinogens, risking error on the side of over-protection rather than under-protection." At least in theory, therefore, OSHA could set a PEL for a carcinogen so that the risk to a highly susceptible worker might, even using conservative assumptions, be almost as low as 10^{-9}, so long as it could show that industry could feasibly meet that extremely strict level.

In fact, it took OSHA 7 more years to promulgate a revised benzene standard, and it chose the same exposure limit (1 ppm) as it had proposed 10 years earlier. In the revised standard, OSHA estimated that the lifetime excess leukemia risk at 10 ppm was approximately 95 per thousand, or 9.5×10^{-3} at the new PEL (again, OSHA concluded that no lower limit was feasible, even though "significant risks" remained at the newly permissible level). Within several months of the

Benzene decision, OSHA had amended its Cancer Policy to strike out all references to automatically seeking to limit carcinogen exposures to the lowest feasible level, and proposed adding extensive new language that would have clarified the role of "significant risk" determinations. Several weeks after President Ronald Reagan was inaugurated, however, OSHA withdrew that proposal, and has never since made explicit use of its generic carcinogen policy. The four justices who dissented from the *Benzene* decision were very concerned that by requiring OSHA "to 'quantify' the risk in order to satisfy a court that it is 'significant,' . . . [the Court] seems to require [OSHA] to do the impossible." The history of OSHA standard setting over the subsequent 25 years provides ample evidence that using QRA to set risk-based standards is far from impossible. But neither is it easy.

The following year, by a 5-to-3 vote (one justice did not participate in this case), the Court upheld OSHA's standard limiting the allowable amount of cotton dust in U.S. workplaces (*American Textile Manufacturers Institute* v. *Donovan,* 1981; see Ashford and Caldart, 1996), rejecting the argument of the textile industry that OSHA must weigh the benefit of reductions in health risks against the costs to industry of achieving them. Together with *Benzene,* the *Cotton Dust* decision means that OSHA must quantify risk to assess its significance but cannot then regulate based on a comparison of the monetized benefits of the risk reductions to their costs.

As early as the 1820s, cotton dust was recognized as associated with a progressive obstructive lung disease now known as byssinosis, or brown lung disease. In the United States, roughly 100,000 workers had developed byssinosis by 1970. It should be noted that within a few years of the Court upholding OSHA's regulation, the number of new cases of byssinosis plummeted to less than 25 per year nationwide, although the gradual decline of the U.S. domestic textile industry certainly contributed to this positive development. In 1974, the threshold limit value (TLV®) for cotton dust was lowered to 200 $\mu g/m^3$, and four years later OSHA promulgated a less stringent set of standards that varied by the industrial process involved, ranging from 200 $\mu g/m^3$ in yarn manufacturing to 750 $\mu g/m^3$ in weaving operations. OSHA performed a thorough QRA of the risk of lung disease from cotton dust at the exposures prevailing at that time and at the proposed new limits and calculated the costs of complying with the standard, but it did not monetize the health benefits and compare them to their costs. The Court said that it "is difficult to imagine what else the Agency could do to comply with this Court's decision in [*Benzene*])." OSHA also rejected the petition of the Textile Workers Union of America that the PEL be set at 100 $\mu g/m^3$, on the grounds that the lower limit was not "within the technological capability of the industry."

The Supreme Court emphasized the phrase "to the extent feasible" in the OSH Act, and concluded that Congress did not intend that OSHA engage in

cost-benefit analysis, but rather must reduce worker risks "limited only by the extent to which this is capable of being done"—now limited further, of course, by the Court's recent instruction in *Benzene* that OSHA cannot further reduce risks that have become too small to be "significant." Interestingly, the Court described the OSH Act as embracing rather than rejecting cost-benefit thinking, but a brand of cost-benefit balancing that "place[s] the benefit of worker health above all other considerations save those making attainment of this benefit unachievable." In a parallel to *Benzene,* the justices also carved out an interpretation of "significant cost," to clarify when controls that *can* be adopted are nevertheless too expensive to truly be "feasible." They concluded that when OSHA can reasonably show (as it did here) that the industry involved can comply with the regulation and "maintain long-term productivity and competitiveness," it has met its congressional test of feasibility. In fact, the Court explicitly left open the possibility that in the future it might also conclude that OSHA regulation that did threaten the profitability of industry might yet be regarded as "feasible."

Chief Justice Warren Burger and Justice William Rehnquist dissented from the majority, concluding that by inserting "to the extent feasible," Congress allowed itself to "mask a fundamental policy divergence" over whether OSHA should be required to use, permitted to use, or prohibited from using cost-benefit analysis, and they chastised their colleagues for inferring meaning from this vague language. Nevertheless, *Benzene* and *Cotton Dust* together make it clear that OSHA can, if it wishes, promulgate health regulations that impose high costs and reduce risks down to small (but not "insignificant") levels.

The Mechanics of Occupational Risk Assessment

Hazard Identification. As the name would suggest, *hazard identification* is the qualitative association of an activity, location, or pollutant with a hazard. Historically, much of the knowledge that we have on the health effects of certain activities, or that are associated with exposure to environmental contaminants, comes from the occupational setting, since in these settings hazards are abundant. For example, exposures experienced by uranium mine workers has led to a better understanding of the effect of radiation exposure in the general population. Similarly, repetitive strain injuries were first noticed in manufacturing settings, where repeated motion is common. Later, it was noticed in office workers and in the general community. However, it is unlikely that study of nonoccupationally exposed individuals alone would have led to the insight obtained from those exposed in workplace settings. Exposures are generally greater, and for longer duration, making the hazard more readily identifiable in the occupation exposed.

Occupational Exposure Assessment. Industrial hygiene focuses on the exposures experienced by individuals who work in industrial or occupational settings and may be viewed as a branch of the larger science of exposure assessment. Some definitions are needed to start. These include the *concentration* of pollutant in an environmental medium, the *exposure* experienced by an individual, and the *dose* received by the individual.

1. *Concentration, exposure, and dose differentiated.* An important distinction to be made is between the related concepts of concentration, exposure, and dose. Consider the following scenario:

> A worker is required to enter an enclosed space that formerly was filled with a volatile solvent. The enclosed space is saturated with the vapor of the solvent.

In order to assess the experience of the worker, we must consider three different concepts: concentration, exposure, and dose.

The concentration in the tank is relatively simple to understand: it is the saturation vapor pressure of the organic solvent. It can be readily measured using appropriate instrumentation or estimated from the physical and chemical properties of the solvent. This is the concentration that the worker experiences in the enclosed space.

But what is her exposure? Exposure, defined as the amount of hazardous substance delivered to some body boundary, can come from one of three different *routes*: inhalation, for which the lung epithelium is the boundary of interest; ingestion, for which the gut epithelium is the boundary of interest; and body-surface contact, for which a body surface, usually the skin, is the boundary of interest.

2. *Pathways.* The specific ways the pollutant moves through the environment can be many and varied and should be distinguished from *routes* of exposure. Let us develop an simple example to distinguish these two concepts better. One may be exposed to sulfur dioxide in various ways, the majority of which lead to exposure through the inhalation route. One particular pathway is the generation of sulfur dioxide through the combustion of sulfur-containing coal, followed by the concomitant release of this gas from the combustion facility, and advection and dispersion in the air. An alternative pathway in an industrial setting might arrive from the use of sulfurous acid in a manufacturing process with the concomitant release of sulfur dioxide at an individual workstation. The worker at his workstation is then exposed directly to sulfur dioxide via the inhalation route. These two pathways differ substantially and would require entirely different control strategies to reduce exposure.

At this point the determination of exposure requires us to gather much more information about the scenario. In an occupational setting such as the one described, the worker should be provided with a respirator that supplies air from outside the tank, as it would be much too dangerous to send an individual into such an enclosed space without such a device. For a saturated vapor in an enclosed tank, the primary concern would be inhalation exposure. If the respirator was fitted perfectly and functioning properly, the worker's actual exposure would be close to zero. However, respirators may be used improperly or not at all, resulting in exposure greater than that expected under this ideal scenario. However, if we presuppose that no other personal protective equipment was required, the worker would still receive an exposure through skin; thus dermal exposure may be an important route and potentially could result in health effects. We must be careful to consider all potential routes and attempt to identify all pathways of exposure.

And what of the dose, the amount of material that actually crosses the body boundary and enters the body? To estimate dose, we would need information regarding the efficiency of transfer across the body boundary. For this case, if no airline respirator were in use, one could infer the exposure by knowing the concentration and breathing rate. The dermal exposure would combine information about the concentration in the air and the amount of exposed skin area. Dose would require further information focusing on the rate of transfer of the specific contaminant through the skin and into the body.

3. *Magnitude, frequency, and exposure duration.* It is also important in understanding exposure to look at the time course of the exposure, sometimes referred to as the *exposure profile.* The definition of exposure requires averaging over time that, in turn, results in a great deal of lost information. Intuitively, we may imagine that exposure to a very high concentration of contaminant for a short duration followed by exposure to no concentration at all for the remainder of, say, a work shift may have different consequences from exposure to a modest concentration over the entire work shift. The total would be the same, but the duration and concentration of exposure would be different. For example, one worker may be welding for 15 minutes in a relatively enclosed space and be subjected to a concentration of metal fumes of 40 mg/m^3. He thus receives an exposure of 40 $mg/m^3 \times 0.25$ $h = 10$ $mg/m^3 \times h$. After welding, he goes on to different activities in a different part of the facility in which he experiences no concentration of welding fumes and thus receives no further exposure during the shift. His coworker, working in the same area but not exposed directly to the fumes, remains for the entire eight-hour shift. Measurement of metal fume concentrations over the course of the day in the location of the second worker gives 1.25 mg/m^3. The worker in this location receives an identical exposure: 1.25 $mg/m^3 \times 8$ $h = 10$ $mg/m^3 \times h$, but the pattern is different.

To account for such differences, it is important for the exposure assessor to be cognizant of the magnitude, frequency, and duration of the exposure. Always ask, What is the peak concentration experienced during the monitoring period? Does it differ significantly from the mean concentration? How frequently are high concentration peaks found? Are the concentrations relatively stable, or is there a good deal of variability from minute to minute or hour to hour? Do the peaks recur regularly, or episodically? What is the duration of the exposure? Is it short followed by no exposure, or does it occur at moderate levels for a long period? Such information can prove invaluable in addressing potential effects and control strategies.

4. Methods of exposure assessment. Exposure assessors typically undertake exposure assessment investigations in one of two ways: (1) direct exposure assessment methods and (2) indirect exposure assessment methods. Direct exposure assessment methods involve outfitting an individual with some type of monitor that measures pollutant concentrations experienced by the individual as he goes about his daily activities. This is most easily visualized for airborne contaminants. In this case, an air monitor collects a sample of the air breathed by the individual over a period of time. That air sample is then analyzed for the contaminant of interest either on a real-time or time-integrated basis (both are commonly used in occupational settings). Similar monitors may be envisioned for exposures occurring via the ingestion or dermal pathways as well. By the direct method, actual exposures experienced by an individual can be observed. This is a major strength in assessing exposure and is generally desirable. However, portable monitors may not exist for the particular contaminant under investigation, or may unduly influence the activity patterns of the individual; that is to say, the normal activities that are undertaken in the workplace. They also may be bulky, require electrical connection, or otherwise interfere with job duties.

An alternative strategy involves indirect exposure assessment, in which microenvironments, or areas or activities likely to give similar and relatively homogeneous exposures, are monitored using, perhaps, more sophisticated monitoring equipment, and where the movement of the individual within and between such microenvironments is noted. Again, the inhalation route is most easily visualized. In this case, air pollution monitors are placed in various locations (e.g., workstations) to determine concentrations found in these locations. Exposure is then determined by having the individual note the amount of time spent in each of the microenvironments, multiplying the concentration measured by the amount of time spent in the microenvironment, and adding all such values together. For other routes of exposure, a similar approach can be used.

An alternative strategy, not involving any direct measurement, can also be envisioned. With this strategy an activity pattern for an individual can be assumed,

perhaps through a large data-gathering effort addressing the locations where individuals typically spend their time. An example is the job-exposure matrix in which certain job titles are assumed to have homogenous and known exposures. Such an approach is used often in occupational epidemiology. An example might include distinguishing between two groups of workers (e.g., manufacturing-line workers and office workers) at the same location. Office workers might be assumed to have low (or even no) exposure, while manufacturing-line workers receive high (or perhaps even quantified) exposures.

5. *Biological markers of exposure.* Exposure to environmental contaminants requires the simultaneous presence of a contaminant concentration and a human subject to receive the exposure. Both the direct and indirect methods described above assume that the exposure occurs if these two components exist. However, the only way to be sure is to use the response of the human subject as a measure. This is what exposure assessors do when they use biological markers (sometimes referred to as *biomarkers;* see Chapter Seven) of exposure. Biological markers of exposure to a given contaminant make use of biological material (e.g., exhaled breath, urine, blood or blood components, fecal samples, or tissues). These samples are analyzed for the contaminant in question, called the *parent compound*, or a metabolite or biological by-product to determine the exposure. Occupational exposure to trichloroethylene, an important industrial solvent, offers a good example. Urine samples can be taken from individuals and analyzed both for trichloroethylene and for its metabolites (e.g., trichloroacetic acid) to ascertain exposure to this class of compound. Using measures of these two compounds, we can infer the magnitude of the initial exposure and, through analysis of the metabolic processes involved, the timing of such exposure.

6. *Other exposure-related issues.* It is interesting to note that exposure assessment is not emphasized in occupational settings because PELs (and other OSHA standards) set the concentration limits through the use of standards similar to the National Ambient Air Quality Standards. Unlike the NAAQS, however, OSHA standards are compared to the actual exposures of individuals, rather than the environments they live or work in; an employer is deemed to be out of compliance if a personal air sampling device attached to a worker shows a concentration above (with statistical significance) a PEL.

Occupational PELs assume that a worker is employed over a 45-year *working lifetime* (essentially from age 20 through age 65) and that risk is accumulated during this period. Contrast this to the full 70-year lifetime assumed by the EPA when projecting cancer risk. Some have suggested that since individual industries and worksites are regulated, exposure—and thus risk—should only be accumulated during the time that the average worker remains with a single employer, perhaps 10 to 15 years (see, e.g., Burmaster, 2000). This argument is weak in that workers

normally change jobs within the same industry and are likely to continue accumulating exposure during their next job as well, if not to the identical substances then to similar ones that act via a common toxicologic mechanism. Workers should be protected for their entire working lifetimes.

OSHA is required to perform exposure assessment when promulgating a regulation. It must, for example, account for the exposures experienced prior to the regulation being put in place and for likely compliance discrepancies. That may result in an over- or underexposure experienced by the workers themselves. This is especially noteworthy because, in practice, working facilities are normally considered to be in compliance if measured concentrations of contaminants at the site are less than 125 percent of the PEL. Further, compliance requirements allow conversion of exposure measurements that take place over less-than-full to full-shift exposures assuming zero exposure during the remaining shift time, biasing inferred exposures. In addition, no allowance is made for previous exposures; exposures are assumed to be fresh each day with no accumulated effects.

Dose-Response Analysis

Dose-response analysis focuses on using animal data to predict health impacts on human subjects. Generally, a relatively small number of animals are exposed to the compound of interest at several levels, up to (and often including) the *maximum tolerated dose*, the highest dose of the chemical that when administered to animals does not cause any of a defined set of clearly adverse systemic health effects, such as substantial loss of body weight. In most cases, cancer is the ultimate outcome of interest, and tumor development in the animal is the way such an outcome is quantified.

The number of dose groups in such an investigation is quite limited, often consisting of no more than three or four; these may include a control group receiving no exposure, a maximum tolerated dose group that receives a high dose, and another group (or two) at some fraction of the maximum tolerated dose. In general, these doses are higher than might be experienced in a normal, nonoccupational setting, even under the most adverse conditions.

A significant question then becomes, How do we extrapolate the effect seen at the high levels of exposure experienced by the animals to the low levels experienced by the human subjects facing the exposure in an environmental or occupational setting? This is not as simple as it seems; there are many ways to do the low-dose extrapolation, and unfortunately they often give wildly different answers. The standard procedure for estimating the effect of low concentrations is a model known as the *linearized multistage model* (LMS) in which the data for all of the dose groups are used to estimate the probability that an animal receiving a given dose would

develop cancer. We will not discuss the details of the model here, but we will point out that there is an implicit assumption in the model that at low doses, the probability of an adverse health outcome increases linearly with increasing doses.

Once the data are fit using the LMS, we must account for differences between human beings and the rodents who are exposed and decide if we want to include safety factors in setting our standard. For nonoccupational standards, the standard approach is to account for the differences in size between, say, mice and human beings, by scaling the dose by a function of the body weight (BW) ratio. In particular, EPA scales by $BW^{3/4}$ as EPA believes that metabolic processes scale approximately this way. EPA also supplies a small (no more than a factor of approximately 4, as can be seen in Hattis and Goble, 1991) margin of safety by looking at the quality of the statistical fit to the dose-group data and using an *upper confidence limit* (UCL) on the linear slope value. That is, the statistical fit would give a number, called the *maximum likelihood estimate* (MLE), but EPA assumes a larger slope is plausible given the uncertainty in the observed response.

For occupational standards, a somewhat different approach is taken. The body weight extrapolation is done in a linear fashion; that is, the scaling is BW^{1}. This is less protective, by roughly a factor of 4 (when rat data are used) or 7 (mouse data) than $BW^{3/4}$. Further, the MLE estimate is taken, rather than the UCL on the plausible slope of the dose-response function, again affording less protection. As is the case for the community standards, occupational standards may be modified to give a more conservative estimate under some circumstances. However, the factors are generally applied to the value determined above, the MLE estimate, rather than the UCL values.

One final difference between the dose-response modeling used to develop occupational standards and those used in the broader setting is the way in which tumor data are used. In the community setting, tumor data collected from rodents is used in the aggregate. That is, all tumors are counted whether they are in the specific target organ or found elsewhere in the body. The converse is generally true in occupational dose-response analysis. For occupational standards, a specific target organ is specified and the number of tumors counted and used to develop the MLE discussed above. An example may clarify. Consider a case in which analysis of the high-dose group of rodents consisting of 50 animals revealed tumors in 20 of these animals. Of these, 15 animals experienced liver tumors while 5 other animals experienced tumors in other organs. For the general population, the number of positive outcomes would be 20, the total number of animals experiencing any kind of tumor, while for occupational dose-response analysis, only the tumors in the target organ, the liver, would be considered (i.e., 15). This lower figure is less protective, again emphasizing the point that occupational risk assessment tends to be less protective than community risk assessment.

Case Study: Methylene Chloride

OSHA's 1997 regulation imposing various restrictions on the industrial use of methylene chloride (MC) provides an unusually wide-ranging look at the scientific and science-policy controversies that can arise in writing and implementing a risk-based regulation. QRA featured prominently in several of these issues, and provided OSHA with an opportunity to innovate in ways that made the MC regulation a cutting-edge one.

MC is a very common chlorinated solvent (U.S. production in 1988 was approximately 500 million pounds), with uses ranging from stripping paint to industrial degreasing to gluing together pieces of polyurethane foam (as in the manufacture of upholstered furniture). The paint-stripping process often involves immersing the object in a tank of liquid MC, as when stripping furniture, or by spraying an MC solution onto large objects, as when repainting airplanes. All of these processes give ample opportunity for occupational exposure. OSHA began considering a regulation for MC in the late 1980s when the United Auto Workers and other unions petitioned OSHA to that effect (during the same period, the FDA banned the use of MC in aerosol cosmetic products). At the time OSHA estimated that approximately 250,000 U.S. workers, employed at roughly 90,000 different establishments (many of them obviously very small businesses), were exposed to MC. Although OSHA inherited a PEL of 500 ppm for MC when the agency was created in 1970, its surveys suggested that almost all of those workers were exposed to concentrations lower than 500 ppm—but that an estimated 60,000 workers routinely encountered concentrations between 25 ppm and 200 ppm.

MC can cause a variety of adverse health effects in experimental animals and in humans. At roughly 2,000 ppm, MC can cause death by asphyxiation; between 1984 and 1993, OSHA received reports of at least 40 fatalities or multiple hospitalizations from accidental overexposures to MC, generally in confined spaces such as tank trucks but also in larger enclosures as in the use of MC to strip paint from the floors of poorly ventilated rooms. In concentrations at or below the 500 ppm PEL, MC can cause central nervous system depression in humans and (because MC in part is metabolized to carbon monoxide in vivo) can increase blood carboxyhemoglobin concentration, raising concern about potential acute and chronic cardiovascular effects. The critical effect of MC in humans, however, is its potential carcinogenicity: several studies, in particular a National Toxicology Program bioassay in male and female mice, showed significant excesses of malignant lung and liver tumors in animals exposed by inhalation to roughly 2,000 ppm MC, only a factor of four above the prevailing PEL. Epidemiologic studies of workers exposed to MC did not provide clear evidence of carcinogenicity, although most of the studies involved relatively small populations in relatively well-

controlled operations. For example, one prominent study examined 1,300 workers whose average MC exposure was only 26 ppm, a level that OSHA eventually concluded would have yielded an excess cancer risk of roughly 3 cases per thousand, essentially undetectable in a cohort of this size.

In light of this evidence, OSHA ultimately promulgated regulations setting a PEL of 25 ppm and a short-term exposure limit (STEL) of 125 ppm (so that no exposure averaged over 15 minutes shall exceed the STEL). OSHA estimated (see below) that the excess lifetime cancer risk at the new PEL was approximately 3.6 per thousand, substantially higher than the 10^{-3} benchmark the Supreme Court had set in 1980 as the highest risk level that could conceivably divide "significant" from "insignificant." OSHA asserted, however, that 25 ppm was the lowest level that all affected industry sectors could feasibly meet (although in no case did OSHA estimate that the cost of complying with the standard would amount to more than 2 percent of the sales revenue of affected firms). Neither the labor unions nor the affected industries challenged the standard in court, after OSHA agreed to make minor changes in one ancillary provision of the standard and to allow several additional months for certain industry sectors to come into compliance. OSHA also estimated, considering the number of workers then exposed to various concentrations of MC, that the new standard would prevent approximately 30 cancer deaths per year and would cost U.S. industry roughly $100 million per year (over a 10-year period) to implement.

Although the general provisions in the MC standard deviated little from the template OSHA had used for its other substance-specific standards after the *Benzene* decision, OSHA's risk assessment for MC broke new ground in at least three major respects.

1. *Incorporation of a metabolic model for interspecies extrapolation.* By the early 1990s, MC had become perhaps the single most extensively studied industrial chemical with respect to the pathways and rates governing its metabolism in both rodents and humans. Various research groups had reached a consensus that both rodents and humans metabolize MC via two competing biochemical pathways: a mixed function oxidase system that converts MC to carbon monoxide and a pathway involving the enzyme glutathione-S-transferase (GST), which produces at least two reactive intermediates known to interact with DNA and RNA. For most of the MC rule-making period OSHA had resisted calls to use a physiologically based pharmacokinetic (PBPK) model for its MC risk assessment, preferring to hold to its generic assumption that human exposure should be estimated from rodent exposure via a simple ratio of the two species' body weights. Note that this is also a less precautionary form of the default intraspecies extrapolation assumption than the surface area or the $(\text{body weight})^{3/4}$ adjustments that other federal agencies

use. New leadership at OSHA recognized, however, that PBPK models for MC were probably more scientifically valid than the generic default, and that they also offered an opportunity for OSHA to estimate risk in light of both the uncertainty in interspecies conversion and the variability in how different humans metabolize MC. With the help of scientists from two universities and a state health department, OSHA refined the basic PBPK model industry had proffered, incorporating quantitative measures of uncertainty in the 46 different parameters (23 in mice and a corresponding number in humans) needed to run the model, as well as measures of pairwise correlation between all relevant parameters. The thought process that led OSHA to conclude that the PBPK approach to assessing MC risk was superior to the default assumption also enabled OSHA to implement one of the major recommendations of both the 1983 and 1994 National Academy of Sciences risk assessment committees (see Chapter 2): that agencies describe for the interested public the quantity and quality of information they deem necessary to depart from a generic default so that researchers can investigate specific questions productively and other stakeholders can gauge whether the agency followed its own advice in making such crucial science-policy decisions. Exhibit 9.1 lists the 11 scientific criteria OSHA developed for possible use in future decisions of this type. This decision represented the first time a U.S. federal agency set a regulatory exposure limit for a toxic substance using a PBPK model for interspecies extrapolation rather than a generic default such as a body-weight or surface-area ratio.

2. *Rejection of an alternative theory claiming that MC causes cancer in mice but not in humans.* Late in the rule-making process (October 1995), after OSHA had already decided to adopt the PBPK model for quantifying interspecies differences between mice and humans, it had to delay the promulgation of the MC standard in order to evaluate a new set of claims put forward by the Halogenated Solvents Industry Alliance (HSIA) (a consortium of U.S. and international companies who produce MC)—that the differences between the two species go far beyond quantitative ones to the extent that humans are completely insensitive to the carcinogenic effects of MC seen in mice. HSIA submitted a series of newly published papers to OSHA that advanced several hypotheses, including (1) that MC produces lung tumors in a type of cell (the Clara cell) that may be relatively much more abundant in mice than in humans; (2) that mouse liver and lung cells may be much more susceptible than human cells to single-strand DNA breaks when exposed to MC; and (3) that the specific GST enzyme that metabolizes MC may be more abundant in mouse cells than in human cells, and that it can be found in the nuclei of mouse cells but may tend to concentrate in the cytoplasm of human cells (i.e., not in as close proximity to the cell's genetic material). HSIA characterized the results of the studies as follows: "This research, which is now complete,

EXHIBIT 9.1. OSHA'S SCIENTIFIC CRITERIA FOR ACCEPTING A PBPK MODEL.

1. The predominant and all relevant minor metabolic pathways must be well described in several species, including humans. (Two metabolic pathways are responsible for the metabolism of MC in humans, mice, rats, and hamsters.)
2. The metabolism must be adequately modeled. (Only two pathways are responsible for the metabolism of MC as compared to several potential routes of metabolism for other compounds, such as benzene and the dioxins. This simplified the resulting PBPK models.)
3. There must be strong empirical support for the putative mechanism of carcinogenesis (e.g., genotoxicity), and the proposed mechanism must be plausible.
4. The kinetics for the putative carcinogenic metabolic pathway must have been measured in test animals in vivo and in vitro and in corresponding human tissues (lung and liver) at least in vitro, although in vivo human data would be the most definitive.
5. The putative carcinogenic metabolic pathway must contain metabolites that are plausible proximate carcinogens (e.g., reactive compounds such as formaldehyde or S-chloromethylglutathione).
6. The contribution to carcinogenesis via other pathways must be adequately modeled or ruled out as a factor. For example, there must be a reasonable analysis of why reactive metabolites formed in a second pathway would not contribute to carcinogenesis (e.g., formyl chloride produced via the MFO pathway is likely to be too short-lived to be important in MC carcinogenesis).
7. The dose surrogate in target tissues (lung and liver in the case of MC) used in PBPK modeling must correlate with tumor responses experienced by test animals (mice, rats, and hamsters).
8. All biochemical parameters specific to the compound, such as blood:air partition coefficients, must have been experimentally and reproducibly measured. This must be true especially for those parameters to which the PBPK model is most sensitive.
9. The model must adequately describe experimentally measured physiological and biochemical phenomena.
10. The PBPK models must have been validated with data (including human data) that were not used to construct the models.
11. There must be sufficient data, especially data from a broadly representative sample of humans, to assess uncertainty and variability in the PBPK modeling.

Source: Occupational Safety and Health Administration (1997, pp. 1533–1534).

shows that mice . . . are uniquely sensitive at high exposure levels to MC-induced lung and liver cancer, and that . . . there are no foreseeable conditions of human exposure in which the carcinogenic effect seen in mice would be expected to occur in man."

OSHA invited the scientific community and other interested parties to review the studies while the rule making was held in abeyance, and received a strong message that the research was neither "complete" nor convincing, and often internally contradictory (for example, the single-strand breaks study suggested that mouse Clara cells did not experience this type of damage). Various experts commented that even if the studies were correct, mice and humans can certainly differ *quantitatively* in their sensitivity to MC (by an amount no greater than the power of each assay to detect such differences), and that the PBPK approach was already tailor-made to account for such quantitative distinctions. Several commenters were particularly dismissive of the claim that mouse and human GST could only exist in fundamentally different portions of the cells of each species; one scientist noted that "this interpretation . . . is profoundly in error and contradicts some of the most well-established and fundamental principles of molecular biology." The fact that in a single rule-making OSHA embraced one alternative (PBPK) to a well-established default model while rejecting another (that mouse tumors were wholly irrelevant to human risk) provides an excellent case study of how a receptive, but not overly gullible, approach to interpreting new scientific information can improve the quality of risk assessment.

3. *Estimating individual risk for a hypothetical person of above-average susceptibility to exposure-related disease.* When OSHA calculated the excess cancer risk of exposure to 25 ppm MC using the PBPK model, it arrived at a slightly lower average value of risk than it had predicted using a simple body-weight extrapolation several years previously (1.2×10^{-3} *versus* 2.3×10^{-3}). However, all of the information on uncertainty and interindividual variability needed to calibrate and run the PBPK model allowed OSHA to explore what the excess risk would be to workers with differing degrees of susceptibility to MC (at least those differences due to variation in individual metabolism), and with different assumptions about uncertainty. Ultimately, OSHA determined that it would be more responsive to the spirit of the OSH Act language that "no employee shall suffer material impairment of health" if it estimated risk for a worker of above-average susceptibility. Due to either uncertainty or interindividual variability (or a combination of both), OSHA estimated there was approximately a 5 percent chance that the excess risk to a randomly selected worker would be at least threefold higher than the mean value of 1.2×10^{-3}, and so it based its final PEL on the basis of this 95th percentile estimate of 3.6×10^{-3}. To our knowledge, this was the first time that a U.S. federal agency quantitatively analyzed interindividual variability in susceptibility to a toxic

substance and explicitly estimated risk to consider persons of above-average susceptibility, although these decisions did not affect the final PEL, which OSHA asserted could not be lowered below 25 ppm because of economic and technological infeasibility. Several more recent developments during the first six to eight years after the MC standard came into effect also shed light on controversial issues of risk assessment and management.

During the last several years of the rule-making process, OSHA was confronted with various claims that the MC standard would exacerbate different "offsetting risks," resulting in fewer lives saved than the MC reductions themselves would achieve, and perhaps even in a net loss of life. The concept of risk-risk tradeoffs is well-developed in the policy literature (Graham and Wiener, 1995; Sunstein 1996), but although some trade-offs do seem inevitable (for example, that the benefits of reducing ground-level ozone will be offset to some extent by the additional skin cancers that will result from lower ozone concentration), questions remain about whether in general, claims of dire secondary outcomes from reducing existing risks are wholly legitimate. Among other claims, various industries warned OSHA (and Office of Management and Budget [OMB]) that the MC standard would result in a rash of fires and explosions as companies that could not meet the standard were forced to switch to acetone—a flammable substitute—as a solvent, adhesive, and so on. Similarly, the trade association representing operators of general aviation aircraft warned that "without MC," repainting of these aircraft would have to be done using substitute paint strippers, which could lead to substandard or less frequent paint removal and "a major risk factor to the flying public" from corrosion and metal fatigue under the paint going undiscovered (House Subcommittee on Workforce Protections, 2001). At the time OSHA told both OMB and the congressional oversight panel that it did not anticipate widespread substitution away from MC (that the new exposure limit could easily be met in these and other sectors), and that in any event, these industries were capable of handling substitutes safely and producing safe products. Now that ample time has elapsed in which any dire offsetting risks would have been evident, it appears that there has been at most one significant industrial fire or explosion involving acetone in processes where MC might possibly have been used (to be sure, that number was near zero prior to the issuance of the MC standard as well), and no reported general aviation accidents where improper paint stripping was a factor.

On the other hand, a different risk-risk trade-off that no one brought to OSHA's attention during the rule-making process has emerged and may well be offsetting some of the health benefits brought about by the MC standard. Within a year or two after the standard took effect, several U.S. and global companies began marketing an unregulated chemical, 1-bromopropane (synonym: *n*-propyl

bromide), as an alternative to having to comply with the new MC standard. Both this compound and a more toxic contaminant (2-bromopropane) formed during its synthesis are known to cause both neurological and reproductive damage in laboratory animals, and the National Toxicology Program concluded in 2003 that at current occupational exposure levels 1-bromopropane poses "serious concern for reproductive and developmental effects in humans" (NTP, 2003). In addition, a neurologist recently reported (Robinson, 2004) that six workers in a foam cushion factory in Utah developed chronic neuropathic pain and difficulty walking after being exposed to approximately 130 ppm 1-bromopropane over a period of several months. OSHA has not indicated any plans to consider regulating these substances, and the NTP is in the final stages of evaluating them for carcinogenicity in animals.

Finally, concerns have been expressed (Finkel, 2005) that compliance with the MC standard is not sufficient. According to OSHA's own data, nearly 40 percent of the MC samples OSHA took between 2000 and 2004 showed concentrations above the PEL, but OSHA continues to inspect only about 50 to 100 facilities each year for MC compliance. If its estimate during the rule making that ninety thousand different establishments use MC remains roughly accurate, then at this level of effort it would take OSHA more than a millennium to inspect a large proportion of these establishments, to determine whether this high rate of noncompliance in the first small fraction of inspections is an aberration or an indication of widespread compliance problems.

Control of Hazards

In an effort to manage risk to the worker, several types of controls have been put in place to limit safety and health risks of workers. In general, control strategies should be implemented following the standard hierarchy of controls that OSHA emphasizes as a matter of policy and enforcement: elimination, substitution, engineering, administrative, and the use of personal protective equipment. This hierarchy is designed to encourage employers to make process changes that remove the risk entirely or, failing that, to reduce exposures through engineering controls and—only if these are not feasible—to resort to measures that place extra burden on workers themselves. Let us examine each of these controls.

Elimination

The first option for removal of hazards in the workplace is the elimination of the hazardous substance or process entirely. This, of course, eliminates the hazard once and for all and offers complete protection for the worker. Unfortunately, this

is not always possible. Some activities, such as operation of hazardous machinery, cannot be removed from the workplace. Hence, alternative control strategies must be invoked.

Substitution

If a material, a process, or an individual piece of equipment is by its very nature hazardous, a reduction in risk for the worker may be efficiently achieved through substitution of a less hazardous process, equipment, or material. Workers would then no longer be exposed to the hazard. This is an effective strategy and offers long-run cost reduction in that lost worker time is reduced along with reduced worker's compensation costs. Initial capital outlays may be large however, especially if a process must be revamped entirely. Development of an effective substitution strategy requires a good deal of thought as well as experience in developing the new procedures.

Process Substitution. The substitution option may be most clearly indicated using some examples. In automotive manufacturing, for example, painting may be accomplished using a spray bay in which aerosolized paint is applied to the metallic frame of the automobile. The potential for inhalation exposure is great in such a spray, and the hazard associated with inhalation of paint and solvent vapors is well understood. An effective substitute for this process whereby the metallic frame of the vehicle is dipped into the paint, thereby reducing aerosolization and exposure, is readily envisioned and has been implemented. The implementation of such a substitution is not without difficulties, however. New paint formulations must be developed that afford good adhesion and attractive finished products. Even drying is problematic and requires further change in process. A significant retooling of the painting component of an assembly line for automaking is the indirect result of this hazard reduction.

Equipment Substitution. While modification of a process offers the best reduction in risk for the worker, the cost of such a modification may be prohibitive. The change of a single piece of equipment may be sufficient to reduce risk substantially at much lower cost. The selection of replacement equipment often requires the expertise of both management and worker in that the financial investment will be supplied by the management side, while familiarity with the process and working environment will be better known to the worker.

Consider the case of solvent use in an occupational setting. Small quantities of solvents are often delivered in glass bottles ranging in size from 250 mL to 4 L or more. The larger bottles are relatively difficult to handle and may be dropped

or dislodged from their storage area with the potential for significant exposure to the worker. Replacement of such bottles by safety storage cans that are unbreakable, or by enclosing the bottle in a plastic case, substantially reduces the risk of breakage. Such modification of storage equipment can be done at low cost and often offers a significant improvement in worker safety.

Material Substitution. In an industrial process, it is often necessary to use hazardous materials. However, the substitution of a less-hazardous material for a more hazardous one can often be effected without loss of efficiency in the process overall. Consider the following examples.

Historically, there are many examples of materials substitution with concomitant improvement in worker safety. Classic examples include the substitution of the red phosphorous allotrope for the white. The latter ignites on contact with air and is thus a hazard for both direct burns to the worker and fire within the facility. The red allotrope is much more easily handled and does not present the same safety concerns. Another example is the substitution of phosphors for radium on watch dials. One early use for radioactive materials was on watch dials to allow them to be visible in the dark. Unfortunately the workers painting these dials suffered from a series of radiation-induced ailments. This substitution improved the health of these workers immensely by reducing radiation exposure risk. The substitution of chlorinated solvents for petroleum naphthas in industry substantially reduced the fire hazard in cleaning operations. We must be careful in the selection of substitution materials, however, to ensure that one hazard is not being replaced by another.

Engineering Controls

Engineering controls invoke the application of mechanical solutions in an effort to reduce exposure to hazards. Engineering controls can be broadly grouped into the following categories: isolation and ventilation.

Isolation. Some processes cannot be changed, nor can the intrinsic risk associated with the process be reduced. In these cases the only real alternative is to remove the worker from direct contact with the process. This is called *isolation.* As the name would suggest, isolation involves placing some type of barrier between the workers and the hazard to which they might otherwise be exposed. These barriers can be *physical,* a wall or simply distance between the worker and the hazard, or *temporal,* a process that operates when the worker is not present until it is complete.

Some equipment is inherently dangerous due to the need for large amounts of energy to run it. Examples include high-pressure hydraulic lines, rotating machinery, and cutting blades. Because of the nature of the processes involved (e.g., moving heavy machinery and cutting metals), there is a significant potential for severe injury. Isolation offers a major reduction in risk. A physical barrier, a fence, enclosing rotating parts in metal, or isolating high-pressure hydraulic lines offers a good solution. Workers are not afforded an opportunity to come into contact with the dangerous equipment.

Certain operations, such as heat treating or cutting and drilling, cannot be nonhazardous. A heat-treating process requires elevated temperatures at the site of the work. These temperatures may be sufficient to burn on contact or may simply raise the ambient temperature to levels that surpass the body's ability to cope. Similarly, noise levels associated with a specific activity may be sufficient to cause permanent hearing loss either instantaneously or through long exposure. Isolation of the process (or the worker) may be the only feasible solution to such a problem.

Perhaps the easiest example to understand involves isolation from radiological or biological hazards. Highly radioactive materials, such as those found in nuclear research facilities, power plants, and in medicine, often require a thick shield to prevent workers from receiving dangerous levels of exposure. The process itself may be isolated in such cases and workers only allowed to interact by remote control or with robotic devices.

An effective strategy for reducing hazard exposure in occupational settings is the *lockout/tag out procedure,* commonly used in electrically or hydraulically powered systems. Power is eliminated from the equipment that is being inspected or repaired by a worker. The worker then attaches a locking mechanism to the source of power and locks the mechanism closed. Until the lock is removed, power cannot be restored to the system. If an additional worker enters the area, she adds a second lock to the system. Each individual entering has his or her own lock, and all locks must be removed before power can be restored. This is an example of physical isolation; no power can be delivered to the dangerous machinery until such time as all workers have left the hazardous area and all have removed their locks. Such strategies can reduce the risk associated with inadvertent starting of a machine while someone is still inside, with concomitant injury, to near zero.

Ventilation. In many occupational settings, the principal hazard is air contamination. Examples have been discussed previously and include nuisance dusts, vapors, metal fumes, and biological contaminations. It is often most convenient to reduce the hazard to the worker by supplying fresh, clean air. This is a direct application of the old adage "the solution to pollution is dilution." Ventilation may be

concisely defined as the removal of contaminated air, the introduction of clean air, or both, in an effort to dilute a physical or chemical hazard to some acceptable level. Ventilation systems are often divided into two large categories, though significant overlap exists between these two rubrics. These are (1) local exhaust and supply ventilation and (2) general exhaust ventilation.

1. *Local exhaust and supply ventilation.* Often in industrial facilities sources of air contamination are somewhat isolated by the process itself. Dust may be generated by a sanding and grinding operation that is limited to a single department or even a single machine. Organic vapors may be associated with a single degreasing tank. A biological hazard may exist at only one laboratory bench. In such cases it makes sense to treat the source of the contamination directly. If the source area could be partially enclosed (thus isolating the process) and the contaminating material removed before it permeates the area, risk to the workers in general could be substantially reduced. This solution is quite effective both in a risk reduction sense and in an economic sense. Exhaust systems can be designed with capture efficiencies approaching 100 percent for small areas.

2. *General exhaust ventilation.* While local exhaust and supply ventilation can be very efficient if sources of contamination within a facility are relatively isolated, they are not an effective solution if sources are dispersed throughout the facility. For example, a foundry may have multiple sources of particulate matter of varying types and indeterminate generation patterns. Local exhaust ventilation methods are not appropriate in such circumstances; it is necessary to rely on general ventilation within the entire faculty to reduce risk to workers.

General exhaust ventilation works much the same way as local exhaust ventilation except that now the entire facility is viewed as the "local" source. Large air-moving devices actively exhaust the contaminated air from within the building and supply fresh, outdoor air in its place. Such systems are costly in terms of capital outlay and in terms of heating and air-conditioning needs for the facility. However, if this situation is as described with numerous dispersed sources of contamination, risk reduction for workers often cannot be effected in any simpler or more cost-effective way.

Administrative Controls

Administrative controls, in which policies and procedures are implemented that reduce worker risk, have historically been the purview of management, but more recently cooperation between management and workers has made these more effective. Administrative controls include education of both management and the workforce on the risks experienced by the worker. While the education of the worker may seem obvious, as he needs to be aware of hazards and take proper steps to reduce them,

the role of management may seem less obvious. Yet the role of management may be even more important than the role of the worker in implementing and maintaining a safe working environment.

With the advent of OSHA in the 1970s, the bottom-line operating costs for a facility could be markedly affected by fines and shutdowns. Management often took an adversarial position with respect to OSHA regulation as well as with respect to organized workers or workers in general. This attitude has changed in the last 35 years. Astute managers have become aware of the potential to reduce workers' compensation premiums to increase productivity and to reduce training costs though the implementation of administrative controls. It is now quite common to see a partnership between management and workers to develop education programs designed to make workers aware of the hazards in a workplace and to take ownership in their own safety and health. OSHA has taken a leadership role in this process as well through the implementation of its voluntary protection program (VPP) whereby facilities that go through rigorous training and evaluation procedures are allowed to reduce the likelihood and scope of OSHA inspections required. Such cooperative interaction is the hallmark of effective administrative control programs, ensuring safe workplaces and more productive facilities.

Personal Protective Equipment

Even when all of the above procedures are implemented, there may still be significant residual risk for workers. Some industrial processes, such as cleaning solvent tanks or handling radioactive material or chemical hazards, are intrinsically hazardous and cannot be made hazard-free. Under these conditions, one is forced to examine the use of *personal protective equipment* (PPE), a form of worker isolation, as a final choice in protecting the worker. Simple examples include the use of safety shoes to reduce foot injuries in occupational settings, and the use of hearing protection in settings where noise is excessive. In areas subject to high levels of air contamination, the use of respirators may be necessary. Respirators supply clean breathing air to the worker and range from simple filters that remove excess dust or organic vapors from the air to more complex apparatus that supply air to a worker entering an enclosed space that might not have sufficient oxygen to sustain life or that might be subject to concentrations of toxic gases high enough to cause injury. For extremely hazardous work in which any contact with the environment comes with substantial risk, full-body protection, sometimes referred to as moon suits, may be required. Such PPE protects the entire body from inhalation exposure, ingestion exposure, and dermal exposure. Such protection is used under the most hazardous of conditions—circumstances where biological, chemical, or other hazards are so great that any contact with the environment might prove harmful.

The Evolution of Industrial Hygiene and the Role of New Professionals

Historically, industrial hygiene has focused on worker exposures to a single contaminant such as specific solvents, nuisance dusts, or radiation. However, recent studies in epidemiology, toxicology, and pharmacokinetics indicate that such a focus may be too narrow. Health outcomes are likely associated with multiple exposures over a lifetime to other compounds that may act as synergists or promoters of disease. To address these new observations, the profession of industrial hygiene is changing. New professionals in the field must now have broad-based knowledge of the mechanisms of contaminant action. They must study biology, toxicology, epidemiology, and other related sciences. The "new industrial hygienist" must be aware of the compounding of effects from, for example, exposure to various related solvents or classes of pesticides. The effects of exposure to some compounds or classes of compounds are now known to accumulate. Thus, an understanding of the historical exposures experienced by workers is necessary. The metabolism of compounds that enter the body must be understood as well; fast-metabolizing compounds may produce toxic metabolites, and slow-metabolizing compounds may accumulate in body-storage compartments and cause health problems years after exposure.

Those aspiring to become industrial hygienists in the twenty-first century must become more general in their education and in their work aspirations. In the coming years, industrial hygienists will still be required to "know their instrumentation" and be able to take samples in the field. But they will also need to be aware of secondary exposures experienced by workers in their nonwork activity as well as the impact of the industrial environment on the surrounding community. More and more industrial hygienists today are being asked to consult on *environmental hygiene,* the impact of the industrial environment on the environment at large. The role of the new industrial hygiene professional will be broader than in the past. Worker health and safety, environmental control of industrial facilities, and the impact on the community environment will be her purview.

Emerging Hazards

As the Industrial Age continues, workers will continue to experience hazards in the workplace. While we hope to have moved past the time of child labor, extremely hazardous working conditions, and exploitation of workers, new hazards are still likely to emerge. Often, the hazards are not evident at first, as with radi-

ation and asbestos, but come to light only after workers have received high exposures long enough to develop frank disease. We hope not to repeat some of the mistakes of the past. Let us examine some emerging concerns in an effort to make ourselves aware of the possibilities of worker injury.

Nanotechnology

Nanotechnology, the use of very small, even molecular-scale, machines, may well be the principal advance of the twenty-first century. Small devices may even eventually be placed inside the human body to repair damaged organs, attack cancer cells, or perform other processes not yet considered. There is potential for worker harm from such systems. It is not science fiction to consider the impact upon worker health associated with inadvertent exposure to nanotechnology devices. Now is the time to examine such possibilities and develop methods of protecting workers from inadvertent injury and illness in the nanotechnology workplace (Service, 2005).

New Industrial Processes

New industrial processes are being developed constantly. Consider the observation that integrated circuits and the concomitant assembly technology has all been developed in the last 35 years. New processes such as genetic engineering, gene splicing, and related biotechnologies are likely to be developed more fully in the next 25 years. Similarly, development of new industries built around fullerenes, the soccer-ball-shaped molecules developed in the last 15 years, is likely to increase as these compounds show great potential in fields as diverse as industrial lubricants and drug delivery systems. We must consider the impact on the health of workers who engage in these industrial activities. Are they at risk for certain known diseases? Are there new diseases that will emerge from these new processes? Some industrial processes will be common 25 years from now that are not even known at this point. How will we set up a mechanism that affords adequate protection to evaluate the impact on workers of these new processes? For a very recent example of a modern hazard only becoming known as a cause of serious occupational disease years after exposures began, see the literature on the relationship between diacetyl (used in artificial butter flavoring) and "popcorn lung disease" (bronchiolitis obliterans) (see, e.g., Schneider, 2006).

Exposure to Mixtures

Historically, industrial processes focused on the manufacture of single items. Steel mills produced steel, the automobile industry used this steel to make cars, and so on. More common now are industrial facilities where multiple exposures are likely

to occur. Pharmaceutical manufacturers use a variety of compounds in the synthesis of their products. Electronics industries use a large amount of silicon, but dope the surfaces with different trace elements to build circuitry with specific properties. Understanding the effects of these mixtures of compounds is a main need for future industrial hygienists. The task is not easy. How will these mixtures be measured? How will the components be weighted with regard to health outcomes? Are there compounds that interact synergistically to produce a large effect on health while each individually produces none? This is the challenge of the future.

Technological Change

Overall, the role of the future hygienist is to adapt to the technological change that is certain to come, while "holding the fort" against hazards known for decades or more, where continued vigilance is necessary to provide workers with a fighting chance to return home safely each day.

Thought Questions

1. What are the most important aspects of occupational risk assessment methodology that tend to make risk estimates *conservative* (prone to overestimation), and which aspects work in the opposite direction? On balance, do you think OSHA risk assessment errs on the side of precaution too much or not enough?
2. What are some of the factors that lead OSHA to devote roughly 90 percent of its resources to safety risks, when the scientific literature suggests that roughly 90 percent of premature deaths among U.S. workers are the result of chronic overexposures rather than acute exposure to safety hazards?
3. It has been 10 years since OSHA last undertook to formally establish regulatory and other priorities. What are the most significant hazards identified in that process that remain insufficiently addressed? What new hazards (or ones that could have been identified in the 1996 initiative) would you urge OSHA pay more attention to in the immediate future?
4. How can society reliably assess the contribution of specific interventions (e.g., regulations, enforcement, partnerships) to observed changes in measured results (fatalities, injuries, illnesses) given the difficulty in knowing what changes might have occurred in the absence of the interventions?
5. Given the many procedural and analytic requirements that slow the pace of OSHA rule making, the concern that EPA actions may tend to give incentives for companies to increase (or not decrease) workplace exposures, and the inefficiencies inherent in having two separate agencies regulating environmental and workplace conditions, what would the merits and pitfalls be of creating a single agency with jurisdiction over environmental and occupational risks?

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CHAPTER TEN

RADIOLOGICAL RISK ASSESSMENT

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Learning Objectives

Students who complete this chapter will

1. Have knowledge of the properties and hazardous nature of particulate and electromagnetic radiation
2. Know the terminology used for describing radiation dose and how dose is determined for exposed human populations
3. Be able to discuss the mechanisms by which radiation interacts with biological systems at the molecular and cellular level and how this can lead to adverse human-health effects
4. Understand the importance of dose-effect relationships derived from animal studies and human epidemiology, and how this information is used in carrying out radiological risk assessments.
5. Be familiar with the major agencies responsible for radiation protection and how radiation protection is regulated

The authors wish to acknowledge the leadership of Dr. Alexander Hollaender, founding director from 1946 to 1966 of the Oak Ridge National Laboratory, which played a significant role in determining the adverse health effects of ionizing radiation.

Ionizing radiation includes the following: (1) particulate radiation such as alpha particles and beta particles emitted from radioactive materials and neutrons from nuclear reactors and accelerators, and (2) electromagnetic radiation, such as gamma rays emitted from radioactive materials, and X-rays from electron accelerators and X-ray machines. Any radiation with energy greater than 12.4 electron volts (eV) per photon, corresponding to wavelengths less than 100 nanometers (nm), is considered to be ionizing.

Exposure to ionizing radiation may occur in a variety of circumstances, both to the public at large and to those in occupational environments. Such an exposure may have undesirable adverse health effects, depending upon the dose and the nature of the radiation. The question to be addressed here is, How does one go about determining the probability of an adverse human health effect upon exposure to ionizing radiation? For this purpose, radiological risk assessments are conducted both for worker safety as well as for protecting the health of the public.

In contrast to the task of determining risk associated with chemical exposure, which involves investigating pathways both outside as well as inside the body, radiological risk assessment is much more straightforward. The reason for this is that the interaction of radiation with tissue occurs directly without intermediate processing. Hence, it can be analyzed using well-defined dosimetric concepts. Dosimetry—the measurement or estimation of dose within a given tissue—is central to any form of risk analysis but is found in its most direct and simplest form in the case of radiological risk assessment.

Consequently, the biological effects of radiation exposure have been investigated more thoroughly than those of virtually any other environmental agent—particularly for exposure to high doses, for which measurable levels of cancer and other adverse health effects have been observed. This knowledge has been prominent in the shaping of human health protection measures for many other environmental hazards.

However, of current concern is the risk to the population from exposure to low levels of radiation for which it is not possible to make a direct observation of adverse health effects. Hence, extrapolations are necessary from the dose-effect relationships obtained at high doses in order to estimate the risk of exposure at low doses. Such extrapolations are carried out using models that make use of information obtained from molecular and cellular biology. The recent publication of the BEIR VII report by the National Academy of Sciences (2006) examines extensively the health risks from exposure to low levels of ionizing radiation. That document serves as the basis for much of the information presented here dealing with low-level radiation from external sources. An additional source of general information is the Toxicological Profile for Ionizing Radiation prepared by ATSDR (Agency for Toxic Substances and Disease Registry, 1997).

The risks from internal emitters of radiation, such as the radon daughters, are also covered, and the basis for this information is contained in the BEIR VII report. Another good source of information dealing with radon can be found in the book *Should We Risk It?* (Kammen and Hassenzahl, 1999), which contains a number of calculations and worked-out problems.

This chapter introduces the student to the basic concepts and background material associated with radiological risk analysis. The risk assessment process or paradigm as applied to ionizing radiation and presented here consists of the following four steps or phases, which are followed by the associated tasks of risk management and risk communication:

1. *Hazard identification.* We describe the physical characterization of ionizing radiation regarding its electromagnetic or particulate nature, sources, penetration depth, energetics, and spectral characteristics. We also discuss sources of radiation and explain how to distinguish between different types of radiation.
2. *Dose-response evaluation.* Dose-effect relationships are determined from experimental observations on the effect of ionizing radiation on systems varying from molecules to animals as well as from clinical and epidemiological observations. We describe the radiation chemistry of water, molecular mechanisms for DNA damage and repair, and the subsequent cellular responses, including chromosomal modifications. From animal studies we obtain dose-response information for mutagenesis and cancer. These biological studies extend the basis for modeling the adverse effects of ionizing radiation on the human population.
3. *Human exposure and epidemiology assessment.* In carrying out a radiological risk assessment we show how to determine the extent to which the population of interest has been exposed to a defined source of ionizing radiation, as determined in step 1 of the risk assessment process. The various epidemiological studies involving human exposures to ionizing radiation provide the approaches used to obtain this type of information.
4. *Risk characterization.* This last step in the radiological risk assessment process integrates information from steps 2 and 3, whereby exposure assessment information (step 3) is used in a model based on dose-effect and epidemiology relationships (step 2) to arrive at a figure reflecting the risk of an adverse health effect.

Having a basis for determining the risk associated with a given exposure allows us to establish regulations and limits for workplace exposures. This process is called *risk management.* In this way the public is protected against unnecessary exposures to ionizing radiation. Various agencies, national as well as international, have been created to participate in this process, each with a different set of objectives and responsibilities aimed at protection and prevention.

Informing the public of the management of risks associated with exposure to ionizing radiation in the ambient environment is called *risk communication*. This task is made difficult by a number of factors, including lack of scientific knowledge, misperception of the risks, and mistrust of governmental agencies, which at times do not appear to be forthcoming in making information available.

Hazard Identification

What is ionizing radiation? Where would you find it? How would you measure it?

In this section we present a brief glimpse of the discovery of ionizing radiation to give the reader an introduction to the physical properties of ionizing radiation, its sources, and how it interacts with matter. Knowledge of the fundamental nature of ionizing radiation can help us understand how it interacts with cellular constituents, how subsequent biological effects occur, and how excessive exposure can be regulated and prevented.

Basically, radiation is the transmission through space of energy in the form of electromagnetic waves or atomic particles. Its ability to penetrate matter as well as being invisible helps explain why ionizing radiation is a hazard. But in addition, its constituents are energetic enough, even at the smallest doses, to strip electrons from atoms, form ions, break chemical bonds, and ultimately cause damage to DNA, the key target molecule for radiation damage. As a result of such damage, adverse human health effects such as cancer (latent effect) as well radiation sickness (short-term effect) can occur. The first step in the radiological risk analysis process is to characterize different forms of ionizing radiation as to how they penetrate matter and cause chemical damage leading to subsequent adverse health effects.

Early Investigations

X-rays. The first evidence for the existence of ionizing radiation was obtained in Wurzburg, Germany, by W. C. Roentgen in 1895, who studied electrical discharge phenomena in tubes filled with gases (Crookes-Hittorf tube). He observed that invisible radiation, emanating from the walls of the tube, could cause a screen located some distance from the tube to fluoresce. He showed that this unknown radiation, which he called X-rays, could penetrate various materials interposed between the tube and the screen and could darken a photographic plate. In addition, the radiation could cause the discharge of an electroscope. This phenomenon was due to the ability of X-rays to ionize air molecules, although this property of the radiation was not recognized by Roentgen at the time. Within a

few months of their discovery, X-ray images on photographic plates of human organs were being made throughout Europe for medical imaging purposes. Thus, within a very short time the essential features of X-rays as we know them today were obtained.

M. von Laue later showed that X-rays underwent diffraction when passed through a crystal, indicating wavelike properties, the spaces between the layers of the crystal giving a measure of the wavelength of the radiation. Thus, X-rays were demonstrated to be electromagnetic in nature.

In a modern X-ray tube, electrons from a heated filament are accelerated by the application of high voltage and directed toward a tungsten target. Following the interaction of a high-energy electron with the target, an electron from the innermost energy level of the target atom is removed, creating an ion in an excited state. Relaxation to a lower energy state of the excited ion results in a release of energy in the form of an X-ray.

Radioactivity. In Paris in 1896 Henri Becquerel observed that uranium salts emitted radiation that could cause the formation of images on a photographic plate covered with various absorbing materials. This new form of penetrating radiation was an intrinsic property of the uranium alone, and was similar to X-rays in that it could also cause the discharge of an electroscope, demonstrating its ionizing properties.

In 1898 Mme. Marie Curie made quantitative measurements of the radiation emitted by uranium salts, using ionization chambers, and showed that it was proportional to the mass of uranium present; that is, it was an atomic property. She called this property *radioactivity,* and subsequently isolated two new radioactive elements from two tons of uranium pitchblend ore: polonium and radium. Radium was found to have a million times more radioactivity than an equal mass of uranium. It was shown that the number of disintegrations per second (dsp) per gram of radium was equal to 3.7×10^{10}, an amount of radioactivity that was assigned a unit, the curie (Ci). Currently, radioactivity, or simply activity (A), is expressed in units of becquerels (Bq), where one Bq corresponds to one dsp. Hence, a curie corresponds to 3.7×10^{10} becquerels.

Identification of the Radiation Associated with Radioactive Decay. In contrast to X-rays, radioactivity consists of three types of radiation that vary in their penetrating ability, which in turn depends upon differences in physical properties as first delineated by Ernst Rutherford in 1899. Using an ionization chamber, he showed that collimated radiation from uranium salts formed three distinct lines on a photographic plate when subjected to a magnetic field, indicating that radioactive decay could give rise to several different types of radiation. Two of the lines, assigned to alpha and beta rays, were deflected in opposite directions because of their charge differences, and a third, undeviated line was assigned to

gamma rays, which had previously been discovered by Paul Villard in 1898. By doing penetrating studies in various materials, Rutherford found that alpha rays were easily absorbed, beta rays were more penetrating, and gamma rays were even more highly penetrating. From the mass/charge (M/e) ratios it was determined that the positively charged alpha rays were helium nuclei and that the negatively charged beta rays were electrons. Gamma rays were subsequently shown to behave like X-rays when subjected to interference and diffraction experiments and were thus identified as being electromagnetic waves.

To summarize, *radioactivity* is defined as the spontaneous disintegration of atomic nuclei resulting in the formation of new elements and the emission of some combination of alpha, beta, and gamma radiations. The reason some atoms are unstable and form radionuclides that undergo radioactive decay is that they have too many or too few neutrons for a given number of protons. Each time a metastable nucleus disintegrates, it gives off some form of radiation, which can be counted. The frequency of counts or disintegrations per second, given as either curies or becquerels, is a measure of the amount of radioactivity present in a given quantity of a substance.

Classification of Radioactive Materials

There are three general categories of radioactive elements or radionuclides, classified as follows:

1. *Primordial.* Some radioactive elements have been on Earth from its initial formation. They include potassium-40, found in all living material, as well as all elements with atomic weight greater than 82, such as uranium-238 and thorium-232. Their half-lives are on the order of one to ten billion years, and the heat from their decay within the earth makes a major contribution to geothermal activity.
2. *Cosmogenic.* Cosmic rays coming from outer space consist of high-energy photons, heavy particles, and muons. When these interact with nitrogen and oxygen in the upper atmosphere, new elements are formed via transmutation, the most notable example being carbon-14 with a half-life of 5,730 years. Ultimately carbon-14 is taken up by plants in the form of carbon dioxide, following which it undergoes radioactive decay. Thus by measuring the $^{14}C/^{12}C$ ratio in ancient plant material one can arrive at the age of the material by this process of radioactive dating.
3. *Anthropogenic.* Humans have also contributed to the existence of more than 1,500 known radionuclides. Those formed as a consequence of nuclear fission, called fission products, are iodine-131 (^{131}I), cesium-137 (^{137}Cs), and strontium-90 (^{90}Sr),

as well as plutonium-239 (^{239}Pu). Nuclides produced using neutron bombardment for use in medical technologies and biomedical research include ^{131}I, ^{99}Tc, ^{32}P, ^{3}H, and ^{14}C.

Half-Life

Radioactive decay follows first-order kinetics, in accordance with the following expression:

$$N/N_0 = e^{-kt}$$

where N is the concentration after time t, N_0 is the concentration at time $t = 0$, and k is the first-order rate constant for radioactive decay. The amount of radioactivity associated with a given radionuclide is proportional to its mass and inversely proportional to its half-life, $t_{1/2}$, the time it takes for the radioactive material to decay by one-half. Setting $N/N_0 = ½$, it follows that:

$$\ln 1/2 = -kt_{1/2}$$

or

$$k = \ln 2/t_{1/2}$$

The more rapidly a nuclide decays, the greater the number of disintegrations per unit time per unit mass. Hence, small amounts of a radionuclide with a short half-life can be as radioactive or have as much activity as larger amounts with a longer half-life. However, short-lived radionuclides disappear much faster than longer half-lived ones and present a risk over a shorter time period.

In light of the above it follows that radiological risk assessment and prevention of human exposure to radioactive materials must take into account not only the amount of material present in the environment and the ultimate target organs but also the rate of radioactive decay as well as the biological half-life. Consider the following scenarios:

1. Reactor accidents release the fission product iodine-131 into the environment. Hence, nonradioactive amounts of iodide are administered in order to reduce uptake of radioactive iodine into the thyroid gland. With an eight-day physical half-life, the threat to an exposed population from iodine 131 is distributed over a relatively short time (months). The biological half-life is 138 days, so the effective half-life in the body is 7.6 days due to partial elimination.
2. On the other hand, used fuel rods contain fission products, which are midweight isotopes resulting from the random splitting of U-235. Many of these are

radioactive and have half-lives of hundreds to thousands of years. Various isotopes of plutonium, formed when neutrons are absorbed by U-238, are also present and contribute to the overall radioactivity of the used fuel rods. (It is estimated that after five hundred years the level of radioactivity is essentially equal to that of an unused fuel rod.) Because of the potential threat to populations far into the future, concerns over the long-term storage of used fuel rods continues to plague efforts to find a long-term solution for their disposal in the United States.

3. Strontium-90, also a fission product, has a half-life of twenty-eight years, and can substitute for calcium in the environment. Its presence in milk could ultimately lead to bone cancer. Hence, long-term monitoring of the environment, particularly grazing land, is required to minimize human exposure. With a fifty-year biological half-life, the effective half-life in the body is eighteen years.

It is useful to remember, particularly when storing radioactive wastes, that over a time period covering seven half-lives, the fractional amount of radioactivity remaining will be $1/2^7 = 1/128$, or less than 1 percent. For ten half lives, the amount remaining will be $1/2^{10}$ or essentially 0.1 percent.

Table 10.1 contains half-lives and energies of the decay products for selected radioisotopes.

Penetration: Range and Half-Layer Values

As first observed by Rutherford, different types of ionizing radiation vary greatly in their ability to penetrate materials of various compositions. For particulate radiation, the larger the charge and mass, the greater the extent to which inter-

TABLE 10.1. HALF-LIVES AND ENERGIES OF THE DECAY PRODUCTS FOR SELECTED RADIOISOTOPES.

Isotope	Half-life	Decay product (MeV)
Tritium	12.35 yr	0.018 β
Carbon-14	5730 yr	0.056 β
Phosphorous-32	14.29 d	1.710 β
Cesium-137	30 yr	0.662 γ
Iodine-131	8.04 d	0.860 β and 0.723 γ
Iodine-125	60.25 d	0.035 γ
Cobalt-60	5.27 yr	1.17–1.33 γ
Plutonium-239	24,065 yr	5.147 α
Strontium-90	29.12 yr	0.546 β
Uraniun-235	7.04×10^8 yr	4.18 α
Uranium- 238	7.04×10^9yr	4.200 α 0.066 γ

actions with the medium occur limiting penetration. For example, alpha particles, because of their size and charge, are blocked by a sheet of paper; they can penetrate only a few centimeters in air and only a few layers of skin. Hence, nuclides that are alpha emitters represent a hazard only when they are present internally or function as internal emitters. Electrons or beta rays, because of their smaller size and charge, can penetrate up to about 0.8 cm of skin. Neutrons and protons have the same mass, but neutron penetration is greater because of zero charge. The distance a particle travels before coming to rest is called the *range,* values of which in air and tissue (water) are given in Table 10.2 for 1 MeV energy particles. Note that upon going from air to tissue, the range decreases by up to three orders of magnitude.

X-rays and gamma rays, because of their lack of charge and mass, travel appreciable distances before interacting with atoms or molecules in their paths. Hence, penetration depths are much greater than with particulate radiation. Because of this, X-rays and gamma rays represent a much greater hazard to humans for external exposures than either alpha or beta particles.

Electromagnetic energy is released exponentially as it passes through matter. If I_0 is the initial intensity of the radiation, and I is the intensity at some distance x, then the relative intensity at x is I/I_0. One then has the relationship:

$$I/I_0 = e^{-\mu x}$$

where μ is the linear attenuation coefficient. The distance at which the intensity is reduced by one half, $x_{1/2}$, is called the half-layer value (HLV) where:

$$(HLV) = x_{1/2} = -ln1/2/\mu = \ln 2/\mu$$

Values of *HLV* for selected types of radiation are shown in Table 10.3. Alternatively, the distance at which the intensity is reduced by $1/e$ is called the relaxation

TABLE 10.2. RANGES OF DIFFERENT SUBATOMIC PARTICLES IN AIR AND TISSUE.

Type of Radiation	Range in Air	Range in Tissue
Alpha 1.0 MeV	6 mm	0.007 mm
Alpha 5.3 MeV (^{210}Po)	4 cm	0.051 mm
Beta 1.0 MeV	300 cm	4.4 mm
Beta 1.71 MeV (^{32}P)	700 cm	10 mm
Proton 1.0 MeV	3 cm	0.04 mm
Neutron 0–15 Mev	0–100 m	0–100 cm

Source: Turner (1986); Johns and Cunningham (1983).

TABLE 10.3. HALF-LAYER VALUES IN TISSUE.

Type of Radiation	Energy (MeV)	HLV (cm)
X-ray	6	16
Gamma ray (^{60}Co)	1.33	11
Gamma ray (Cs-137)	0.663	8.05

length given by $\mu 1/u$. Half-layer values for X-rays and gamma rays in cement and lead, two materials widely used for shielding, are given in a later section dealing with exposure prevention.

Energy Deposition and Linear Energy Transfer (LET)

As radiation passes through matter its energy is released, leaving in its path a track of ionized and excited molecules. Alpha particles travel in an almost straight path, energy being lost incrementally. Beta particles lose energy in larger amounts, and undergo large deflections, resulting in a tortuous path. Photons interact with matter in three different ways as follows:

1. *Photoelectric effect*, whereby all the photon energy is transferred to an electron.
2. *Compton effect*, where partial transfer of energy to an electron occurs, resulting in a photon of lower energy and an energetic electron.
3. *Pair production*, in which 1.02 MeV of a photon's energy is converted into an electron-positron pair that either interacts with tissue or recombines to form two 0.511 MeV photons.

Linear energy transfer (LET) is the term used to describe this process of transferring energy from the radiation to the surrounding medium. It is the rate of energy transfer per unit distance along a charged-particle track and is expressed in units of keV per micrometer of water. Because alpha particles have limited penetration, they release their energy over a short path-length, are densely ionizing, and have high LET. Beta particles or gamma photons of the same energy penetrate to a greater extent, release their energy over a longer path-length, are sparsely ionizing, and have low LET. In all cases, ionization requires energy sufficient to remove an electron from an atom, that is, to overcome its binding energy, which requires at least 12.4 eV.

Dosimetry

In the following discussion the notation employed is consistent with that proposed by the International Commission on Radiological Protection (ICRP) in 1991.

Exposure. The term *exposure* is used to denote the amount of radiation deposited in a given amount of dry air; it evolved from early measurements of radiation using electroscopes or ion chambers. It applies only to measurement of X-rays and gamma rays, and the unit of exposure, the roentgen (R), was originally defined as the deposition of 1 esu per cubic cm of dry air. This amount of radiation produces 1.61 x 10^{12} ion pairs per gm of dry air or 2.58 x10^{-4} coulombs of charge per kg of dry air. The roentgen is rarely if ever used today, however, when discussing the interaction of a biological system with ionizing radiation. As noted below, the units that are now used to denote doses absorbed in tissue are the rad and the gray. (1 R is equal to 0.869 rad in air and 0.96 rad in tissue; hence, it is often stated that 1 R is roughly equal to 1 rad.)

Absorbed Dose. *Dosimetry* is the process of quantifying the absorption of energy per unit of mass. The resulting dose is an essential component of any discussion of radiological risk. One measures absorbed dose in terms of either rads (1 rad = 100 erg per gram, using the older conventional or cgs system), or grays (1 Gy = 1 joule per kg, using the Systeme Internationale [SI] international system based on mks units). It follows that one gray is equal to 100 rads. As defined in this way, absorbed dose is purely a physical quantity representing the actual amount of energy deposited by exposure to a particular type of radiation (R) in a specific tissue (T), and it is denoted by the symbol $D_{T,R}$.

Relative Biological Effectiveness (RBE). Based largely on experimental studies, it has been determined that the RBE of various forms of radiation varies greatly; that is, absorbed dose alone is not a good indicator of how much biological effect one can expect. Experimentally, one determines RBE as a ratio of two doses, the bottom dose being that necessary for some form of radiation to achieve some level of biological effect such as cancer or lethality, and the top being that dose necessary for 200 keV X-rays to achieve the same level of biological damage. Simply put, based on equivalent amounts of absorbed dose, X-rays, gamma rays, and electrons are more or less equally effective, neutrons about five to twenty times more effective, while alpha rays are about ten to twenty times more effective in causing biological damage.

Equivalent Dose. The incorporation of RBE into dosimetry results in transforming absorbed dose into a more biologically significant quantity. One multiplies absorbed dose, a physical quantity, by a radiation weighting factor, W_R, and sums over R, the various types of radiation to arrive at the equivalent dose (H_T) for a specific tissue (T):

$$H_T = \Sigma W_R \times D_{TR}$$

The weighting factors for different forms of radiation currently used in radiation protection are given in Table 10.4. When the absorbed dose is transformed into the equivalent dose, the unit of dose changes from rads to rems and from grays to sieverts, a factor of 100 separating the two different set of units, that is, 1Sv = 100 rem.

Note that previously, instead of a radiation weighting factor, a quality factor Q was used, which served the same purpose as W_R and had essentially the same values. Multiplying the absorbed dose by Q gave a quantity called the dose equivalent. Currently, instead of Q, we use W_R as the radiation weighting factor, and the transformed dose is called the equivalent dose instead of dose equivalent. Note also that these factors, Q and W_R, are fixed by convention, whereas RBE is purely an experimentally determined value.

Effective Dose (Formerly Effective Dose Equivalent). Various tissues vary as to their response to ionizing radiation. Each type of tissue has a different probability for forming fatal cancer, nonfatal cancer, hereditary effects, and length of life lost. One can lump these four probabilities together and arrive at W_T, the tissue weighting factor shown in Table 10.5 that takes into account the relative overall sensitivity of a given tissue to ionizing radiation.

If we now multiply this factor times the equivalent dose we obtain the effective dose for a given tissue E_T. If we sum over T for the different types of tissue, we arrive at the effective dose E for the whole organism, still in units of either rems or sieverts:

$$E = \Sigma\ W_T \times H_T$$

Committed Dose Equivalent. The term *committed dose equivalent* refers to the dose received by organs in the body from internal emitters over specific time periods (usually fifty years); it allows us to enable estimation of the risks to those who are exposed continuously to a variety of nuclides that remain in the body for long time periods.

TABLE 10.4. RADIATION WEIGHTING FACTORS (W_r).

Type of Radiation	Radiation Weighting Factor (W_r)
Alpha	20
Beta	1
Gamma and X-ray	1
Neutrons (various energies)	5–20
Protons (various energies)	1–5

TABLE 10.5. TISSUE WEIGHTING FACTORS (W_T) USED BY ICRP AND BY THE USNRC (IN PARENTHESES).

Tissue	Weighting Factor
Gonads	0.2 (0.25)
Breast	0.05 (0.15)
Red bone marrow	0.12
Lung	0.12
Thyroid	0.05 (0.030)
Bone surface	0.01 (0.03)
Colon	0.12
Stomach	0.12
Bladder	0.05
Liver	0.05
Esophagus	0.05
Remainder	0.05
Whole body	1.00

Radon: An Internal Emitter

Alpha rays can penetrate only a few layers of cells. Hence, alpha-emitting radionuclides represent a health threat only when they are located inside the body in close proximity to cells sensitive to ionizing radiation. As such they are referred to as *internal emitters.* Radon-222 and its decay products are examples of internal emitters.

Radon is widespread in the environment being a decay product of radium-226 (half-life 1,600 years), which in turn is a decay product of uranium-238. Figure 10.1 shows the decay scheme for the formation of radon and its daughters.

Radon gas seeping out of the ground has a 3.82-day half-life, and gives off an alpha particle when it decays. The amount of radon coming from the ground varies enormously with location. Furthermore, its presence in a home depends upon the ease with which it can enter the home as well as the amount of circulation available for releasing the radon to the outside environment.

When radon decays, its progeny or daughters have relatively short half-lives, ranging from fractions of a second to twenty-seven minutes. The daughters, no longer in gaseous form, bind electrostatically to dust particles or aerosols and remain airborne. Upon entering the lungs they lodge in the bronchi where they undergo a series of decay, ultimately forming lead-210 with a half-life of twenty-two years.

Estimates of the number of lung cancers due to radon exposure range from three thousand to forty thousand cases per year in the United States. The major contribution to this estimate is not from radon itself but from the alpha-emitting

FIGURE 10.1. DECAY SCHEME LEADING TO RADON AND ITS DAUGHTERS.

Uranium-238 (7×10^9 years)

↓ α

Radium-226 (1,620 years)

↓ α

Radon-222 (3.82 days)

↓ α

Polonium-218 (3.05 minutes)

↓ α

Lead-214 (26.6 minutes)

↓ β

Bismuth-214 (19.7 minutes)

↓ β

Polonium-214 (1.6×10^{-4} seconds)

↓ α

Lead-210 (22 years)

radon daughters, polonium-218 and polunium-214. Hence, for each radon molecule decaying in the gas phase, two more alpha particles are emitted by these daughters. These alpha emitters are one hundred to one thousand times more effective in causing lung cancer than radon itself, because they lodge deep in the bronchi in close contact with sensitive lung tissue.

Levels of radon are expressed in terms of picocuries per liter (pCi/L), where 1 pCi/L = 37 Bq/cubic meter of air. The actual measured level of radon in the air is taken as a proxy for the level of radioactivity due to radon as well as to its decay products (daughters), which represent a much more serious hazard. Twelve percent of U.S. homes have levels exceeding 4 pCi/L, for which remediation is recommended.

In the occupational environment, radon activity is expressed in terms of *working levels* (WL), which are defined in two different ways. In general, one WL represents the concentration of short-lived progeny in one liter of air that will undergo

decay and produce 1.3×10^5 MeV of alpha energy. This amount of decay applies for those conditions where equilibrium doesn't exist between radon and its daughters. For the special case where the radon daughters are in equilibrium with the parent radon gas, one WL is also equal to 100 pCi of radon per liter of air.

A working-level month (WLM) is the product of the exposure in WL and the duration in hours divided by 170, the average number of working hours per month. One WLM corresponds to an absorbed alpha dose of approximately one rad. Estimated lifetime risk for lung cancer mortality is 3.5×10^{-4} per WLM. Current U.S. exposure limits are four WLM per year.

The National Radon Safety Board (NRSB) lists a number of radon measurement methods (see http://www.nrsb.org/measurement_method_definition.htm). Several of these methods require a skilled technician or relatively sophisticated equipment. For use in the home, two basic methods are available. In one method, a canister containing activated charcoal is exposed to the atmosphere for two to seven days, allowing radon to be absorbed on the charcoal. The canister is then sealed and sent to a laboratory where the radioactivity of the bound radon is measured in a scintillation counter. In the second method, instead of charcoal, a special film capable of being damaged by alpha particles is employed. The extent of alpha tracks formed on the film are then analyzed in the laboratory using a microscope. This method requires an exposure period of three to twelve months. A diffusion barrier can be used to prevent radon daughters from entering the canister so that only tracks due to radon decay are measured. Table 10.6 contains a list of the terms and units used in radiation dosimetry.

When ionizing radiation is absorbed by matter physical and chemical changes occur, which can be measured and used to quantitate the amount of radiation absorbed. These changes may include an increase in temperature as measured by calorimetry, ionization of a gas in an ionization chamber as measured by electrometry, charge separation in semiconductors/transistors resulting in changes in current flow/threshold potentials, electron-hole formation in a crystal leading to thermoluminescence, changes in a chemical dosimeter resulting in a measurable increase in optical absorbance, alterations of photographic and radiographic film, stable free radical formation as detected by ESR, and formation of fluorescent radiolysis products.

Absolute Measurements of Absorbed Radiation

Ionization Chambers. The only direct method of measuring absorbed dose is by *calorimetry,* a method that actually measures energy. But it has not been extensively developed by standardization laboratories. Instead, absolute measurements of ionizing radiation are made using ionization chambers, which measure the formation

TABLE 10.6. TERMS AND UNITS USED IN RADIATION DOSIMETRY.

Term	Symbol	Unit (abbreviation)	Description
Activity in conventional units	A	Curie (Ci)	Quantity of radioactive material = 3.7×10^{10} dps
Activity in SI units	A	Becquerel (Bq)	Quanity of radioactive material = 1 dps
Exposure		Roentgen (R)	Amount of ionization in air by photons; one R = 2.58×10^{-4} coulomb per Kg of air
Absorbed dose (conventional units)	$D_{T,R}$	Rad	Energy absorbed of 1 erg per gm
Absorbed dose (SI units)	$D_{T,R}$	Gray (Gy) = 100 rad	Energy absorbed of 1 joule per Kg
Radiation weighting factor	W_R		Factor to account for RBE of absorbed dose
Equivalent dose (conventional units)	$H_T = \Sigma W_R \times D_{TR}$	Rem	Absorbed dose in rads times W_R
Equivalent dose (SI units)	$H_T = \Sigma W_R \times D_{TR}$	Sievert (Sv) = 100 rem	Absorbed dose in grays times W_R
Tissue/organ weighting factor	W_T		Factor to account for radiation sensitivity of irradiated tissue
Effective dose (conventional units)	$E = \Sigma W_T \times H_T$	Rems	Equivalent dose in rems times W_T
Effective dose (SI units)	$E = \Sigma W_T \times H_T$	Sieverts	Equivalent dose in grays times W_T
Working level	WL		Concentration of 1.3×10^5 MeV of alpha energy per liter of air
Working-level month	WLM		Exposure to 1 WL for 170 hours

of ions in response to the radiation. In radiation biology, free-air ionization chambers have been used exclusively. Exposure to ionizing radiation results in a current that flows in proportion to the degree of ionization of a gas contained within a small glass chamber. Such devices can be manufactured using tissue-equivalent material in the wall, in accordance with the Bragg-Gray principle, to provide a measure of absorbed dose in tissue.

The calibration of such devices is traceable to facilities such as the National Institute of Standards and Technology (NIST), which serve as standardizing laboratories where primary exposure standards are maintained. The transfer of exposure calibration to field instruments is accomplished through transfer standards maintained at commercial facilities that offer calibration services. In the laboratory, ionization chambers, calibrated to within 2 to 3 percent, represent the absolute standard against which other types of dosimeters may be calibrated for use in radiation biology.

Chemical Dosimetry. Certain chemical solutions respond to ionizing radiation by forming radiation products that can be measured using absorption spectroscopy or some other analytical method. An advantage it has over other methods is that the dosimetric solution fills the volume of the container being irradiated. Hence, the geometry of the object being irradiated is easily taken into account, and we can determine the total absorbed dose in the volume of interest.

Another advantage of chemical dosimetry is that once a method has been established there is no need for calibration, as there is with a relative method. The quantitative response to radiation is contained in the form of a predetermined G value, a constant that relates absorbed dose to product formation. Hence, the dose can be simply calculated from an easily observable end point, such as a change in absorbance. In this respect chemical actinometry represents an absolute rather than a relative method of measuring dose because once the G value has been determined calibration is unnecessary.

For many years the Fricke dosimeter has been the most widely employed chemical dosimeter. It utilizes an acidic aqueous solution of ferrous sulfate, which upon exposure to ionizing radiation is oxidized to ferric sulfate. The absorbance at 304 nm due to the ferric ion is directly related to the absorbed dose. The lower limit of detection is 10 Gy (Johns and Cunningham, 1983).

More recently a chemical dosimeter has been developed by Rahn, Gerstenberg, and Varina (2002) consisting of an iodide/iodate solution that forms triiodide upon irradiation. The absorbance measured at 352 nm is directly related to the absorbed dose. The dose response is linear over the range 0.25 to 6,000 Gy, making it much more sensitive than the Fricke dosimeter and more useful in the biological dose range.

Relative Measurements of Absorbed Dose

These methods require calibration against an absolute standard such as an ionization chamber, which in turn has been calibrated against a transfer standard traceable to NIST.

ESR of Amino Acid Pellets. Exposure to ionizing radiation forms stable free radicals in pellets of the amino acid alanine, which is a tissue-equivalent material. The concentration of free radicals is proportional to the amount of absorbed dose. Precalibrated pellets can be commercially obtained from NIST. Following exposure, the concentration of free radicals is measured using an electron spin resonance spectrometer. Because such an instrument is costly ($50,000) the pellets are usually sent back to NIST where quantitative ESR measurements allow estimates of the radiation exposure to be determined. The minimum useful dose for this method is said to be Gy, although it is normally used at much higher doses.

Thermoluminescence. Small (<1 cm^3) precalibrated crystals of LiF can be commercially obtained, which when exposed to ionizing radiation produce crystalline defects. These defects (holes and electrons) undergo recombination upon heating and emit light (thermoluminescence), the amount of which is proportional to the amount of absorbed radiation. Relatively expensive instruments ($25,000) that carry out the heating and light detection processes are commercially available. The area under the glow curve is proportional to the amount of radiation absorbed. Levels on the order of 10 microGy up to 1000 Gy can be measured. Such devices are commonly employed in radiation therapy to monitor the radiation at sites on the body located in areas removed from the working beam.

Solid-State Devices. Semiconductor devices (silicon with p-n junctions) can be used as dosimeters and are eighteen thousand times more sensitive than ion chambers of equal volume. Irradiation results in electron-hole pair formation resulting in a measurable current flow opposite in direction to the normal diode current flow and proportional to the incident exposure. Such devices require connection to an electrometer and provide a measure of the radiation exposure in real time. We can measure dose rates on the order of 100 rads/min. Metallic oxide semiconductor field effect transistors (MOSFETS) represent another type of solid-state device for measuring gamma radiation. These devices undergo a change in threshold voltage when irradiated, which is linearly proportional to dose. Because the change is permanent these devices have the advantage of being irradiated without being connected to a readout device. They can be stored and measurements made at a later time. The linear range of detection is 500 mGy to 10 Gy.

Dosimeters Used for Personal Protection

Film. Film badges are the most popular choice for general personnel radiation monitoring, but not necessarily for quantitative measurements because of the difficulty of calibration. There are two types of film, *radiographic* or *photographic* film, which makes use of silver halide crystals and is light-sensitive, and *radiochromic* film, such as the GAF Chromic film, which uses dyes imbedded in a plastic film and is not light-sensitive. The dyes undergo polymerization when irradiated and change color.

Geiger Counters and Scintillation Detectors. The Geiger counter and the scintillation detector are used almost exclusively for the clinical measurement of radionuclides. They have enough sensitivity to measure the emission of a single particle or photon released during disintegration of an atom. In this respect they are more sensitive than other dosimetry methods discussed here and are mainly used to detect the level of ionizing radiation present in the occupational environment

A Geiger counter is essentially an ionization chamber designed for use in the field. However it is used in a high-voltage mode so that a much higher electron current results; that is, the electrons generated by the radiation have enough energy to produce further ionizations by collision events resulting in an avalanche of electrons. Hence, the current generated can undergo up to a millionfold amplification over that produced at low voltages. For detection of alpha radiation we can use a zinc sulfide filter, which acts as a scintillator. Generally, such an instrument is not used for quantitative dose measurements because of the difficulty of calibration.

A scintillation detector consists of a sodium iodide crystal positioned next to a photomultiplier. Exposure of the sodium iodide crystal to ionizing radiation induces free electrons, which then cause excitation of the atoms in the crystal, leading to the emission of visible and UV light. The light thus generated hits the photosensitive surface of the photomultiplier generating photoelectrons, which are amplified a millionfold via the dynode chain. Such an instrument is used to measure the presence of radionuclides present in the environment and obtained using swipes or some other means of sampling.

Dose-Response Evaluation

Ionizing radiation is hazardous because it interacts with biological systems and causes adverse health effects. What are these adverse effects? How do we measure or quantify the potential of ionizing radiation for causing these effects? How can the end results of exposing cells to ionizing radiation—death, transformation, chromosomal changes, biochemical changes—be used in radiological risk assessment?

Radiation Chemistry and DNA Damage

Knowledge of the mechanisms by which radiation produces biological damage is useful for modeling risk assessment. It is well-established that DNA is the critical target molecule for ionizing radiation injury; that is, damage to DNA accounts for the subsequent biological response of a cell to ionizing radiation. The uniqueness of the DNA molecule and its role as the master blueprint for the operation of the cell make it the most sensitive component in the cell to radiation damage. Substitution of radiation-sensitive bromouracil for thymine in DNA enhances the sensitivity of cells to radiation damage and demonstrates the role of DNA as a target molecule. Similarly, cells containing tritiated thymidine in the DNA show greatly enhanced lethality due to beta decay. Enhanced sensitivity to ionizing radiation is also found when cells lack adequate DNA repair mechanisms. For plant cells and viruses, we have found a direct correlation between the size of the DNA—the target—and the lethality of ionizing radiation. Finally, by using a microscopic beam of radiation it is possible to show that irradiation of the nucleus as compared with the cytoplasm is far more effective in producing cell killing.

Ionizing radiation damages DNA either directly or indirectly. Direct damage occurs either by transfer of energy from the primary radiation beam to DNA or by interactions of energetic secondary electrons with DNA. In either case ionization events occur in DNA, resulting in DNA damage.

Indirect damage to DNA occurs when DNA reacts with radicals or reactive molecules generated in the media by the ionizing radiation. Cells contain a relatively large amount of water (roughly 70 percent by weight), so when ionizing radiation passes through a cell a significant amount of energy is absorbed by the water, resulting in the ionization or radiolysis of water. Subsequently, hydroxyl radicals, solvated electrons, and hydrogen atoms are formed. These radiolysis products diffuse away from the primary track and react with DNA. The reaction of the hydroxyl radical (half-life 10^{-11} seconds) with DNA has been the most widely studied, the initial step being hydrogen atom abstraction from the DNA by the radical. The subsequent radical formed in the DNA, at either the base or the sugar, subsequently undergoes further modification.

In radiation biology, the *oxygen effect*, whereby the biological effects of ionizing radiation are at least several times less when irradiation is done under hypoxic as compared with normal conditions, is well-known. This enhancement of the potency of radiation in the presence of oxygen may be due to its ability to react with radical sites on the DNA to form peroxy radicals. Also, in the presence of oxygen, radiolysis of water may result in the formation of hydrogen peroxide, hydroperoxy radicals, and hydroperoxy ions, all of which are chemically reactive and are longer-lived (half-lives 10^{-10} sec) than the hydroxyl radical.

Overall, the resulting damage to the DNA following exposure to ionizing radiation consists of base damage, base removal, and modifications in the sugar-phosphate backbone. Damage to the latter can lead to alkali-labile bonds, frank single-strand chain breaks, and double-strand chain breaks. Estimates of DNA damage relative to 1,000 single-strand breaks are given in Table 10.7.

Double-strand breaks could be the result of two single-strand chain breaks formed separately on opposite strands of the DNA, the formation of which would follow a square dependence on absorbed dose. But they also could result from a single ionization event, or an ionization cluster, in close vicinity to the DNA, leading to simultaneous formation of damage on both strands of the DNA. For the latter, the kinetics of formation should be linear with dose. In fact, linear formation of double-strand breaks for ionizing radiation occurs down to very low doses (3mGy), demonstrating that they are not formed from individual single-strand breaks.

The nature of this form of damage to DNA is referred to as *locally multiply damaged sites* (LMDS) and is characteristic of damage caused by ionizing radiation. The likelihood of LMDS formation increases with LET; hence, alpha particles have a much higher probably of forming such sites than gamma rays because of the higher concentration of ionization events per unit distance. If the fraction of absorbed energy that can lead to LMDS increases with LET, then, for the same amount of absorbed dose, more biologically effective damage occurs. This notion is consistent with the fact that alpha particles are generally ten to twenty times more effective biologically than gamma rays.

TABLE 10.7. ESTIMATES OF DNA DAMAGE.

Type of Damage	UNSCEAR[a]	ATSDR[b]	BEIR VII[c]
Base damage	200	—	1,000–2,000
Single-strand breaks	1,000	1,000	500–1,000
Double-strand breaks	50–70	63–70	50
Protein-DNA cross-links	150	—	—
Bulky lesions	450	—	—
Locally multiply damaged sites	—	440	—

[a]The number of lesions induced in the DNA of a mammalian cell per D(37) of absorbed radiation energy (United Nations Scientific Committee on the Effects of Atomic Radiation, 2000).

[b]Lesions formed by 1 Gy (Agency for Toxic Substances and Disease Registry, 1997).

[c]Lesions normalized to 1 Gy based on a background radiation dose of 5 mGy, which results in an average of one electron track per cell, giving rise to 5–10 damaged bases, 2.5–5 single-strand breaks, and 0.25 double-strand breaks (National Academy of Sciences, 2006).

It is thought that clustered or closely spaced damage on both strands of a DNA molecule (LMCD) represents a situation refractory for DNA repair. A repair enzyme complex would have to deal with two sites on opposite strands simultaneously, a situation leading to misrepair or repair failure. Therein lies the rationale for LMCD being a lethal lesion.

In contrast, damages caused by oxygen containing radicals, formed mainly in the mitochondria during normal metabolism, occur as single events, are nonclustered and therefore more easily and/or faithfully repaired. The levels of spontaneous base damage normally occurring in cells over a twenty-four-hour period are presented in Table 10.8. These results demonstrate the high level of enzymatic repair activity taking place in a normal cell necessary to maintain a low steady-state level of damage.

Mutagenesis and Cell Transformation

Misrepaired or unrepaired damage in DNA may ultimately be expressed in the form of a mutation, provided the cell undergoes DNA synthesis and division (mitogenesis) following irradiation; mitogenesis leads to mutagenesis. If unrepaired, a damaged base will code for the wrong base during synthesis, leading to a mutation in the newly synthesized strand. Although the frequency of mutations typically increases linearly with dose, the rate of formation is greater at high dose rates than at low-to-intermediate ones, suggesting that DNA repair is more efficient at the latter dose rates than at higher or lower ones. Approximately 10^{-5} to 10^{-6} mutations occur per locus per Sv.

In accordance with current theories of cancer etiology, mutations in a combination of genes that controls cell growth, mortality, or contact inhibition may result in cell transformation, which in turn can lead to cancer, a monoclonal disease; that is, mutagenesis leads to carcinogenesis. Promotion of the transformed

TABLE 10.8. BACKGROUND LEVELS OF DNA DAMAGE PER CELL PER DAY.

Type of Damage	Frequency of Occurrence per Day	Steady State Concentration per Day
Depurination	10,000	<100
Deamination	100–500	<100
3-methyladenine	600	<50
8-hydroxyguanine	500–1000	100

Source: National Academy of Sciences (2006).

cell to neoplastic status requires additional changes, which may be caused by agents called *promoters,* a class of agents that includes ionizing radiation. It should be pointed out that current theories suggest that only certain cells can undergo transformation and that these cells, numbering approximately one in one hundred, represent or are analogous to stem cells capable of generating new cells.

Clastogenesis: Chromosomal Aberrations

Chromosomal changes in number and structure, as well as sister chromatid exchanges, have been observed in irradiated tissue culture and human blood lymphocytes exposed to ionizing radiation. Chromosome breakage and failure to rejoin result in gene deletions in the next generation, whereas misjoining of broken ends gives rise to distortions categorized as follows:

- *Inversion.* A rearrangement of pieces on the same chromosome.
- *Reciprocal translocation.* The balanced exchange of pieces between two chromosomes.
- *Dicentric distortions.* The unbalanced exchange of pieces between two chromosomes, a more detrimental aberration than a reciprocal translocation.
- *Sister chromatid exchanges.* Not necessarily chromosomal aberrations, but interchange and reunion of homologous strands during DNA replication.

The frequency of these aberrations in lymphocytes has been used as a biodosimeter to determine the radiation dose to individuals exposed to various levels of ionizing radiation. Current technology allows detection of chromosomal changes at doses about three times the maximum annual permissible dose for radiation workers, or fifteen Rem. It is thought that double-strand breaks (dsb) are the major contributor to chromosomal aberrations with approximately thirty to sixty dsb/cell/Gy

Differences in the effectiveness of various types of ionizing radiation in producing chromosomal aberrations is demonstrated in Table 10.9.

TABLE 10.9. EFFECT OF RADIATION TYPE ON CHROMOSOMAL ABERRATIONS IN HUMAN LYMPHOCYTES.

Radiation type	Dicentrics per cell/Gy
15 MeV electrons	0.0055 (+/– 0.011)
^{60}Co gamma rays	0.0157 (+/– 0.003)
250 KV X-rays	0.0476 (+/– 0.005)

Source: National Academy of Sciences (2006).

Effects on Cells

A variety of cellular alterations can occur in an irradiated cell, including cell death. In general, a dose of one to two Sv reduces a dividing cell population by 50 percent. Dividing cells are much more sensitive to ionizing radiation than nondividing or stationary cells. According to the *first law of irradiation* proposed by Bergonie and Tribondeau in 1904, the radiosensitivity of cells is related directly to their reproductive capacity and inversely to their degree of differentiation. In dividing cells, DNA synthesis occurs, and, if unrepaired, DNA damage may result in a mutation in the next generation. Furthermore, rapidly dividing cells provide less time for DNA repair as opposed to stationary or slowly dividing cells. Also, unrepaired DNA damage in a cell undergoing differentiation is greatly magnified as the cell develops, the effect of the damage being proportional to the number of times the cell divides. The most sensitive cells in the body are bone marrow stem cells and cells undergoing rapid turnover found in the epidermis, hair follicles, intestinal mucosa, and testis. These cells are roughly an order of magnitude more sensitive than the least sensitive cells found in striated muscles and long-lived neural tissue.

DNA repair is essential for maintaining healthy cells. Tissue culture studies on cells taken from individuals in the population that lack appropriate or effective DNA repair capability provide insight into the biochemistry of this type of genetic disorder. Human cell lines have been developed from ataxia-teleangectasia (AT) patients, which show enhanced sensitivity to ionizing radiation, and from xeroderma pigmentosum (XP) patients, which show enhanced sensitivity to both UV radiation and, for some variants, ionizing radiation.

Animal Toxicology

Obviously, humans cannot serve as experimental test subjects. Hence, animals are used to investigate in a controlled manner the radiation-induced formation of diseases such as cancer or heritable mutational changes. From animal studies we obtain dose-response information useful in extrapolating to irradiated human populations. Animal or toxicological studies form one cornerstone of the risk assessment process, complementing human epidemiological data, which will be presented in the following discussion of human epidemiology.

Health effects in response to ionizing radiation are either short-term (acute) or long-term (latent). Risk assessments rarely if ever deal with acute responses, mainly because they are a consequence of accidental exposures involving high levels of radiation, and represent situations where the risk assessment process has

little or no application. Hence, studies of interest deal with low levels of radiation, which by convention are doses of ten rads (100 mSv) or less.

Mutagenesis. Following the use of the atomic bomb in 1945 and the beginning of the Nuclear Age, questions were raised as to the possibility that persons exposed to ionizing radiation, such as the Japanese A-bomb survivors, would pass on to their offspring altered genetic material resulting from an increased mutation frequency. Hence, research projects were initiated by the Atomic Energy Agency to examine radiation-induced mutations in animal model systems. Large-scale animal experiments on the order of a million mice were conducted at the National Laboratories on radiation-induced genetic alterations, using in-bred strains of mice with unique genetic characteristics.

At the highest levels of radiation used in these experiments, many offspring of the exposed mice were born dead and considered to have inherited dominant lethal mutations. However, a small number of mice showed genetic alterations, the frequency of which increased in proportion with the dose. The mutation rate per gamete, or per cell, ranged from 10^{-2} to 10^{-3} per Gy for high-dose-rate, low-LET radiation exposures and was several times lower than this for exposures at low-dose rates; fission neutrons were about five times as mutagenic as low-LET radiations at high dose rates and up to fifty times as mutagenic at low-dose rates. The frequency of mutations varied appreciably among different genetic loci, but averaged about 1.09×10^{-5} per locus per Gy. On the basis of the available data, the dose of low-LET radiation required to double the mutation rate in the mouse when received at low-dose rates is estimated to be approximately 1 Gy.

Teratogenesis. Much of our knowledge of the teratogenic effects of ionizing radiation comes from studies on laboratory animal models, usually mice and rats. Such effects include many types of birth defects, behavioral alterations, and growth retardation. These effects are a consequence of the fact that rapidly dividing, undifferentiated cells are much more sensitive to DNA damage than slowly dividing, differentiated cells. The type of teratogenic effect induced depends on the stage of development at the time of irradiation, with threshold doses of twenty-five to fifty rads generally being observed.

Carcinogenesis. The other major effort involving animal studies has been to examine the frequency of cancer in mice, rats, dogs, and other species. Such studies have generally involved hundreds of animals per experiment, in which the animals have been observed throughout life following irradiation to determine their cancer rates. A diversity of benign and malignant growths has been observed to increase in frequency in such animal populations, with the result that ionizing radiation has come to be regarded as a *universal carcinogen*. This does not

mean, however, that radiation is capable of inducing every type of cancer or of increasing the incidence of every induced cancer equally by a given dose. On the contrary, from the wealth of data that are now available, the following can be concluded:

1. Neoplasms of most, but not necessarily all, types can be induced by irradiation under appropriate conditions in animals of suitable susceptibility.
2. The relation between dose and incidence varies, depending on the type of tumor in question, the dose, dose rate and linear energy transfer (LET) of the radiation, the sex, age, genetic background, and physiological state of the exposed animals, and other variables.
3. Low-LET radiations, such as X-rays and gamma rays, are generally less tumorigenic for a given dose than are high-LET radiations, such as alpha particles, and their tumorigenic effectiveness decreases with decreasing dose rate, in contrast to that of high-LET radiations, which tend to be relatively independent of the dose rate.
4. For no type of neoplasm do the existing data suffice to define the dose-response relationship unambiguously at doses in the range of only a few mSv, but for some neoplasms the data are consistent with a linear-no-threshold dose-incidence relationship.
5. Irradiation may act to increase the incidence of neoplasms through a variety of mechanisms, some that involve direct effects on the cells that undergo transformation, and others that are mediated through effects on neighboring cells (*bystander effects*) or effects on more remote organs and tissues.
6. The various effects in question include the activation of oncogenes, the inactivation or loss of tumor-suppressor genes, effects on other regulatory genes, and alterations in hormone levels, other growth factors, immunological responses, and other homeostatic mechanisms.
7. The process of radiation-induced neoplasia characteristically evolves through a sequence of steps, including initiation, promotion, neoplastic transformation, and progression, completion of which may occupy a considerable fraction of the normal life span.
8. The degree to which the risk of cancer may be increased by a given dose of radiation depends on the extent to which the process is influenced by other factors before, during, or after irradiation, including the homeostatic action of adaptive responses.

In summary, cancer is characteristically a monoclonal disease in that it is derived from a single transformed cell as a result of a succession of genetic changes

in that cell. It follows that a single event in a single cell can in principle contribute to the development of cancer. Thus, in principle, radiation-induced cancer would appear to be a stochastic event with no apparent threshold.

Human Exposure and Epidemiology Assessment

What are examples of human exposure to ionizing radiation that apply to the task of estimating radiological health risks? In addition to animal studies, epidemiological information is used to determine the relationship between exposure to ionizing radiation and subsequent adverse health effects in the human population. In order to detect the small increases above background levels in cancer frequency resulting from low doses of radiation, we must study sizeable numbers of exposed human populations. Such populations studied thus far fall into four categories: (1) A-bomb survivors, (2) medical patients receiving either diagnostic or therapeutic radiation, (3) populations receiving environmental exposures, and (4) persons receiving occupational or workplace exposures.

In all these cases, the information required for risk assessment purposes includes an estimate of the dose distribution received by the population under study and the types and frequencies of latent adverse-health effects in the population. In these studies not only is the dose-effect relationship of importance but also the dose rate and the time necessary for cancer to appear—for example, the latent period.

Because the available epidemiological data are in most cases derived from retrospective studies, the relevant dose estimates require reconstruction of the circumstances resulting in radiation exposure. Making such dose estimates is a difficult and complex process. For example, analysis of the dose received by the Japanese A-bomb survivors is an ongoing process as evidenced by data presented in the recent BEIR VII report (National Academy of Sciences, 2006).

Furthermore, each exposed population may have to be followed for an adequate length of time. For cancer, studies may cover up to fifty years, depending upon the type of cancer being followed. For mutational changes in the population, several generations of offspring may be followed.

Moreover, the induction of cancer over background levels has been detected only after relatively large doses (greater than 0.1 Sv). Hence, the risk associated with exposure to low levels of radiation cannot be determined solely from analysis of human epidemiological data. Extrapolations must be made from high to low doses, and mathematical modeling is required. Such modeling utilizes, in addition to the epidemiological data, both animal data and basic mechanistic information derived from molecular and cellular studies.

Background Exposures

On an everyday basis people are unavoidably exposed to low-level amounts of radiation. This background level must be taken into account when estimating the radiological risks from additional exposures. In the United States, the estimated average annual effective-dose equivalent received by a person living at sea level amounts to about 3.6 mSv, of which radon, an internal emitter, affecting primarily the lungs, contributes 55 percent. Other contributions include cosmic radiation (8 percent), rocks and soil (8 percent), and internal sources in food and water (11 percent). These natural exposures are highly variable. Cosmic radiation varies with elevation and radioactivity in rocks, soil varies with geographic location, and indoor radon levels vary from house to house.

The remaining contribution to the background level is from man-made sources, the majority being from nuclear medicine (4 percent), X-rays (11 percent), and consumer products (3 percent). Exposure from nuclear fallout contributes less than 1 percent. Note that the average dose from one computed tomography (CT) whole-body scan is 12 mSv, while that from one chest X-ray is 0.08 mSv and from one mammogram 0.13 Sv, the latter two not representing whole-body exposures.

If we exclude the average estimated dose to the respiratory tract from radon (2 mSv), the risks associated with the remaining 1.6 mSv of background radiation can be estimated only by extrapolation, based on dose-response models. Such models imply that less than 4 percent of all cancers in the general population are attributable to natural background irradiation. It is not surprising, therefore, that epidemiological studies of the extent to which the rates of cancer vary in relation to natural background have failed to detect any significant correlations, except for an increased frequency of lung cancer in association with elevated indoor residential radon concentrations, average values of which are estimated to cause up to 10 percent of all lung cancers in the U.S. population.

Occupational Exposures

Workers in various occupations are exposed to ionizing radiation in amounts that vary, depending on the nature of their work and working conditions. In the days before modern safety standards, workers in a number of occupations were at high risk of radiation-induced cancers.

Early workers in the medical and research fields were unaware of the potential harm associated with exposure to X-rays and radioactive substances. Consequently, serious radiation burns were common in such workers, particularly on the hands. Soon other medical complications, including leukemia and other can-

cers, were associated with exposure to ionizing radiation. Early martyrs included the following:

- Radiologists and radiation workers, many of whom developed cancer of the skin on their hands through the handling of radioactive sources and the practice of focusing their primitive X-ray machines on the bones of their own hands and fingers. Leukemia was also common; prominent victims include Marie Curie and her daughter Irene, both of whom died from radium exposure.
- Early painters of luminous clock and instrument dials, many of whom developed bone cancer after long latent periods (fifteen-plus years) through the practice of bringing their fine-tipped brushes to a point between their lips, thereby gradually ingesting toxic quantities of radium, the average dose being 3.6 micrograms of radium.
- Underground hard-rock, uranium, and pitchblende miners, many of whom (up to 50 percent) developed lung cancer (over an estimated seventeen-year latent period) through repeated inhalation of the radon that was present in high concentrations in the mines.

In all these cases a similar pattern occurred: workers were unwittingly exposed in the workplace to harmful levels of ionizing radiation; an adverse health effect emerged; doctors and scientists came to realize the relationship between exposure and health effects; standards for safe exposure were established; and appropriate regulations were set in place, which were revised with each acquisition of new information. A similar pattern can be found for exposure to chemicals in the workplace.

Thanks to the exposure limits that have since been instituted, the risks of radiation-induced cancers have been all but eliminated in today's radiation workers. Pooled analyses of multiple cohorts of such workers have suggested, however, that they still show a dose-dependent increase in the risk of leukemia, consistent with that seen in the atomic bomb survivors.

Environmental Exposures

Increased rates of chromosome aberrations and cancer have been observed to be associated with exposure to elevated levels of radiation from environmental sources in a number of populations, notably:

- Marshall Island Islanders who were exposed to radioactive fallout from a thermonuclear weapon detonated at Bikini Atoll in 1954

- Populations in the United States residing downwind from the Nevada Nuclear weapons Test Site during the 1950s
- Populations in eastern Europe residing downwind from the Chernobyl nuclear reactor accident in 1986
- Populations exposed to radioactive wastes discharged into the Techa River early in the 1950s

In some of these populations, cancers of the thyroid gland have occurred with increased frequency, especially in those exposed during early childhood, owing primarily to the ingestion of toxic quantities of radioactive iodine via contaminated cow's milk or other foodstuffs. In other populations, the frequency of leukemia and other cancers has been observed to be increased in proportion to the amount of exposure. Notably, however, populations living around nuclear facilities have not shown a definite or consistent increase in cancer rates attributable to radiation.

Dosimetry of A-Bomb Survivors

The bombs that were exploded in the air over Hiroshima and Nagasaki in 1945 exposed the populations of those two cities to a mixture of gamma rays and, to a lesser extent, fission neutrons. A total of at least sixty-four thousand people died immediately. The Radiation Effects Research Foundation (RERF) has been conducting a Life Span Study (LSS) of the survivors, consisting of a cohort of more than 86,600. The doses of radiation, which were received instantaneously by the survivors, decreased inversely with the square of their distance from ground zero. As a result, only about one in every four of the 86,611 survivors for whom quantitative dose estimates are available is estimated to have received a total dose in excess of one hundred mSv.

Mutagenesis in A-Bomb Survivors

After World War II concern for genetic damage prompted studies on the offspring of the survivors for genetic changes linked to exposure to radiation. While dose-dependent increases in the frequency of mutations and chromosome aberrations have been observed in the circulating lymphocytes of the survivors, such as sister chromatid exchanges, no increase in the frequency of heritable genetic abnormalities has been detected in their offspring, as measured by untoward pregnancy outcomes, neonatal deaths, malignancies, balanced chromosomal rearrangements, sex-chromosome aneuploidy, alterations of serum or erythrocyte protein phenotypes, changes in sex ratio, or disturbances in growth and development. The data, while largely negative, do not suffice to exclude an increase

in the frequency of heritable mutations in the survivors' germ cells. One should bear in mind that most mutations are recessive and that for such a mutation to be observed in an offspring, a defective gene must be inherited from both parents for altered expression.

The main problem with estimating the likelihood of genetic damage or mutagenesis is that the postulated rate of occurrence is less than the variation in the normal background frequency. Considered in the light of the animal data and other relevant information, the available evidence suggests that a dose of at least one Sv would be required to double the frequency of heritable mutations over background in human germ cells. Thus, the data suggest that less than 1 percent of all genetically determined diseases in the human population can be attributed to natural background radiation.

Teratogenesis in A-Bomb Survivors

The embryo, or unborn organism, is particularly sensitive to both chemical and radiation exposures because small changes at the beginning of the differentiation process are greatly magnified in the fully developed organism. At the very earliest stage of development—namely, immediately following conception—it is likely that damage to a single gene in a cell could prevent further development, resulting in a high spontaneous abortion rate. In humans it is estimated that perhaps 30 percent of conceptions spontaneously abort, although this is difficult if not impossible to verify. Severe congenital abnormalities occur at a rate of twenty-three thousand per million births of which seventeen thousand result in perinatal deaths.

As an embryo continues to develop, it becomes less sensitive to the lethal effects of ionizing radiation, and, depending upon the stage of development, exposure of the mother can lead to abnormalities of the body and/or mental deficiencies in the newborn. Human embryos at approximately twenty-eight days undergo limb bud development or organogenesis, and radiation damage at this stage to only a few cells can lead to birth defects involving altered arms and legs.

Later in embryogenesis a critical stage in brain development occurs. Survivors who were exposed prenatally (i.e., eight to fifteen weeks after conception) to atomic bomb radiation have shown dose-dependent decrements in stature and head circumference. This has been accompanied by severe mental retardation and marked decrements in intelligence and school performance. The dose-dependent downward shift in the distribution of intelligence levels within the entire cohort was similar to the known neurotoxic effects of certain chemicals (e.g., lead, mercury, and alcohol) on the developing brain. Human fetuses exposed to doses of ionizing radiation between one and seven weeks or later than twenty-five weeks after conception showed no such effects.

Because of the extreme sensitivity of the embryo to ionizing radiation (it is estimated that a dose of 1 mSv causes two cases of severe hereditary effects per million births), pregnant women exposed to 0.15 Sv or more should consider the possibility of terminating their pregnancies. The recommended exposure limit for a pregnant radiation worker is five milliSv or 0.5 rem per year.

Carcinogenesis in A-Bomb Survivors

Epidemiological follow-up of the survivors has disclosed dose-dependent increases in the frequency of most, but not all, forms of cancer in this population. Leukemia was the first of the cancers to appear in increased numbers, after a minimum latent period of two to three years, reaching a peak of six to eight years after exposure. The overabundance of leukemias varied with the hematological type of the disease in question and with the age of the affected survivor at the time of irradiation. The dose-response curve varied roughly as a linear-quadratic function of the dose. Of the 296 fatal cases of leukemia observed in the total population (over eighty thousand survivors) by the year 2000, 93 are estimated to have resulted from A-bomb irradiation.

Solid cancers appeared later than leukemia and increased in frequency with the attained age of the survivors. Although the various types of solid cancers differed in their dose-response relationships, the total incidence of all solid cancers combined increased linearly with dose, even at doses in the range of zero to 150 mSv. As of the year 2000, a total of 10,127 deaths from solid cancer had been observed in the total population, 479 of which are estimated to have resulted from irradiation. In women who developed breast cancer after having been irradiated in childhood, the disease appeared only upon reaching sexual maturity, indicating the important influence of hormonal stimulation in the pathogenesis of this disease.

Life Shortening in A-Bomb Survivors

In addition to their heightened mortality from cancer, atomic bomb survivors have also suffered from a dose-dependent increase in the frequency of heart disease, respiratory disorders, and various other nonneoplastic diseases, all of which have led to a shortening of their life spans.

Medical Exposures

Radiographic examination for diagnostic purposes accounts for over 80 percent of the radiation from man-made sources to which the general population is exposed. Although the average dose received by a given individual is only a fraction

of that received from natural sources, larger doses have been received by some groups of patients who have subsequently developed cancer as a result. These include the following:

- Infants in whom the incidence of childhood leukemia was increased as a result of having been exposed prenatally to diagnostic levels of X-radiation through the radiographic examination of their pregnant mothers' abdomens
- Women in whom the incidence of breast cancer was increased as a result of their having received repeated fluoroscopic examinations of the chest during the treatment of pulmonary tuberculosis
- Patients in whom the frequency of leukemia was increased by radiotherapy of the spine for ankylosing spondylitis (a crippling form of arthritis)
- Patients treated with X-rays to the scalp for ringworm in childhood in whom the frequency of thyroid and brain cancers was subsequently increased
- Various other radiotherapy patients, including those treated with radium 224 for TB of the spine who later developed bone cancer as a result

Parameters Affecting Response

A number of radiological and physiological variables influence the response to a given dose of radiation. Among the former are the spatial and temporal distribution of the dose. In general, low-LET radiation is less damaging than high-LET radiation for a given dose, and its biological effectiveness decreases substantially with decreasing dose rate, in contrast to that of high-LET radiation, which is relatively dose-rate-independent. Also, a dose is characteristically less damaging if limited to only a small fraction of a given organ than if delivered to the organ as a whole.

Among the physiological variables influencing the response to a given dose are age, gender, genetic background, and physiological state. Because the radiosensitivity of cells generally varies directly with their rate of proliferation and inversely with their degree of differentiation, children and young adults in a growing state are typically more radiosensitive than older adults to most types of radiation injury, including carcinogenic effects. Also, because of the modifying effects of hormonal influences, susceptibility to the carcinogenic effects of radiation on the thyroid gland and the breast is higher in females than in males, and decreases with increasing age at the time of irradiation.

Radiosensitivity is also increased in persons with ataxia-telangiectasia, Fanconi's anemia, Bloom Syndrome, and other inherited DNA repair deficiencies. In combination with radiation, the effects of another physical or chemical agent may be additive, synergistic, or inhibitory, depending on the particular agent and exposure conditions in question.

Risk Characterization and Regulatory Aspects

What is the estimated incidence of an adverse health effect in a given population exposed to ionizing radiation? How do we integrate exposure and dose-response data using modeling? How are regulatory standards set?

In this section we describe the methods by which estimates of risk are made and how regulations are formed based on dose-effect relationships. In the previous section we presented examples of human exposure and subsequent adverse health effects. This information, together with modeling, allows us to estimate the risks attributable to low-dose radiation exposure. Subsequently, we can establish regulations for radiation protection. Regulatory aspects and the setting of exposure standards are still being examined, the BEIR VII report (National Academy of Sciences, 2006) being one of the most recent examples of this effort.

Ionizing radiation represents a unique hazard in the regulatory world in the sense that we are all being continuously exposed to some naturally occurring background level of ionizing radiation. Hence, zero exposure is impossible, and only recently has the presence of radon in our environment been taken into account, more than doubling the public's average background exposure. Hence, the regulation of ionizing radiation differs from that of so-called man-made chemicals in that the former takes into account the occurrence of natural radiation in the environment while the latter often strives for a zero-tolerance level. Given that we are all exposed to low-level background radiation, regulation of the disposal of radioactive waste may arguably appear to be excessively precautious. As pointed out by Nobel Laureate Rosalyn Yalow in testimony before Congress in 1979, our bodies contain 0.1 microcurie of potassium-40 and 0.1 microcurie of carbon-14. According to NRC rules, however, a dead animal that has received this amount of radioactivity would have to be disposed of as radioactive waste. Likewise, in the cleanup of the reactor accident at Three Mile Island, water contaminated with very small amounts of radioactive material underwent decontamination at the expense of many millions of dollars, whereas its release into the environment would have resulted in a negligible contribution to the natural background level of radioactivity.

Early Attempts to Set Maximum Exposure Standards

Over time, exposure standards have been lowered as more knowledge has been gained about the harmful effects of ionizing radiation, especially long-term or latent effects such as cancer. Exposure regulations or standards have changed significantly over time, reflecting increasing awareness of the risk associated with

radiation exposure. Initially, there was no knowledge about the long-term biological effects of radiation such as cancer. Also, the technology had to be developed in order to obtain quantitative measurements of absorbed dose that were reproducible worldwide. Exhibit 10.1 shows the primary organizations involved in radiological risk assessment in the United States and abroad.

Early "safe" dose levels were defined as follows:

- In 1902 "harmful" radiation was that which could cause fogging of a photographic plate in seven minutes or less. This level is seven-hundred times greater than the permissible dose today.
- In 1925 the "safe" dose was reduced from 10 percent to 1 percent of the dose necessary to cause erythema or reddening of the skin over a cumulative 30-day period. This level is still 15 times greater than is allowed today.
- In the 1930s more quantitative measurements of dose set the tolerance limit at 1 to 2 mGy (0.1 to 0.2 rad) per day for radiation workers. This dose amounts to 35 to 70 rads per year, or 7 to 14 times the currently allowed permissible dose.

Cancer

Given an estimate of radiation exposure, one can calculate the risk to an individual or to the public using models based on mechanistic and dose-effect data. This integration of exposure assessment with dose-response data from animal experiments and human epidemiological research constitutes the fourth step in the risk assessment process/risk characterization. The following expression best describes the cancer risk $R(d)$ associated with a dose d of ionizing radiation:

$$R(d) = R_0[1 + f(d)g(b)]$$

where R_0 denotes the age-specific background risk, $f(d)$ is a function of dose—linear quadratic for leukemia and linear for other types—and $g(d)$ is a risk function dependent upon parameters such as gender, age at exposure, and time after exposure. This model presumes that there is no level of radiation exposure that does not present some degree of risk, no matter how small.

Different dose-response scenarios are presented in Figure 10.2 based on this model. The linear model with a threshold is not considered valid for ionizing radiation. For low-dose-rate and low-LET radiation, we assume a linear, no-threshold, dose-response relationship. This follows from the BEIR VII recommendations and is used for setting regulations for low levels of radiation exposure.

It is evident from experimental and epidemiological data that at low dose rates there is a lower risk of adverse health effects (e.g., cancer, chromosomal translocations, and life-span shortening) per unit dose of low-LET radiation than at high

EXHIBIT 10.1. ORGANIZATIONS CONCERNED WITH RADIOLOGICAL RISK ASSESSMENT AND THEIR PRINCIPAL RESPONSIBILITIES.

Advisory Bodies

Agency for Toxic Substances and Disease Registry (ATSDR). Evaluation of health risks associated with exposure to ionizing radiation and determination of minimal risk levels (MRLs).

Health Physics Society. Radiation protection and risk and benefit assessment.

International Commission on Radiological Protections (ICRP).

International Commission on Radiological Units and Measurement (ICRU).

National Academy of Sciences, National Research Council, Division of Earth and Life Studies, Board on Radiation Effects Research, Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation. Issues BEIR reports. This seventh report was initiated in 1996 and made available to the public in 2005. It deals with radiological risks from low doses and low dose rates such as those experienced by radiation workers and the general public.

National Cancer Institute (NCI). Government-supported research institute devoted to cancer research.

National Council on Radiation Protection and Measurements (NCRP). Congressionally chartered, it provides reports on a wide variety of issues related to radiation protection and measurement.

Radiation Effects Research Foundation (RERF). Studies of long-term effects in Japanese A-bomb survivors.

United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). This advisory body of international experts has produced at regular intervals since 1958 an authoritative series of assessments of the sources and levels of ionizing radiation to which the world's people are exposed and of the health effects that can be considered to have resulted from those sources.

Agencies That Issue Regulations

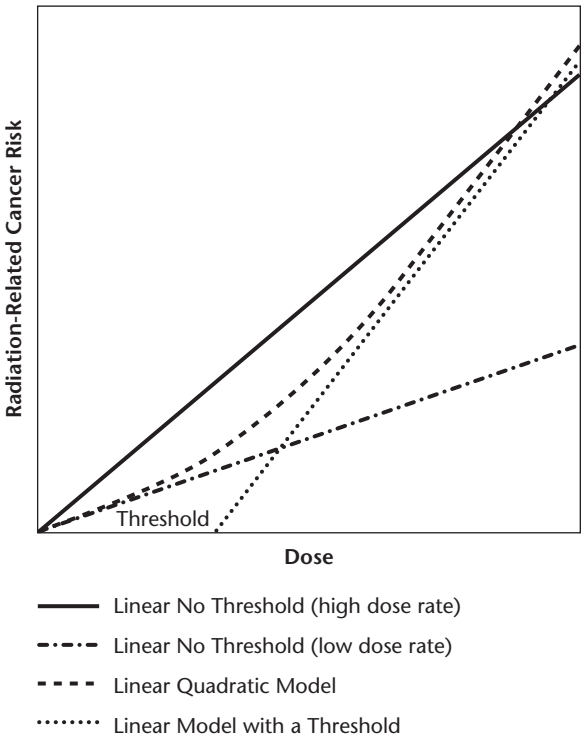
U.S. Department of Energy (DOE). Issues regulations for all DOE facilities.

U.S. Department of Transportation (DOT). Regulates transportation of radioactive wastes.

U.S. Environmental Protection Agency (EPA). Government agency that regulates the discharge of toxic materials into the environment and has responsibility for managing the cleanup of radioactive materials at Superfund sites.

U.S. Nuclear Regulatory Commission (NRC). Regulates all aspects of radiation associated with nuclear generation.

FIGURE 10.2. DOSE-RESPONSE SCENARIOS.



dose rates. So a dose rate effectiveness factor (DREF) is incorporated into the modeling that has a value of 1.5 to 2.5 for various human cancers (National Academy of Sciences, 2006). Consequently, at high-dose rates, the model for solid cancer shows a higher dose-response curve but remains linear.

Leukemia follows the lower curve at low doses and then approaches the upper curve at high doses. Thus, it follows the linear-quadratic dose-response model.

Table 10.10 provides estimates of cancer incidence and deaths over the lifetime of 100,000 people of mixed ages without radiation exposure, and the excess cases and deaths expected in this population due to a single whole-body exposure to 0.1 Gy.

It is interesting to calculate how many cases of cancer develop as a consequence of exposure to the low levels of radiation that make up normal background radiation. Since the average dose from natural background radiation

TABLE 10.10. FREQUENCY OF CANCER AND DEATHS IN 100,000 PEOPLE AND FREQUENCY OF EXCESS CANCERS AND DEATHS FROM EXPOSURE TO A SINGLE RADIATION DOSE OF 0.1 Gy.

	Solid Cancers	Leukemia
All cases (no exposure)	41,200	710
Deaths (no exposure)	19,800	620
Excess cases from 0.1 Gy	1,050	85
Excess deaths from 0.1 Gy	510	60

Note: Data for males and females have been combined.
Source: National Academy of Sciences (2006).

(low-LET and high-LET combined) in the United States is estimated to approximate 2.4 mSv, data from the table imply that less than 2 percent of the population will get cancer from natural background radiation over a 70-year lifetime, a risk too small to be detectable.

Genetic Changes

Two models are used to estimate the risk for radiation-induced hereditary disease:

1. Direct method based on high doses to animals and then extrapolating to humans
2. Doubling dose method that estimates risk based on the dose needed to double the frequency of mutations over the natural background frequency

Based on the above, it is estimated in the BEIR VII report that a dose of 1 Sv would be required to double the frequency of mutations in a human germ cell.

Regulations

Occupational Exposure. Occupational exposure guidance is provided by the International Commission on Radiological Protection (ICPR), which set forth the following principles for radiological protection:

1. No work practice involving exposure to ionizing radiation should be adopted unless it produces sufficient benefit to the exposed individuals or the society to offset the detriment it causes.
2. All radiation exposures must be kept as low as reasonably achievable (ALARA), economic and social factors being taken into account.
3. The whole-body radiation dose from all relevant sources should not exceed the prescribed dose limits, which amount to 5 rems in a given year and not more than 10 rems over a 5-year period. Doses to the skin, or hands and feet, can be 10 times higher. For radon daughters, dose limits are 4 working-level months (WLM). A pregnant woman should not receive more than 50 mRem in a given month.

Nonoccupational Exposure. Essentially no formal regulations exist to protect members of the public from ionizing radiation exposure in the ambient environment. As a rule of thumb, human activity generating excessive radiation exposure is maintained at levels no more than twice the normal background level, or about 1 mSv per year of low LET radiation. The guiding principle of radiation protection is to avoid all unnecessary exposures. Regulations set forth by the EPA regarding release of radioactive materials into the air, water, and soil are designed to minimize exposure of the public to ionizing radiation in accordance with this principle.

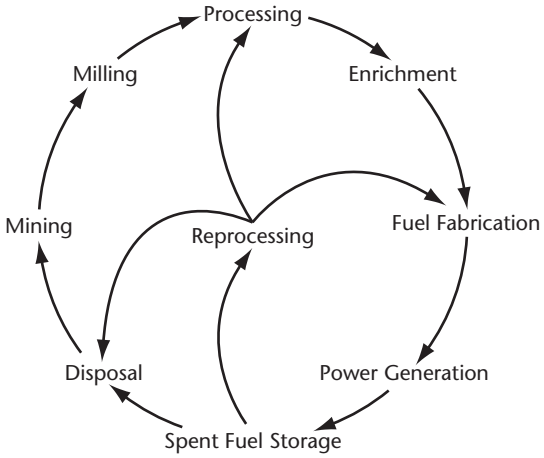
Environmental and Occupational Exposure to Ionizing Radiation

Because medical radiographic examinations and indoor radon constitute the most important controllable sources of exposure to ionizing radiation for members of the general public, prudent measures to limit irradiation from these sources are called for. Other potential risks to human health and the environment that call for increased attention are those posed by the millions of cubic feet of radioactive and mixed wastes (mine and mill tailings, spent nuclear fuel, waste from the decommissioning of nuclear power plants, dismantled industrial and medical radiation sources, radioactive pharmaceuticals and reagents, as well as heavy metals, polyaromatic hydrocarbons, and other contaminants), which are accumulating in ever-growing quantities and which severely tax existing storage capacities at numerous sites.

Production of Nuclear Energy

The nuclear fuel cycle (see Figure 10.3) represents the path by which nuclear energy is produced, starting from the mining of the uranium ore to the final disposal

FIGURE 10.3. NUCLEAR FUEL CYCLE.



Schematic of the Nuclear Fuel Cycle

of the radioactive waste associated with used fuel rods. Tailings from the mining and milling of the ore probably represent the most serious threat to public health because of the high levels of radon present. The improper dispersal of these tailings around the community of Grand Junction, Colorado, forced the Department of Energy (DOE) to carry out a major remediation project, removing tailings around homes where they were used as fill. In addition, uranium miners, as well as those involved in the milling process, are subjected to high levels of radon.

The most controversial aspect of the cycle with respect to public exposure is that of disposal of the used fuel rods. A site in Nevada at Yucca Mountain has been under development for many years, and questions still remain as to whether it will ever be used for storage of the used fuel rods. Before use the rods are easily handled because of the low levels of radioactivity of uranium-235 and -238 due to their long half-lives. Fission results in the formation of radioactive fission products as well as the neutron-induced formation of plutonium-239, which has a half-life of about 24,000 years and plutonium-240, which has a half-life of 6,560 years. Hence, there is concern over the proper storage of this highly hazardous material for tens of thousands of years. Currently, used fuel rods are stored at the reactor site, initially immersed in water.

An alternative to storage is reprocessing whereby the pellets in the used fuel rods are removed and the contents subjected to chemical separation allowing the recovery of plutonium-239 and uranium-235. This process can be hazardous and has not been carried out in the United States for many years. It was halted during the Carter administration in an attempt to reduce the spread of weapons-grade materials. However, recent decisions prompted by the need for the United States to become more energy-independent indicate that reprocessing may be restarted.

There are 436 nuclear power plants in 31 countries, but no country has yet to develop a long-term storage facility for used fuel rods. France generates 78 percent of its energy using nuclear reactors: spent rods are kept on site for one year in storage pools, then transported to a central site where they are kept for another two to three years in storage pools before undergoing reprocessing. Any high-level waste is then vitrified and stored until long-term geologic disposal is available.

Workers located at nuclear energy power plants and DOE facilities are required to wear radiation badges and are monitored regularly for possible exposure. Human error can sometimes lead to excessive exposure, but in general the safety record is quite good. Numerous epidemiological studies have been carried out on this population without consistently finding any significant long-term health effects; however, analyses of data pooled from multiple-worker cohorts have revealed dose-dependent increases in mortality from leukemia and other cancers similar to those observed in the atomic bomb survivors.

Risk Management and Prevention

In order to minimize the risks of injury, the guiding principles set forth earlier need to be observed. Implicit in these guidelines are the requirements that any facility dealing with ionizing radiation must (1) be properly designed; (2) carefully plan and oversee its operating procedures, including dose calibration; (3) maintain a well-conceived radiation protection program; (4) ensure that its workers are adequately trained and supervised; and (5) maintain a well-developed and well-rehearsed emergency preparedness plan in order to be able to respond promptly and effectively in the event of a malfunction, spill, or other type of radiation accident.

Strategies for reducing unwanted exposure to ionizing radiation make use of the following three factors:

1. Increase distance from radiation source
2. Decrease time of exposure
3. Provide suitable shielding

Most facilities employ concrete barriers and lead shielding to prevent excess exposures to ionizing radiation. This level of protection is really only necessary for electromagnetic radiation, as particulate radiation is much less penetrating. Examples of half-layer values are given in Table 10.11 for X-rays and gamma rays of various energies.

Risk Communication and Perception

Some feel that the hardest part of risk assessment is translating analysis to policy-relevant information, advice, and action for decision making. This requires communication with all interested and affected parties. Such communication should occur at each stage of the assessment process, should take into account the needs and values of all those impacted, and should be a continuous, ongoing process.

Ionizing radiation presents some unique aspects regarding the public's perception of the risks associated with its exposure. Given the stochastic nature of radiation-induced cancer, even at the lowest levels of exposure, there may be some finite probability of carcinogenesis. On the other hand, background radiation is part of our life, and we can't escape it.

People's perception of risk and their response to radiation exposure varies with whether the exposure is voluntary or involuntary, controllable or uncontrollable. Also, radiation is invisible, has no odor, is capable of penetrating matter, shows no obvious signs when it interacts with the human organism, and its biological effect may be delayed for years. So it's understandable why people would have an almost irrational fear of radiation. Therein lies the difficulty in bringing scientific analysis into the public domain, where mistrust coupled with an emo-

TABLE 10.11. HALF-LAYER VALUES FOR GAMMA AND X-RAYS IN CONCRETE AND LEAD.

Type of Radiation	Half-Layer Values in Concrete	Half-Layer Values in Lead
500 KeV X-ray	1.4 in	3.6 mm
4 MeV X-ray	3.6 in	16.4 mm
0.662 MeV gamma (^{137}Cs)	1.9 in	7 mm
1.17 -1.33 MeV gamma (^{60}Co)	2.6 in	12mm
0.364 MeV Gamma (^{131}I)	1.6 in	3 mm

Source: Goodwin, Quimby, and Morgan (1970).

tional mind-set and a lack of technical background renders the task of risk communication formidable.

Examples of Radiological Risk Assessments and Risk Management

1. *Radon in the home.* James and others (2004) estimated the radiation doses delivered to target cells in the lung from radon progeny under indoor and mine exposure conditions. The purpose of this study was to aid in the extrapolation of risk estimates from data based on underground miner cohorts to the case of residential exposures.
2. *Groundwater contamination.* In the course of Superfund cleanups the EPA has issued several reports dealing with radioactive contamination in groundwater (Environmental Protection Agency, 1994, 1996).
3. *Radionuclides in soil at Superfund sites.* Radionuclides in soil can be ingested, inhaled, or can provide external human exposure. The concentration in the soil is measured in pci/gram. The risk to the public per year per pci per gram of soil is contained in tables developed by the EPA called health effects assessment summary tables (HEAST). The data are in the form of slope factors (Environmental Protection Agency, 2001).
4. *Contaminated nuclear weapons complexes.* A study done by the Center for Risk Management (2000), located at Resources for the Future, examines the problem of contaminated nuclear weapons complexes and their cleanup.

Abbreviations, Acronyms, and Key Terms

Many of the units used in science are broken down into smaller units or expressed as multiples, using standard metric prefixes. For example, a kilobecquerel (kBq) is 1,000 becquerels; a millirad (mrad) is 10^{-3} rad; a microrem μ (μrem) is 10^{-6} rem; a nanogram is 10^{-9} grams; and a picocurie is a 10^{-12} curies.

Abbreviations	*Acronyms*
Ci curie	**AER** absolute excess risk
Bq becquerel	**DREF** dose rate effectiveness factor
g gram	**ERR** excess relative risk
Gy gray	**LCD** lung cancer deaths
hr hour	**LET** linear energy transfer
kg kilogram	**LSS** life span study

Abbreviations *Acronyms*

L liter

m meter

m^3 cubic meter

ppm parts per million

Sv sievert

yr year

Key Terms

Adaptive response A homeostatic process elicited by injury or stress; can increase latency period, but not eliminate lifetime risk of forming cancer

Bystander effects Effects on an unirradiated cell resulting from the exposure of one or more neighboring cells

Rad A unit of radiation absorbed dose (1 rad = 100 ergs/gm)

Rem Roentgen equivalent man

Thought Questions

1. Given the background levels of ionizing radiation present in the environment, to what extent should the public be concerned about radiation from normally operating nuclear power plants and the on-site storage of spent fuel rods? How would you, as a public health official, address a group of concerned citizens protesting at a nuclear power plant?
2. Do you feel that the current recommendations for permissible levels of exposure to ionizing radiation for public as well as for occupational exposures are adequate for protection against adverse health effects? Who is responsible for making these recommendations?
3. Ionizing radiation is used to treat cancer, yet it causes cancer. How would you explain this paradox to a nonscientist?
4. What are the properties that make ionizing radiation an environmental hazard? Compare differences in the adverse health effects caused by whole-body exposure to X-rays in the workplace, exposure to radon in the home, and exposure to the fission products iodine-131 and strontium-90 released from a nuclear facility accident.
5. Studies of the Japanese A-bomb survivors and their offspring show no long-term heritable genetic changes in the population. There was some increase in

the frequency of cancer, but nothing overwhelmingly major for the population as a whole. Are these results surprising? What does this say about the sensitivity of humans to ionizing radiation, particularly at the genetic level regarding germ cell mutations?

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CHAPTER ELEVEN

MICROBIAL RISK ASSESSMENT

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Learning Objectives

Students who complete this chapter will be able to

1. Describe what microbial risk assessment is and what essential concepts are involved in it
2. Identify the characteristics that distinguish microbial risk assessment from other forms of risk assessment
3. Explain how microbial risk assessment is used to improve public health

Since the early 1970s, the Centers for Disease Control and Prevention (CDC) and the U.S. Environmental Protection Agency (EPA) have collected data on water-related outbreaks of illnesses. In 2001–2002, there were 15 deaths and more than 95 outbreaks involving over 3,500 people; these disease outbreaks were related either to drinking water or to recreational water sources. Over half of the outbreaks were linked to exposures from groundwater, swimming pool, or wading pool exposures (Blackburn and others, 2004; Yoder and others, 2004). In addition, CDC has monitored the occurrence of food-borne outbreaks using the FoodNet surveillance system. For the 1998–1999 period, an estimated 195 million cases of gastroenteritis occurred nationally; nearly 40 percent were estimated to be food-borne, of which only 18 percent were linked to causal pathogens. Illness rates are

similar in other developed countries (Flint and others, 2005). The World Health Organization (WHO) estimates that worldwide there are 3.4 million water-related deaths; a large proportion of the 2.1 million diarrheal deaths per year are due to contaminated food or water largely occurring in developing countries (Organisation for Economic Cooperation and Development, World Health Organization, 2003; World Health Organization, 2005; Havelaar and Melse, 2003). In addition, for every clinical case seen there are 10 to 500 times that in unseen cases, depending on the microbial pathogen (Haas, Rose, and Gerba, 1999). Clearly, microbial pathogens are a major global public health concern.

Microbial risk assessment (MRA) refers to the structured process used to estimate the likelihood of adverse human health effects following exposure to a microbial pathogen (such as a specific bacterium or virus). Exposure may occur directly, as from air or drinking water, or indirectly, through a contaminated matrix such as sewage residues. Quantitative or qualitative assessments may be done to meet broad societal goals (e.g., setting national food regulations) or address more localized problems (e.g., contamination of a lake used for swimming, fishing, and/or boating). The common goal, however, is to protect the public's health through policy-making processes informed by scientifically credible information and data. MRA results may be used to set regulatory standards, develop guidelines, support public decision processes, educate and inform policy makers and the public, identify differences between risk management options, and prioritize risk and/or research issues.

Some unique characteristics of microscopic disease-causing agents result in important differences between MRA and other forms of risk modeling. Estimates of the health risks related to *Cryptosporidium* in drinking water, *Listeria monocytogenes* in ready-to-eat foods, and enteroviruses in recreational water, for example, are important to both public health decision makers and the public. Without reliable evidence-based estimates, however, informed and effective decision making about personal and population protective actions becomes very difficult.

Background

From the earliest eras of recorded history human populations around the world have taken action to protect themselves from disease-causing agents related to food and water. Some civilizations relied on household and community-level solutions, while other societies used larger-scale approaches such as pipelines and food restrictions. Especially before scientific methods evolved, these actions were based on beliefs and experience. Many of these early protective solutions worked quite well until the Industrial Revolution, when large numbers of people moved to cities.

Rapid urban growth made contamination of food and water, as well as human-to-human spread of infectious diseases, much more frequent and apparent. Since the discovery of bacteria in the late 1800s, exposures to specific microbial pathogens have been scientifically shown to present hazards to human health (Rosen, 1993).

In the United States, Upton Sinclair's *The Jungle* (1906) raised widespread concerns, which led to the passage of the Federal Food and Drug Act and the establishment of the first federal agency to ensure food safety. From the first few decades implementing this law, scientists and policy makers developed the earliest approaches to formal risk assessment. The concepts of safety, avoidance of harm, and safety factors evolved; animal testing began; and statistical models to quantify health risks were created.

In 1970 the EPA was formed, bringing greater focus to addressing human health hazards in increasingly systematic ways. While research methods developed in EPA to estimate environmentally related human health risks, the U.S. Food and Drug Administration (FDA) collected food consumption data and defined protocols for assessing acute health effects linked to foods (Rhomberg, 1995; Hutt, 1997). Most risk assessment activity in the 1970s and 1980s addressed chemical hazards, evidenced by the classic *Red Book* publication that attempted to harmonize risk assessment methods across federal agencies (National Research Council, 1983). Although Haas (1983) published a critique of existing approaches to estimating risks to low doses of microorganisms, compared to chemical risk assessment (CRA) (see Chapter 2), far less attention during this period was given to advancing models specifically for microbial pathogen risks. In the early 1990s, several risk assessors applied the chemical risk paradigm to microbial pathogen issues, but each set of investigators identified problems with using this framework for estimating health risks (Regli, Rose, Haas, and Gerba, 1991; Rose, Haas, and Regli, 1991; Haas, Rose, Gerba, and Regli, 1993; Sobsey and others, 1993).

During the 1980s and early 1990s, ecological risk assessment evolved at the EPA (Environmental Protection Agency, 1992). Although ecologic modelers also were informed by the CRA approach, they recognized that that paradigm did not entirely fit their needs. Ecological risk assessment demands a comprehensive, systems-oriented context and modelers with different backgrounds and training. As a result, it is often difficult and inefficient to undertake an ecological risk assessment without having a clearly defined problem statement. This problem formulation step in risk assessment was not clearly described in the *Red Book*, so ecological risk assessors created and explained how to implement it (Environmental Protection Agency, 1992). Along with new knowledge about the interactions between agents and hosts that are living entities having several life stages, the work of ecological risk assessors contributed valuable insights for advancing MRA concepts and methods.

Later events brought even greater urgency to advancing microbial risk assessment strategies. In 1993 there was a major cryptosporidiosis outbreak in the City of Milwaukee. It was linked to *Cryptosporidium parvum* in a portion of the city's drinking water supply; estimates are that thousands of people were hospitalized and over one hundred died (Mac Kenzie and others, 1994; Kramer and others, 1996; Griffin, Dunwoody, and Zabala, 1998). With the passage in 1996 of the Amendments to the Safe Drinking Water Act and the Food Quality Protection Act, EPA and FDA attention to microbial risk assessment became essential (FQPA, 1996; SDWA, 1996). The Fall 2001 airborne anthrax attacks in the United States added further urgency to developing microbial risk assessment methodologies. The massive flooding of New Orleans after Hurricane Katrina in 2005 highlighted the need for crisis applications of MRA.

Although researchers had conducted earlier quantitative MRAs, in 1998 the first formal quantitative microbial risk assessment was published by a U.S. regulatory agency, the U.S. Department of Agriculture's Food Safety and Inspection Service (Dennis, Buchanan, and Miller, 2001–2002). MRA advancements in the United States and Europe since that time have been considerable.

Frameworks

Microbial risk assessment has not emerged in isolation from other forms of risk assessment; it has been most influenced by approaches and concepts developed for chemical and ecological risk assessments.

Chemical Risk Assessment

Chemicals in foods were first approached in a public policy framework in the mid-1800s, when they were viewed as adulterants. In the early twentieth century, however, chemicals were considered food safety and poisoning issues; these chemicals were later regulated as if there were a safe threshold below which people could be exposed to chemicals without being harmed (National Research Council, 1983; Hutt, 1997). As animal testing produced more data, the underlying assumptions used to estimate the chemical risks came under question and led to intense debates. One result of these tensions was the publication of the so-called *Red Book* (National Research Council, 1983), which codified the approach that should be used to assess chemical risks and described the state of knowledge and underlying assumptions for the method. The four-step model involving hazard identification, dose-response, exposure assessment, and risk characterization was used extensively

in the following decades. As a result, the CRA framework was the prevailing context from which many modelers approached microbial risk assessment.

Some of the problems identified when using the chemical risk paradigm for microorganisms were that

- The paradigm does not account for the fact that microorganisms can grow, evolve into different life stages, and die off.
- These pathogens behave differently under different temperature and time conditions, as well as in different media and matrices (e.g., water versus food, and different types of foods and soils).
- Microbial pathogens are not evenly distributed, and may even be found in clumps presenting very uneven probabilities of exposure.
- Chemical risk assessment does not have a component to deal with secondary or person-to-person transmission, as occurs in many infectious disease processes.

These and other unique issues were considered extensively when the following frameworks were developed.

Modified Framework

Some organizations, for example, the FDA and Codex Alimentarus (or Codex of WHO), use a modification of the chemical risk assessment framework for food-related MRA. The four components that these organizations use are hazard identification, hazard characterization, exposure assessment, and risk characterization (World Health Organization, 2002; Federal Drug Administration, 2003); both have also included a preliminary step—statement of the problem—in some of their guidelines (World Health Organization, 1999; Dennis, Buchanan, and Miller, 2001–2002). As shown in Exhibit 11.1, these organizations have also described the essential parts of each MRA step.

Both FDA and WHO have also articulated certain principles, which serve as the underlying bases for their MRA processes. These principles emphasize the importance of ensuring transparency, allowing for iterations of the modeling and estimation process, separating the sources of uncertainty and variability, assessing the quality of the data, documenting fully the assumptions and uncertainties inherent in the estimate, validating the model, providing informative products to policy makers and stakeholders, and utilizing peer review processes to ensure the quality and credibility of the estimate and final documentation. In 2003 WHO issued a set of draft principles and guidelines for the conduct of microbial risk management (World Health Organization, 2003b). Among the 13 principles listed, additional key concepts focused on protection of human health, early clarity of

EXHIBIT 11.1. STEPS IN THE MODIFIED FRAMEWORK.

Statement of the Problem

1. State clearly the specific problem and scope to be addressed.
2. Define the nature and form of the MRA output and output alternatives.
3. Create a preliminary model "from farm to fork."

Hazard Identification

1. Identify the microorganisms or microbial toxins of concern.
2. Determine relevant sources of data (such as clinical studies, epidemiological studies or surveillance, and laboratory studies).
3. Gather evidence about the pathogen, its presence in foods, and the adverse health effects (including severity and subpopulations at risk) associated with human consumption of contaminated foods.

Exposure Assessment

1. Define the actual or expected extent of human exposure.
2. Determine the scope and frequency of food contamination based on factors such as the microbial ecology of the foods (or matrices) of concern, potential for cross-contamination from contaminated to uncontaminated objects, sanitation and controls in production processes, methods of food handling and packaging, and temperatures during storage and preparation.
3. Assess characteristics of consumers (e.g., demographics, behaviors, knowledge, perceptions of food hazards, and prior illness).
4. Examine patterns of consumption, e.g., by seasonality and region.
5. Describe clearly the pathway from production to consumption.
6. Consider using scenarios to identify variations in exposures.
7. Estimate the level of pathogens and the probability of their occurrence in foods at the time of consumption.

Hazard Characterization

1. Determine the severity and duration of adverse health effects.
2. Examine potentially important characteristics of the microbe of concern (e.g., its ability to replicate, virulence and infectivity, potential for secondary and tertiary spread among hosts, time course from infection to the range of illness outcomes, and impact of food attributes on the pathogenicity of the microorganism).
3. Evaluate the importance of host characteristics (e.g., integrity of physiological barriers, factors that influence susceptibility and time course from infection to illness, and population characteristics).
4. Estimate the dose-response relationship, clearly noting the end points used for response (e.g., infection or illness).
5. Examine the shape of the dose-response relationship and validate with real-world data when possible.
6. Consider the importance of severity and duration of disease.

EXHIBIT 11.1. STEPS IN THE MODIFIED FRAMEWORK, Cont'd.

Risk Characterization

1. Integrate the prior three steps using conceptual and computational models to develop a risk estimate
2. Estimate the likelihood and severity of adverse heath effects in a given population.
3. Describe the impacts of the assumptions and sources of uncertainty and variability embedded in the estimate.
4. Critically evaluate the strengths and weaknesses of the data used (for example, comment on the weight of the evidence integrated).

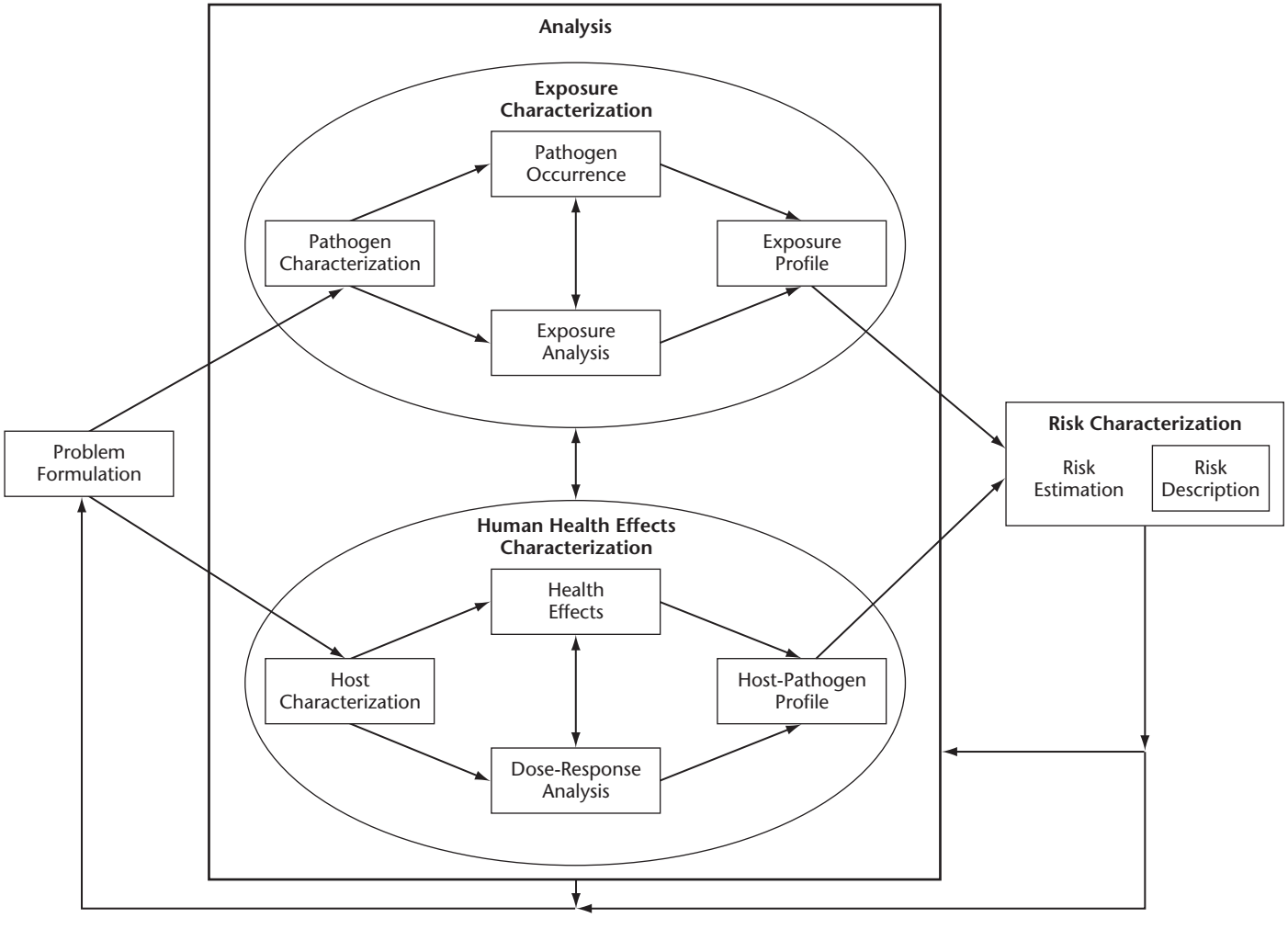
the MRA objective, clear communications among and effective involvement of stakeholders, structured conduct and scientific integrity of the MRA, examination of the full context of the risk issue (e.g., from "farm to fork"), and functional separation of risk management and assessment.

International Life Sciences Institute

The EPA Office of Water needed to develop estimates of microbial pathogen risks associated with drinking water, as a basis for decision making about potential regulatory standards. In 1995, the Office and the International Life Sciences Institute (ILSI) convened a workshop of experts from diverse disciplines; the participants collaboratively developed a conceptual framework for assessing microbial pathogen risks, with a particular focus on water (ILSI, 1996). Two groups of researchers applied the ILSI framework to evaluate its utility for two different pathogens in drinking water: *Cryptosporidium* (Teunis and Havelaar, 1999) and rotavirus (Soller, Eisenberg, and Oliveri, 1999). These case studies led to further refinements in the model and guidance documentation, leading to the final model shown in Figure 11.1. This revised framework was designed primarily for assessing microbial risks associated with consumption of contaminated food and water.

Although this generalized conceptual framework has four compartments, these are not the same four steps as in the CRA or the modified paradigm used by FDA and WHO. The process has three phases: (1) problem formulation, (2) analysis, and (3) risk characterization; these parallel the traditional three steps in decision analysis (problem statement, analysis, and interpretation) (Drucker, 2001). Analysis in the ILSI method involves two processes that occur side by side: characterizations of exposure and human health effects. Both of these components are considered in the problem-formulation and risk-characterization phases. The ILSI framework can and usually is used iteratively; that is, when new information enters into the

FIGURE 11.1. COMPONENTS OF A MICROBIAL RISK ASSESSMENT.

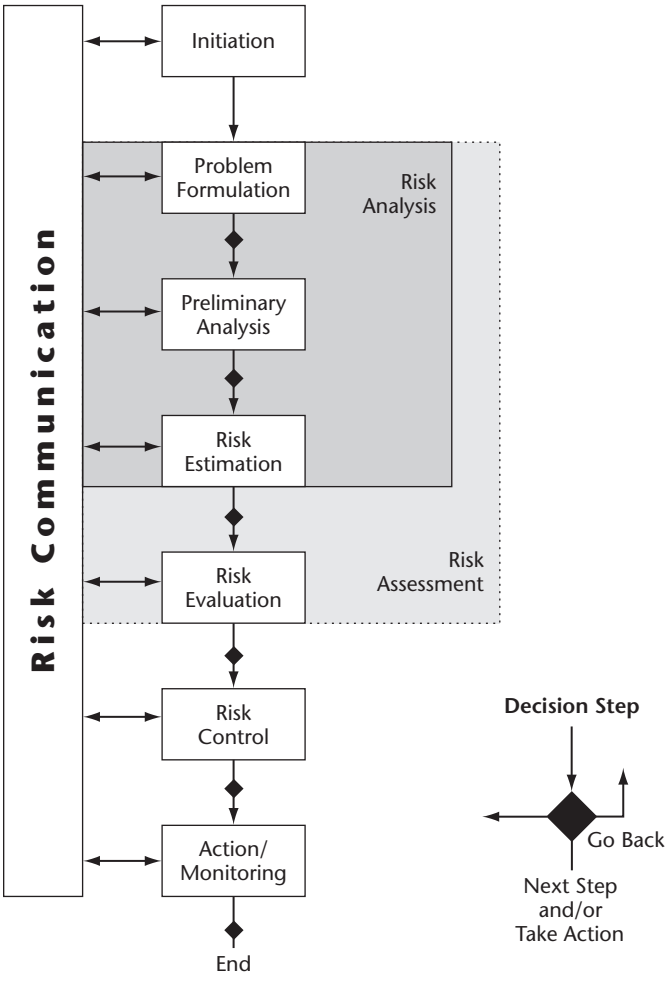


Source: Adapted from International Life Sciences Institute (2000).

process the assessor may need to return to an earlier phase or step and reshape the assessment. When this occurs, stakeholders and decision makers should be informed about why the reiteration is required and what impacts it has on the assessment process. Risk assessment should be a dynamic learning process involving a series of new insights and refinements that result in new knowledge (ILSI, 2000).

It is important also to note that risk assessment is only one part of a comprehensive risk management process (see Figure 11.2). The management context

FIGURE 11.2. RISK MANAGEMENT PARADIGM.



Source: Adapted from the Canadian Standards Association (1997).

is very important in shaping the scope and focus of the MRA, just as the results of the assessment are crucial to ensuring sound decision making and actions to reduce human health risks.

Problem Formulation. This planning and scoping phase is crucial to the data analysis and final uses of the results. When defining the problem, goals, and objectives, stakeholders and decision makers should develop common expectations and mutual understanding that will serve as foundations for a productive process and the selection of appropriate risk management options.

Once the MRA foundations are determined, the conceptual model is designed; for example, hydrologic or air models and disease transmission models are created and linked (Eisenberg and others, 2004; Liao, Chang, and Liang, 2005), or food processing and infectious disease models are described and related to one another (World Health Organization, 2002). The complexity of the conceptual model indicates the types and amount of data needed to conduct an effective risk assessment. A simple model may be necessary due to limited data, or it may be sufficient to characterize specific components of the model (e.g., dose-response as in Moon, Chen, Gaylor, and Kodell, 2004).

Ensuring that the conceptual model is complete and evidence-based is crucial to maximizing the MRA's value to decision makers. For example, careful consideration must be given as to whether secondary or indirect pathways of exposure may be important to the disease end point (as in Eisenberg and others, 2004). Further, knowledge about susceptible subpopulations at risk and the severity of their health outcomes must be developed. If susceptible populations exist or severity is important, these factors must be accounted for in the problem-formulation phase and the modeling process.

The results of this step should be the clarification of the human population(s), pathogen(s), and health outcome(s) of interest as well as the explicit statement of the questions to be addressed by the assessment. The sources of data, methods of data collection and analysis, assumptions anticipated, and MRA endpoints (e.g., number of what types of cases per person per year) need to be described as well.

Initial assessments are then completed to characterize the exposure and anticipated health effects. Pathogen and host characteristics and the relationships between the two entities, the pathways of exposure, and the conditions under which they occur must be identified. The completion of these initial assessments reveals whether the conceptual model can be implemented, whether additional data are needed, what assumptions are needed to fill gaps in knowledge, and whether the problem scope or model should be modified before proceeding.

Linking Environmental and Infectious Disease Models: SARS in Three Settings

Airborne transmission of microbial pathogens is a well-known but poorly quantified phenomenon. WHO estimates that among the 57 million annual deaths worldwide due to infectious diseases, nearly 4 million are caused by viral respiratory agents. Understanding what factors determine the spread of viruses under different conditions is crucial for developing effective control strategies. This study was conducted to elucidate the relationships between SARS (severe acute respiratory syndrome) infection rates, building characteristics, breathing rates, and exposure duration under different conditions; for example, airplane, hospital and elementary school. An exponential dose-response model for estimating the risk of infection, the Wells-Riley Poisson model for approximating exposure concentrations indoors, differing infection rates in different indoor environments, and a standard susceptible-infectious-recovered population model were used. The transmission of disease was examined in a probabilistic framework, relying on data-derived knowledge of disease dynamics and the occurrence of cases due to secondary transmission. The most important parameters in the model were transmission rate and recovery rate. The output of the model was the daily probability of infection for each susceptible person, based on the probability of contact with an infected person. The airplane and hospital settings were found to have higher disease rates than the elementary school. While increasing ventilation can reduce transmission rates, it is not sufficient to eliminate pathogen spread.

Key assumptions included: one droplet with one infectious microorganism was sufficient to initiate infection, droplets were uniform in size, ventilation was constant and homogeneous, steady-state exposure occurred, the reduction of infectious particles by ventilation was more important than other means, and one infected person at the start of a day exposed others for a defined number of hours.

Source: Liao, Chang, and Liang (2005).

Analysis. In this second phase of the MRA framework, two characterizations—of exposure and human health effects—are done simultaneously and interactively so that each may inform the other. These effects are typically examined at deepening levels of detail as far as the available evidence and models will allow or until further refinements would not substantively change the risk estimate.

Exposure Characterization. Exposure characterization involves examining data and information about the pathogen (its spatial and temporal occurrence, persistence, and viability under different conditions), the interaction between the microorganism and human populations, and the environments in which the agent and hosts occur. The microbe's traits that influence its pathogenicity (strain, virulence, life cycle, pathogenicity traits, mechanisms of infection, potential for secondary spread) and the ways in which human populations interface with the microorganism are described. The risk assessor must also evaluate the pathogen's resistance to control (such as from water treatment processes), distribution by space and time including seasonality, and survival under different environmental conditions (acidity, temperature, diverse matrices including food and soil).

Further, the means by which humans become exposed to the pathogen (where, when and under what conditions exposure occurs in the population(s) of interest) need to be documented. The medium (e.g., food, water), route(s) (e.g., oral, dermal), seasonality, and amount of exposure are described. The average cups of drinking water used per person per day is one possible exposure metric; breathing rate by age may be another metric. In addition, the size and nature of the human population exposed is identified. In one study of recreational water exposures to enteroviruses (Soller and others, 2003), young boys were found to be the population of primary concern. In this case, swimming behaviors, associated with exposure to river-borne pathogens, varied by season and by age.

Bringing the pathogen and exposure information together produces an *exposure profile*; this describes the magnitude, frequency, and patterns of human exposures to the pathogen. An evaluation of the assumptions and uncertainties involved in obtaining the exposure profile is an essential aspect of this step. Often, many assumptions are necessary due to the lack of available data (Eisenberg and others, 2004). Analysis of uncertainties may reveal problems with measurements or errors in estimating the concentration of pathogens in media to which humans are exposed. For instance, microbial clumping in water often causes difficulties in estimating the environmental concentrations. Counts of pathogens are averaged over a very large volume of water sampled; these averages do not capture the variations that actually occur in water supplies or human exposures.

Human Health Effects Characterization. Just as the pathogen and exposure analyses are conducted in parallel, so too are the health effects and dose-response steps to create a host-pathogen profile. In the *human health effects characterization* step, not only are the host and human health effects identified, the dose-response relationship between the pathogen and host is defined. One of the most important features of MRAs is host characterization and, within that step, consideration of host sus-

ceptibility. Unlike other forms of risk assessment, the microbial risk assessor must determine whether humans enter and leave different states of susceptibility in relationship to transmission of the microbial pathogen in the human population. Susceptibility may vary by age, gender, other demographic characteristics, prior disease or immune status, and/or access to medical care (Balbus and Parkin, 2000). The issue is to determine which, if any, of these factors are crucial influences on the population's vulnerability to the microbe. In recent years, researchers have discovered that first exposure to different strains of the same pathogen (e.g., *Cryptosporidium*) may or may not confer immunity or lasting immunity upon hosts (Chappell and others, 1999). Further, different subpopulations may experience more or less severe forms of the outcome of interest, making the precise definition of the outcome and availability of appropriate data all the more important (Makri, Modarres, and Parkin, 2004). Describing the health effects associated with exposure is dependent on the extent of knowledge about susceptibility and severity. While a spectrum of outcomes may be caused by a specific pathogen (e.g., from diarrhea to paralysis associated with *Campylobacter jejuni* infections), there are rarely enough data to assess more than one outcome (Haas, Rose, and Gerba, 1999). Severity and/or duration of illness data, however, may be available and sufficient to conduct an MRA (Makri, Modarres, and Parkin, 2004).

The dose-response step depends on the state of knowledge about the pathogen-population relationship, the pathways of exposure, initiation of infection versus detectable health outcomes, and the mechanisms by which the pathogen penetrates the human body and triggers a pathological response. Abilities to describe the infectivity of the microorganism and to detect and record the magnitude of health responses affect how accurately the dose-response curve will reflect reality. Unlike CRA, few animal models are available for determining the dose-response relationships; this is because pathogens commonly behave differently in animals than in humans. Most health effects data for MRAs come from human challenge clinical trials, or outbreak investigations. In the absence of data, risk assessors usually assume that exposure to one microorganism is sufficient to cause adverse health effects (Haas, 2002). This constitutes a protective public health assumption, as it will result in protecting more people than, for example, a linear dose-response assumption would. To complicate matters further, multiple dose-response curves may be needed in an MRA to account for distinct subpopulations (e.g., HIV/AIDS patients, pregnant women, or the elderly) (World Health Organization, 2002). In addition, there may be several time cycles that operate due to the differing virulence of various microorganism strains, secondary spread, and other dynamic factors in both the pathogen and host populations.

Comprehensive Approaches to Dose-Response: *Salmonella* Enteriditis in Eggs and Broiler Chickens

For two decades, the occurrence of *Salmonella* Enteritidis has been increasing in many nations; hen eggs and broiler chickens have been identified as major vehicles related to these cases. The purposes of WHO's assessment were to: develop a resource document of all relevant and available information about *Salmonella* in eggs and broiler chickens, provide an example risk assessment framework and model, and use the results to evaluate the efficacy of selected risk management interventions. This extensive document details the organization and analysis of data on the existence of the pathogen in the environment through human exposure and health impacts. Each medium—eggs and broiler chickens—was considered separately in the exposure assessment and risk characterization steps. Summary comments about common data gaps, research needs, and issues in conducting MRAs were discussed at the end of the document.

The data used in the egg portion of the risk assessment were derived from published and unpublished studies, and national reports of *Salmonella* occurrence and disease incidence. The dose-response data from a variety of sources was reviewed and a new dose-response model was developed from real world outbreak data, judged to be more appropriate for estimating the probability of illness upon ingestion of a dose of *Salmonella.* The authors also considered whether different dose-response curves were needed for two types of *Salmonella* and for different human subpopulations, based on age and susceptibility. They noted that their dose-response model may not apply beyond developed countries, the only sources of available data. Severity of illness could not be modeled because there were insufficient data available for quantifying necessary model inputs.

For the egg assessment, the model contains modules for egg production, egg processing and distribution, egg product processing, and preparation and consumption. The results show that human illness is more directly related to *Salmonella* prevalence among chicken flocks, and egg storage time and temperature than to the number of *Salmonella* Enteriditis in contaminated eggs when laid.

Source: World Health Organization (2002).

The types and magnitude of health effects are described in the *host-pathogen profile,* which results from merging the findings of the host characterization, health effects, and dose-response steps. The limitations of the data and model, assumptions made, and uncertainties should be clearly documented.

Risk Characterization. In this last phase of MRA, the results from the exposure and host-pathogen profiles are integrated using a two-step process: risk estimation and risk description. The results of the analysis phase are synthesized into a coherent, complete, and practical summary in order to inform decision makers. This integration requires modeling techniques, data quality assessments, judgments, and a sound basis of diverse knowledge to evaluate and create insightful and relevant products. Goals of risk characterization range from simply linking the model with the problem statement to discussing the public health implications and risk management options for the effects identified (Haas, Rose, and Gerba, 1999; Parkin, 2002). Another purpose includes informing both stakeholders and decision makers, thereby supporting collective processes and effective actions.

Risk Estimation. Risk estimation focuses on describing the effects anticipated as a result of direct and/or indirect exposure. The probability of infection, illness, or death is presented and critically analyzed for sources of uncertainty, variability, and limitations. The measure of exposure (e.g., number of microorganisms per person per day or at given consumption rates) is linked to the probability of illness for each exposure level or range of exposures. The resulting estimate may be expressed in individual or population terms (e.g., the probability of illness for a person [one in a ten-thousand chance of becoming ill] or the annual number of cases in a defined area [20 cases per year in a specific location]).

Risk Description. The *risk description* step requires documenting the nature, severity, and outcomes expected following different levels of exposure, as well as exploring the limitations of the risk estimate(s). In this step, the weight of the evidence is examined, the conceptual model validated (whenever data permit), the impacts of assumptions and variables tested (sensitivity analysis), and a determination of the level of confidence in the results made. If extensive problems are found, consideration should be given to returning to an earlier MRA step and revising the assessment. Identification of the key factors that affect the risk estimate is crucial to providing decision makers with effective guidance.

All MRAs should clearly document the data and assumptions used, the sources of uncertainty in the final risk estimate, and the degree of variability found in the data (e.g., age and susceptibility) and risk estimates. If susceptible subpopulations are a concern in the assessment, the results for each of these subgroups

should be clearly noted. Last, the documentation should link the results back to the question(s) posed in the problem formulation and address each one explicitly.

The ILSI microbial risk assessment paradigm borrows from both chemical and ecological risk assessment approaches. These two frameworks were adapted for MRA to account for the unique characteristics of living, microbial hazards and the dynamics that occur in the environment and human populations in the presence of these pathogens. The ILSI structure is sound, but a great deal of work needs to be done for many microorganisms. There is a lack of knowledge, for example, about the mechanisms that cause progressions from infection to disease and about the dynamics of susceptibility in human populations.

Underlying Concepts

Several fundamental concepts are often used to frame and conduct MRAs. In the absence of seasonality or other data, modelers assume that microbes are spread evenly in the environment. Similarly, there are limited data to indicate the number of microorganisms necessary to cause adverse health effects. Due to variations in strain, life stage, and survivability, not all individual pathogens in the environment are capable of inducing illness; however, for modeling purposes they are all assumed to be viable and pathogenic.

In the human population the wide ranges of age and immune status are usually ignored due to the lack of data. Although detailed consumption data sometimes exist, modelers tend neither to collect relevant data nor to consider the range of available food and water consumption levels (Barraj and Petersen, 2004). Most modelers use a point estimate or population average (e.g., two liters of water per person per day) (Environmental Protection Agency, 2000).

Researchers have used many datasets to develop dose-response curves for a variety of microorganisms. These efforts have produced about ten different mathematical forms to consider for MRAs (Haas, Rose, and Gerba, 1999). For many microbial pathogens two-parameter models, such as the commonly used beta-Poisson model (Haas, Rose, Gerba, and Regli, 1983), have been found to perform at least as well and sometimes better than more complex models (Moon, Chen, Gaylor, and Kodell, 2004).

In addition, most modelers assume that outbreak or surveillance data are sufficient to use in MRAs (Soller, Eisenberg, and Oliveri , 1999), but others have noted the important limitations of these data and questioned their value for modeling microbial pathogen risks (Makri, Modarres, and Parkin, 2004; Flint and others, 2005). However, in the absence of better data, surveillance and outbreak data, with all of their potential flaws, are often the best data sources available. In some

instances it may be possible to adjust these reported data and estimate the number of all actual cases, both reported and unreported (Flint and others, 2005).

Needs

Many important data gaps remain a hindrance to effective MRAs (Haas, 2002; Gardner, 2004). The reliability of diagnostic testing, case reporting, measurement of exposure and dose, consumption patterns, environmental concentrations and determination of strain are only a few areas requiring additional datasets and knowledge before MRA can be substantively improved.

The lack of animal models and the ethical limitations of human challenge clinical trials restrict the rate at which new dose-response knowledge can be obtained. Models to characterize the dynamic growth processes of microbial populations are needed (Bernaerts and others, 2004), as are models to describe the movement of pathogens in the environment (Soller and others, 2003).

Modeling Approaches

Because of the complex interactions between microorganisms and human populations, risk assessors must construct a comprehensive conceptual model to identify the many crucial elements and relationships that will have to be considered. Creating a diagram of the essential components and processes can facilitate problem formulation among diverse stakeholders and decision makers (Eisenberg and others, 2004).

However, a conceptual model is not sufficient for conducting a quantitative microbial risk assessment. The conceptual model must be converted into a computational model that can organize, utilize, and generate relevant data. Modelers must determine what forms of modeling and which specific models will be needed. For example, environmental models (the ecology of microbes in air, rivers, biosolids, and foods) and disease transmission models need to be linked (Federal Drug Administration, United States Department of Agriculture, and Centers for Disease Control, 2003; Soller and others, 2003; Eisenberg and others, 2004; Liao, Chang, and Liang, 2005). The modeling decisions depend not only on the characteristics of the microbe and human populations but on the availability of data and knowledge to inform each component of the conceptual model. An important part of problem formulation, then, is an inventory of the data relevant to each aspect of the model components and a determination as to the level of modeling that can be completed.

Comprehensive Data Collection and Modeling: Enteroviruses in Recreational Water

Recreational water includes lakes, oceans, rivers, pools and spas; this study focused on risks associated with swimming in the San Joaquin River in central California. The purpose of this MRA was to characterize the incremental health risk benefit achieved when tertiary wastewater treatment—compared to secondary treatment—was used during the winter season to reduce viral gastroenteritis. Conduct of the MRA required a wide range of relevant data so that a hydraulic model could be combined with a dynamic infectious disease model. Data from aerial surveys and interviews were used to estimate the number of recreational events by geographic area, season of the year, holidays and weekends. Experiments were conducted to evaluate the reduction in viruses during secondary and tertiary wastewater treatment processes. No data for estimating risks among susceptible subpopulations (e.g., children) were found.

An important aspect of the model was estimating the movement of the population between several epidemiological states; for example, susceptible, infectious asymptomatic, infectious symptomatic, non-infectious post-symptomatic and infectious post-symptomatic. The two factors that most strongly affected the background level of viral gastroenteritis incidence in the community were the percentage of infected individuals who develop symptoms, and the background disease transmission rate. Although the secondary wastewater treatment methods achieved disease levels below EPA's standard of 8–14 illnesses per 1000 recreational events, the modeled tertiary treatment was estimated to reduce illnesses an additional 15–50 percent. The number of winter illness cases that would be avoided by instituting tertiary treatment was estimated to be about 1 in one million recreational events.

Assumptions had to be made in order to operationalize the model. For example, all swimmers were assumed to ingest contaminated river water, and the clinical characteristics of the illness were assumed to be the same as for rotavirus (the most infectious virus for which human dose-response data were available). It was also assumed that enteropathogenic viruses were as persistent in the environment as *E. coli,* and that data reported as non-detectable were present at the limit of detection.

Source: Soller and others (2003).

There are two broad categories of models used in MRAs: the *static approach* and the *dynamic approach*. The former assumes that dynamic aspects of the pathogen, environment, and host are negligible, while the latter attempts to account for the changes that occur in any or all three entities. Regardless of the modeler's interest in completing a dynamic model, the lack of data to successfully conduct such a model may push the modeler to the simpler approach, the static or snapshot method. In some instances—especially where time cycles are very long and have little or no impact on disease transmission—combining static and dynamic models to address different aspects of the problem may be appropriate. Based on the references used in this chapter, key issues involved in MRA modeling have been listed in Exhibit 11.2; these issues vary in importance for static and dynamic models.

EXHIBIT 11.2. KEY ISSUES IN MODELING MICROBIAL PATHOGEN RISKS.

Microbial Pathogen

- Taxonomy
- Strain
- Ecology
- Survival
- Characteristics that affect growth
- Life stage
- Viability
- Infectivity and incubation period

Environment

- Medium (e.g., food, water, soil, and air)
- Characteristics of the medium (acidity and presence of other microorganisms)
- Temperature
- Time, season

Human Host

- Age
- Gender
- Nutritional status
- Immune status
- Preexisting disease
- Susceptibility to the specific microbial pathogen

EXHIBIT 11.2. KEY ISSUES IN MODELING MICROBIAL PATHOGEN RISKS, Cont'd.

- Range of health outcomes
- Severity of outcomes
- Proximity and behaviors of infected and susceptible populations

Relationships Among the Pathogen, Host, and Environment

- Virulence of the microbe
- Host specificity
- Environmental conditions that contribute to exposure
- Mechanisms of infection
- Secondary spread

Modeling

- Adequacy of conceptual framework
- Ability to characterize all aspects of the framework
- Static versus dynamic models
- Characterization of the dose-response relationship

Sources of Uncertainty and Variability

- Data quality
- Measurement
- Assumptions

Model Validation

- Availability of data

Static Models

The traditional form of MRA is the static approach (Haas, Rose, and Gerba, 1999). While estimating the health risks associated with a microbe at a point in time may be suitable for many illnesses and in many decision-making contexts, static models may underestimate the true level of disease. When secondary or person-to-person transmission is important, there will be two or more waves of cases that may vary in severity. The static model may only estimate the first set, requiring modelers to further estimate and decision makers to anticipate the subsequent cases. These models also do not consider the differing time cycles in which pathogens, environments, and human populations change, thereby making estimations of further waves of outcomes even more difficult to project.

Static Modeling: *Cryptosporidium* in Drinking Water

This static (stochastic) MRA was conducted to study the ILSI MRA methodology, develop a predictive model on a regional scale while accounting for susceptibility, and validate the model's accuracy in predicting regional incidence of cryptosporidiosis. In order to conduct this MRA, the authors had to locate one region where *Cryptosporidium parvum* levels in drinking water, population and subpopulation data, as well as cryptosporidiosis data were available for the same time period. The only location found where all of these data were publicly available was New York City in 2000. Expected numbers of cases and incidence rates for the region and boroughs, as well as for age groups and AIDS and non-AIDS groups, were estimated based on model results and population data. Published real world and scientific data were available to populate each component of the ILSI framework, making a quantitative model feasible. Key assumptions were that a single daily exposure occurred for each person; a single oocyst could survive host barriers to initiate infection; exposures were long-term and low dose; other sources of exposure (e.g., spas, recreational water, international travel and other behaviors) were insignificant contributors to the number of cases observed; and surveillance data were accurate. A multiplicative model was used to estimate incidence (illness) and severity (prolonged illness) of cryptosporidiosis. Compared to differences among age groups, there were very large differences between AIDS and non-AIDS populations.

Despite their apparent limitations, surveillance data were used to validate the model. Although the model over-predicted the numbers of cases, these results were likely due to conservative assumptions made in the modeling process. The model was sensitive, however, to geographic differences and AIDS prevalence. Limitations of the model and research needs were discussed.

Source: Makri, Modarres, and Parkin (2004).

Dynamic Models

Since the mid-1990s dynamic MRA models—based on decision analysis, civil engineering, and infectious disease methodologies—have been emerging (Eisenberg, Seto, Oliveri, and Spear, 1996). They have been used to characterize the ecologic and susceptibility aspects of various microbial pathogen scenarios, including exposures from airplanes and buildings (Liao, Chang, and Liang, 2005), recreational water (Soller and others, 2003), food processing (Federal Drug Administration,

Dynamic Modeling: Enteroviruses in Biosolids

Biosolids, including sludge, are products of wastewater treatment processes. There is increasing use of these products and increasing interest in identifying beneficial uses of these materials, but related health risks are largely unknown and unquantified. EPA needs MRAs for developing risk-based standards for microbes in biosolids.

Using a population-based, deterministic model to account for unique infectious disease properties (e.g., secondary spread and immunity), the authors demonstrated the value of using a risk-based method to estimate the number of cases associated with the ingestion of enterovirus-contaminated soil. The disease transmission portion of the model included six different disease states and, using a series of delay equations, estimated the rate of movement of individuals between these states. Further, both partial and temporary immunity were accounted for in the model. A beta-Poisson dose-response function was used to determine the probability that at any given dose level an exposed person would become infected. The viral half-life in soil, incubation period, shedding times, duration of antibodies, soil consumption levels and other factors were evidence-based. Including both direct and indirect (or secondary) exposures, the model produced estimates of cumulative incidence; that is, the number of new cases of disease in a one-year period divided by the population at risk (2.61 cases per person per year).

The authors also used an analytic approach to determine which factors were most important in influencing risk and used the results to produce a decision tree to aid decision makers in selecting risk management options. The key factors were found to be biosolids treatment processes, pathogen shedding rate of infectious individuals, secondary transmission, and the immune status of individuals in the population at risk.

Important assumptions included: enteroviruses were assumed to be present in the human population, no sources of exposure other than infected individuals were present, the virus and human community were homogeneous (e.g., no variability in viral strains or susceptible subpopulations were present), the level of protection (immunity) declined linearly from full to no protection, pathogens were transferred to the biosolids site by human activity or outside sources, wastewater treatment and natural conditions reduced the viability of the enterovirus population, and biosolids were applied to land one time only. Stochastic changes in the disease states of the population were assumed to be small, compared to the overall directions of the model outputs, and were more important the smaller the population at risk.

Source: Eisenberg and others (2004).

United States Department of Agriculture, and Centers for Disease Control, 2003; World Health Organization, 2002), and biosolids (Eisenberg and others, 2004). Important time-dependent aspects of dynamic models may relate to seasonality, temperature, microbial life stages, proportion of pathogens viable in different matrices, changes among animal reservoirs, human host susceptibility, and secondary transmission of the pathogen.

Critical elements of dynamic models include the scope of the problem, the identification of the driving factors of change, and the rates at which changes occur; collection of data to populate each component of the model; and modeling the linkage of the ecologic and host population dynamics. As shown in Exhibit 11.2, important limitations involve the quality of the available data, the impacts of the assumptions (e.g., homogeneity of the microbial and human populations), human consumption levels, the selection of the health outcome and whether it adequately reflects the outcomes of interest, the inability of modeling strategies to account for cumulative risk, the inability to characterize the complete microbial exposure scenario and sources of exposure, and the inability to fully identify and characterize the immune status of general and susceptible subpopulations. (For examples of these issues, see the methods and discussion sections of Soller and others, 2003, and Eisenberg and others, 2004.)

Risk Management

Frameworks

Several agencies have described generic risk management (RM) frameworks (e.g., Presidential Commission on Risk Assessment and Risk Management, 1997; Canadian Standards Association, 1997), but only one has been specific to microbial risks (World Health Organization, 2003a). WHO's four components for managing microbial pathogens are (1) preliminary risk management activities, (2) evaluation of risk management options, (3) implementation of the risk management decision, and (4) monitoring and review. It is in the first step that risk assessment, including scoping of the risk issue and developing a risk profile, is conducted.

Role of Risk Assessment

WHO and FDA use essentially the same MRA framework for food-borne risks, but tend to use the two middle steps (hazard characterization and exposure assessment) in reverse order (World Health Organization, 2002; Federal Drug Administration, United States Department of Agriculture, and Centers for Disease Control and Prevention, 2003). Both frameworks use MRA for determining food

safety standards, guidelines, and/or related documentation. WHO places MRA in their preliminary risk management step as follows:

1. Identifying the food safety issue
2. Initiating immediate interim decisions
3. Determining the risk profile to enable additional decisions
4. Making the initial risk management decisions
5. Defining the purpose and scope of the MRA
6. Establishing policies for the MRA
7. Commissioning the MRA
8. Interacting during the MRA
9. Presenting the results of the MRA
10. Considering the MRA results

In step 5, the MRA goals and specific questions are clarified among the risk managers and assessors. The questions posed depend on the scope of the problem, specific contexts of the microbial risk issue (e.g., the agent, food matrices, and exposure pathways involved), and the intended use of the MRA results. Ensuring that the MRA is conducted in a systematic, transparent, and well-documented manner is essential to step 6. Policies that apply generally to MRA and specifically to the problem to be addressed are identified in this step. When the decision makers direct that the MRA be done (step 7), the mandate and outcome measures, as well as the roles and responsibilities of risk assessors and managers, must be clear. Although communications need to occur between assessors and managers before and during the MRA (step 8), these communications should be objective and focused on necessary informational, not policy, decisions. Risk assessors are responsible for ensuring that the MRA results are provided in a manner that is relevant, useful, and informative to decision makers (steps 9 and 10).

MRA serves a crucial role in risk management paradigms; it is pivotal for ensuring that the quality of synthesized information is high and that related management options provided to decision makers are as complete as possible and relevant to the originally defined problem and scope.

Impacts on Public Health

Microbial risk assessments are not academic exercises; they are conducted to characterize microbial risks to human health, identify key contributing factors and ways to reduce the impacts of those factors, and ultimately to implement ways to reduce or eliminate adverse health effects caused by microbial pathogens. As MRA methods and databases improve, the extent of suffering and death associ-

Risk Assessment Informs Risk Management Decisions: Listeria Monocytogenes in Ready-to-Eat Foods

In the United States, foodborne listeriosis has hit a plateau but remains a serious—often fatal—infection in susceptible subpopulations, demanding a new approach to reducing risks. This extensive MRA was conducted to estimate relative risks of serious illness and death in the United States associated with consumption of a variety of ready-to-eat foods potentially contaminated with *Listeria monocytogenes.* The assessment offers innovative approaches to microbial exposures in different matrices; for example, to streamline analysis of over 100 reported sources of exposure ready-to-eat foods were clustered into 23 groups having similar characteristics. A "growth module" was developed for each of the clusters to estimate the numbers of *L. monocytogenes* in the foods when consumed. Key factors in these modules included refrigeration temperature, and the rate of growth and maximum number of pathogens each food cluster would support.

The MRA included modules for food processing, distribution, and retail and home environments. The MRA relied on data from published scientific literature, research and government-conducted surveys, population health statistics, outbreak data, nutritional surveys, and unpublished survey data from state, federal and other organizations. Unlike most MRAs, mouse data were used along with epidemiological data to construct the dose-response relationships for three age groups (perinatal, elderly, and all others); monkey data were used to validate the curves. The model also relied on an additive approach to the factors that contribute to human exposure.

Another key aspect was the focus placed on linking the MRA results with consumer and public health goals. The outcome measures were decreased risk per serving (to meet consumer needs) and decreased risk per annum (to meet decision makers' needs), provided in a relative risk matrix. For each set of audiences, the results provided clear indications for reducing risks through changes in policy and/or food handling processes. These results were presented with effective discussions of sources of uncertainty and variability, and were demonstrated to be robust under a variety of scenarios. The presentation of the results in clusters (very high to very low risk) summarized a complex analysis in highly tractable terms for consumers and decision makers.

Source: Federal Drug Administration, United States Department of Agriculture, and Centers for Disease Control and Prevention (2003).

ated with microorganisms in food, water, air, and soil will be reduced through a variety of policy and RM options. Involvement of professionals and stakeholders from diverse backgrounds is essential to achieving these goals.

Thought Questions

1. Identify and describe at least three responses for each of the following.
   a. Differences between microbial and chemical risk assessment.
   b. Similarities between microbial and chemical risk assessment.
2. The modeling strategies used by the Federal Drug Administration, United States Department of Agriculture, and Centers for Disease Control and Prevention (2003) and Eisenberg and others (2004) differ in several important ways. Based on the information presented in this chapter, identify at least four things that either group did that the other group did not in modeling the outcomes they selected. Explain how one of these approaches could have been used by the other set of authors.
3. Developing an MRA approach may require deciding whether to use static and/or dynamic models. Explain in depth at least two major issues that must be considered when making this choice.
4. Describe at least five types of public health decisions that could be made more confidently based on results from an effective MRA.

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CHAPTER TWELVE

CHILDREN'S RISK ASSESSMENT

Natalie C. G. Freeman

Learning Objectives

Students who complete this chapter will be able to

1. Identify unique characteristics of children needed to conduct and interpret children's risk assessments
2. Determine how these characteristics influence exposure through the inhalation, dermal, dietary ingestion, and nondietary ingestion routes
3. Identify relevant biomarkers of exposure for children
4. Learn about available risk assessment methods and models used to assess children's risks to environmental contaminants
5. Identify deficiencies and uncertainties in available data and model defaults used to assess children's risks to environmental contaminants

When you think of a child, what image comes to mind? Is it a baby in its mother's or father's arms, a toddler clutching a favorite toy or sucking his thumb, a little girl playing in a sandbox or making mud pies, a teenage boy playing soccer or basketball, or perhaps a teenage expectant mother or her fetus? Whatever the image, it is correct, since each one represents a period in what we call childhood. The mental images that we have conjured up are to some extent representative of the life stages of the child.

Childhood is considered as extending from the fetal state or birth to 18 or 21 years of age. At no other period in our lives do we go through such rapid changes in height, weight, language development, or cognitive and motor capabilities. While these obvious changes are taking place, concomitant changes are taking place within the body. Neural connections are being formed between the spinal cord and brain, and neural connections and cells are both growing and dying within the brain. Changes in endocrine functions in many organs are taking place, and structural and functional changes are occurring in the digestive track, reproductive system, lungs, and bones. Each of these changes has the potential for influencing how the child is exposed to, incorporates, and processes environmental contaminants and influences what organs or tissues the contaminant will affect.

Children Are Not Little Adults

The point to keep in mind is that childhood is not a static point in time; it is a dynamic period full of changes. The mantra for children's vulnerability to environmental contaminants is that "children are not little adults." While this phrase is easy to remember, it is necessary to explore what it actually means in order to adequately understand the degree to which children are similar to or different from adults in terms of risks from exposure to environmental contaminants and health effects that result from the exposure. It is not simply that children are not little adults but that infants are also different from school-aged children; they, in turn, are different from adolescents. In addition, there are gender differences, which are expressed more strongly at some ages of childhood than at others and can influence children's potential exposure to and risks from environmental contaminants.

While information about similarities and differences in behaviors and physiology for some age groups is well-documented, this is not the case for all age subsets of children. In addition, detailed information of similarities and differences in biomarkers of exposure for children of most age subsets are not well-characterized. In conducting age-specific risk assessments we tend to rely on toxicological studies to provide basic information about the toxicity of the chemicals of interest. For some chemicals, the range of toxicological studies upon which to determine hazard may not include age-specific tests or tests that are specifically relevant to developing organisms. This lack of information makes risk assessments for children problematic and may lead to development of risk assessments using extrapolations from existing databases that contain gaps or are based on chemicals whose similarity in function to the chemical of interest may be marginal.

There are numerous intrinsic and extrinsic factors in which differences between adults and children have been found and which also differ depending on

the age, and some cases gender, of the child. Intrinsic factors include physical characteristics such as respiration rate or surface-to-volume ratio and metabolic processes such as liver and kidney function or clearance rate of chemicals from the bloodstream. Extrinsic factors include behaviors and dietary habits that can modify both the potential opportunities for exposure to environmental contaminants and routes of exposure to environmental contaminants.

Similarities and Differences in Physical Characteristics

A variety of physical characteristics may influence both exposure to and dose of environmental contaminants. Table 12.1 shows some of the many changes that occur in physical parameters with age. The table shows that the daily volume of air taken into the lungs increases with age and that during adolescence the inhalation rate for boys is greater than that for girls. For all measures of lung capacity, including total lung volume, inspiration, and forced expiratory volume (FEV), there is generally a positive correlation between lung capacity and height of children (Lyons and Tanner, 1962), especially for children age 6 and older. For some of these metrics, the slope of the association is nonlinear. If we normalize the inhalation rate by the weight of the child, it becomes apparent that proportionally, young children take in more air than do older children. For infants and toddlers, lung-function differences are not simply related to size. Newborn children have fewer alveoli and bronchi than adults, and these develop during the first years of life, after which there is a period of expansion of the lungs. For children this means that both lung structural and functional differences can influence how airborne pollutants are handled.

Inhalation exposure is influenced by both respiration and inhalation rates. *Respiration rate* is the number of breaths an individual takes per minute. *Inhalation rate* refers to the volume of air inhaled per day (m^3/day) and is a function of respiration rate and lung size. While the respiration rate of young children is more rapid than in older children and adults, their lung capacity is smaller. These two factors contribute to more frequent inhalation of airborne contaminants and a more thorough bathing of the lung surface than would occur for older individuals. These potentially negative influences in risks associated with inhalation exposure may be counterbalanced by the fact that alveolar development in young children is incomplete. Limited alveolar surfaces may reduce the potential absorption of contaminants into the bloodstream, since transfer from the alveoli to the bloodstream is the primary route of entry of contaminants from the lungs.

The blood's circulatory system is the major vehicle for carrying contaminants through the body. Blood volume is proportional to size. Both the size of the heart and blood pressure increase with age (De Simone and others, 1997). A rough

TABLE 12.1. SELECTED AVERAGE PHYSICAL CHARACTERISTICS OF CHILDREN.

Characteristic	Infants	1–3 Years Old	4–11 Years Old	12–18 Years Old
Inhalation rate (m^3/day)	4.5	6.8	8.3	12 females 15–18 males
Inhalation rate/ m^3/kg/ bw/day	0.6	0.5	0.27	0.22 females 0.26–0.31 males
Respiration rate (breaths/min)	29–48	21–35	16–20	14–16
Skin surface area (m^2)	na	0.60–0.66	0.71–1.30 females 0.73–1.23 males	1.40–1.63 females 1.34–1.80 males
Weight (kg)	7.6	12.0	31.0	53.0 females 58.0 males
Metabolic rate (kcal/day)	416	734	1143	1393 females 1682 males
Bone/weight	0.33	0.39	0.40	0.45
Heart rate (beats/min)	120–160	80–140	70–115	80–90
Blood pressure (mmHg)	85/37	88/45	96/60	110/65
SA/BW ratio	na	0.064	0.059	0.034
Heart rate/height (breaths/kg/min)	18.4	8.5	3.0	1.5

Source: Environmental Protection Agency (2000).

na = data not available

estimate of heart size can be determined by the size of the individual's fist. Both systolic blood pressure and diastolic blood pressure tend to be positively associated with height and weight within age groups, and among adolescents there are gender differences as well. Heart rate (beats/min) declines with age. When normalized for weight, the heart rates of young children are dramatically greater than for adolescents or adults. Heart rate is an important indicator of the cardiac effort used in moving blood throughout the body and distributing chemicals carried through the bloodstream. So that while the blood volume of young children is less

than in older children or adults, its circulation through the body may be repeated more frequently due to the higher heart rate.

Since blood is a major transport vehicle for contaminants in the body, an understanding of the volume and behavior of blood in the body is therefore essential for understanding how contaminants are circulated through the system. Price and others (2003) identified several differences in relations between blood volume and body weight and height among children and adults. For example, for children less than one year old the relationship between these metrics can be expressed as:

$$\text{Log BV} = 0.789(\log \text{BW}) + 0.0041\ (\text{BH}) + 1.812$$

Where BV is blood volume
BW is body weight and BH is height.

As children get older, two things are observed, the contributions of BW and BH to blood volume changes, and the change is both age- and gender-dependent. For male children between 2 and 14 years and females 2 and 6 years, the relationship between these metrics can be expressed as:

$$\text{Log BV} = 0.646(\log \text{BW}) + 0.0027\ (\text{BH}) + 2.032$$

And for female children between 7 and 14 years the equation is:

$$\text{Log BV} = 0.641\ (\log \text{BW}) + 0.0012\ (\text{BH}) + 2.217$$

These indicate a decline in both the influence of BW and BH on blood volume relative to younger children and to males. In contrast, for adults, the influence of body weight on blood volume for males is approximately nine times greater than for females, and the influence of body height on blood volume is approximately three times greater for adult females than adult males, with the contributions of BW and BH to blood volume substantially larger in adults than in children and less consistent.

Other organs such as brain, kidney, and liver show relatively greater increases in mass during the first years of life compared to later in childhood. Liver growth shows a secondary increase during adolescence, while the rate of brain growth continues to decline with age (Ginsberg, 2003). It has been suggested that the rate of cell division in these organs also is greater during these periods of rapid growth and that these periods put the child at greater risk for damage from environmental insults. Toxicological studies on rats suggest that there is greater susceptibility for liver cancer and kidney cancer during these growth periods. Additional support for changes in susceptibility comes from data on endocrine disruptors such

as estrogens and organochlorine pesticides in which major influences are observed when the developing animal is exposed prenatally or parinatally. Changes in anogenital distance and other structural changes are observed in male rat pups exposed to endocrine disruptors in utero. There are reported increases in male children born with *hypospadias,* a condition in which the urethal opening is displaced on the penis (Baskin, Himes, and Coburn, 2001; Sulton and others, 2001). Normal development is a function of prenatal exposure to fetal testosterone during weeks 9 through 12 of gestation. While a clear-cut link between environmental contaminants and increased expression of hypospadias has not been demonstrated in humans, animal models suggest that estrogenic chemical exposure during the prenatal time period can produce this effect.

Similarities and Differences in Toxicokinetics and Toxicodynamics

Toxicokinetics refers to the manner in which the body handles and eliminates chemicals, and *toxicodynamics* refers to the manner in which the chemicals and their metabolites behave in the various body compartments. For example, a given chemical may be ingested, enter the gut, and be passed directly through the digestive tract and passed out in the feces with little or no change in structure. The same chemical if inhaled may be stuck in the lungs, coughed up as part of sputum, or taken through the alveolar lung tissue into the bloodstream. Where the chemical goes once in the bloodstream depends in part on the composition of the chemical and also on the age of the individual. The range of toxicokinetic factors can include differences in cardiac output, ventilation rate, gut absorption factors, permeability of the blood-brain barrier, liver and kidney function, and differences in endocrine function (Renwick, Dorne, and Walton, 2000). Responses to neurotoxicants are of particular interest, since the blood-brain barrier of infants is more permeable to water-soluble chemicals than is the barrier of adults.

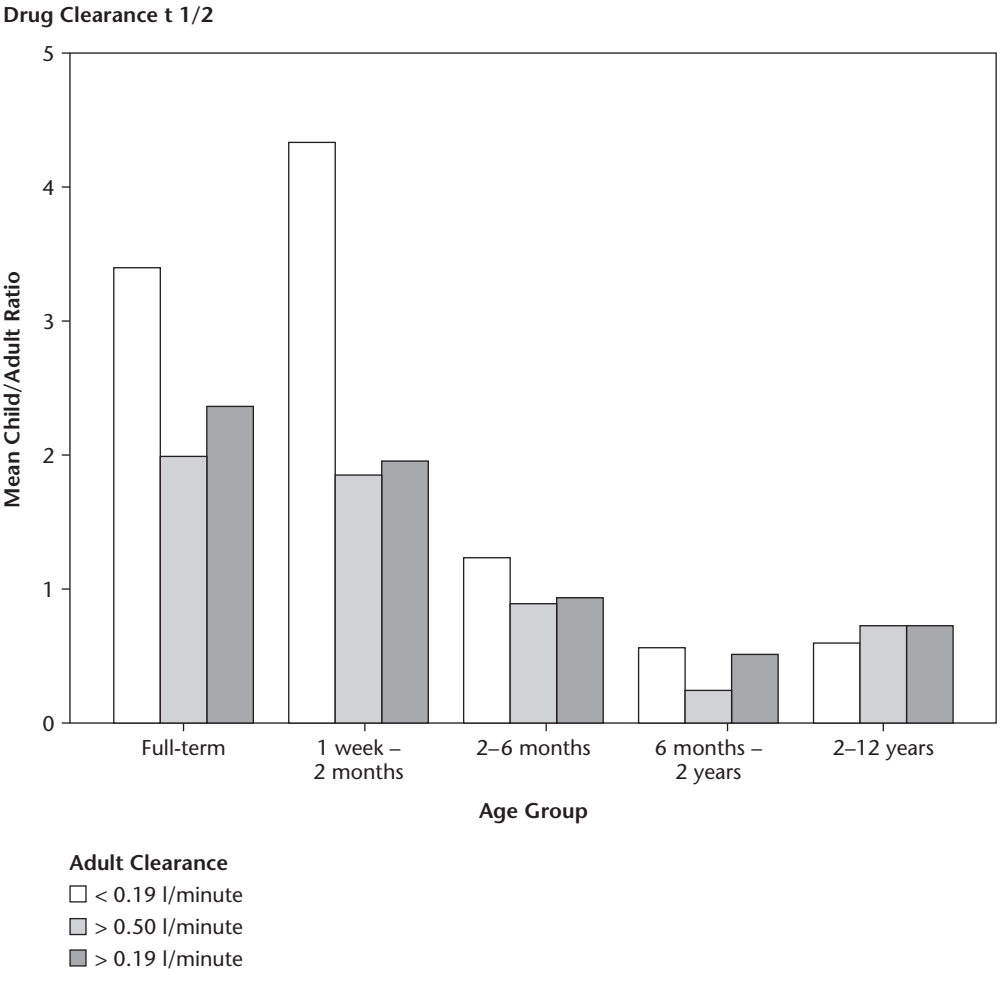
Young children may metabolize the chemical differently from the way adults do or at a different rate. A child's sensitivity to one chemical does not mean that he or she will have a similar response to other chemicals. Depending upon whether the chemical or its metabolite is the more biologically active material, the rate and manner of metabolism may have a significant influence on how the chemical affects the individual. Data from animal studies suggest that there is no clear-cut rule established for the types of toxicokinetic differences that would be expected between adults and children. In some cases, younger animals are more sensitive to the initial insult from a chemical but may have better repair mechanisms and greater potential for recovery. In other cases, younger animals are less sensitive to the chemical.

The relationship between body functions and anthropometric measurements is an underlying factor used in understanding toxicokinetic differences in adults

and children. Figure 12.1 shows the ratio of blood clearance rates of a range of drugs by children of various ages that have been categorized by their clearance rates in adults (Ginsberg and others, 2002; Ginsberg and others, 2004; Hattis and others, 2003).

If the clearance ratio is one, children and adults process the chemical at a similar rate. If the ratio is greater than one, the child processes the chemical faster;

FIGURE 12.1. CHANGES IN BLOOD CLEARANCE RATE IN CHILDREN RELATIVE TO ADULT CLEARANCE RATES.



Source: Adapted from Ginsberg and others (2002).

if the ratio is less than one, the child processes the chemical more slowly than an adult. What can be seen is that for neonates and infants many of the drugs have substantially longer clearance rates than for adults, and that as children get older the clearance rates for some drugs can become similar to that in adults or be much shorter than would be expected for adults. These inherent differences for drugs are likely to also occur for a variety of environmental chemicals to which children are exposed.

Adipose tissue volume and distribution in the body are also of importance in understanding the toxicokinetics of chemicals in the body. Lipophilic chemicals such as organochlorine pesticides and volatile organic compounds are stored in adipose tissue and may be remobilized during periods of rapid growth and/or weight loss. In adults, adipose tissue is correlated to body weight in both men and women, with women having relatively larger amounts of adipose tissue than men, and with its distribution in the body primarily in the hips, belly, and breast; this is in contrast to men, where it resides primarily in the belly. For children, adipose tissue is well-distributed throughout the body. The adipose tissue volume in children is inversely related to age, with infants and toddlers having relatively greater adipose volume than older children. The influence of age on adipose volume is greater for boys than for girls. This may be related to the greater changes in height that boys undergo compared to girls during adolescent growth, and the increased development of muscle mass in boys during this period.

Differential intestinal absorption of lead has been observed in children and adults, with children absorbing more lead than adults. It is likely that this is not specific to lead and therefore would occur for other chemicals. A variety of animal models suggests that this is the case, although it has not been thoroughly documented in humans (Daston and others, 2004). In infants, the digestive tract's ability to process complex carbohydrates and proteins is not fully developed. Pediatricians discourage parents from feeding these foods to infants because exposure to these foods early in life has been associated with the development of allergies (Koletzko, 2000).

Similarities and Differences in Behavior

Each of us intuitively knows that children behave differently from adults, and infants do not behave in the same way as teenagers. To develop exposure scenarios useful for risk assessment, it is necessary to numerically characterize these behavioral similarities and differences so that the information can be incorporated into equations (Environmental Protection Agency 1997, 2000). Population-based data on behaviors and use of microenvironments by children and adults that may influence exposure and risk has been obtained by several surveys, including the Na-

tional Human Activity Pattern Survey (Tsang and Klepeis, 1996; Klepeis, Tsang, and Behar, 1996) and the National Human Exposure Assessment Survey (Freeman and others, 1999). In addition, other databases have been generated for a variety of purposes and incorporated into CHAD, EPA's Consolidated Human Activity Database (McCurdy and others, 2000). These surveys asked about where individuals spend time, what they did, or what their proximity was to pollutant activities or sources. They are valuable resources both for identifying what is known about activities of various age groups and for pointing out areas where knowledge is lacking and will contribute uncertainties to risk assessments.

The behaviors of individuals have a direct influence on the significance of various exposure pathways. The media from which individuals may be exposed to environmental contaminants include ambient and indoor air, soils and sediments, house dust, water, foods, and manufactured products. The relative influence of the three major routes of exposure, inhalation, ingestion, and dermal absorption, vary with the compound of interest, the media in which the compound is found, and the behaviors of the individual who is potentially exposed.

Selected data from NHAPS in Table 12.2 show both the variability in activities across age groups and the age group for which there is no population-based information. One of the difficulties in creating exposure scenarios for risk assessments is that data for very young children are often lacking or are only from specific studies where the children may not represent a larger population.

Children can be exposed to waterborne contaminants through multiple routes: dermal exposure, inhalation exposure, and ingestion. The importance of each route of exposure depends on the character of the chemical, the age of the child, and the behavior of the child. Water contacts differ across age groups and hence will change the characteristics of exposures to waterborne contaminants. Young children are less likely than adolescents to take showers and therefore will be less exposed through the inhalation route to volatilized materials in shower water. On the other hand, the younger children will spend more time with most of their body submerged in tub water and potentially will have greater dermal exposure both because of the duration of submersion and because of their greater surface to body weight ratio. Water-consumption patterns differ across age groups, with water consumption increasing with age. However, when water consumption is normalized for body weight, the volume of water consumed by infants and toddlers is substantially greater than for older children.

Pollutants in ambient air are more likely to be important for individuals who spend considerable time outdoors. To give a more graphic example, the adolescent who rides his bicycle to school during rush hour has the potential for greater inhalation exposure of motor vehicle fumes than one traveling the same route in an enclosed vehicle (Figure 12.2).

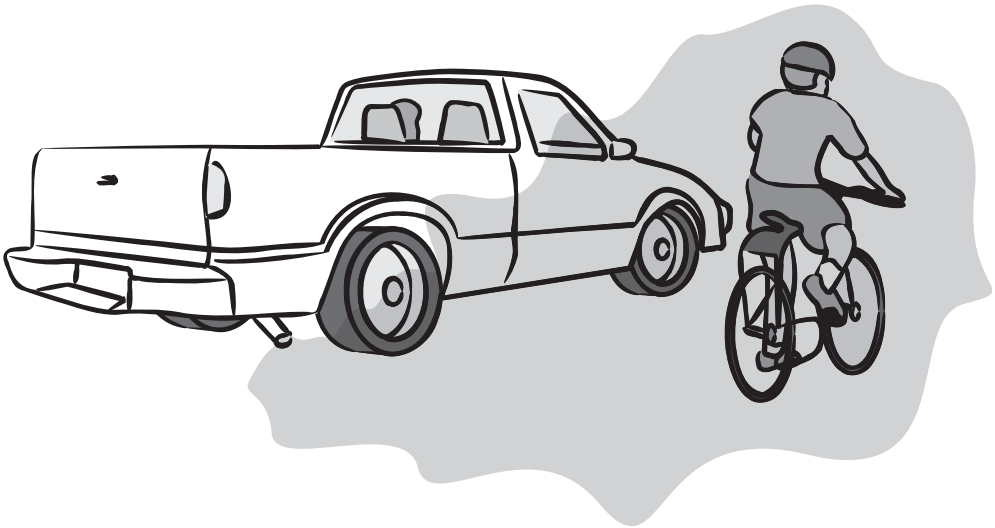
TABLE 12.2. COMPARISON OF ACTIVITIES ACROSS CHILDREN AGE GROUPINGS.

Behavior	Infants	1–3 Years Old	4–11 Years Old	12–18 Years Old
Water consumption (l/day)	0.3	0.61	0.87	0.97
Take shower (% pop)	nd	16	40	83
Take bath (% pop)	nd	72	38	14
Tap water consumption (% pop)	nd	57	74	73
Carbonated drinks consumption (% pop)	nd	26	51	73
Indoors at home (% time)	nd	84	70	67
Time in kitchen (min/day)	nd	74	60	55
Time sleeping (% time)	nd	51	43	39
Play outdoors (min/day)	nd	135	150	113
Hand to mouth (frequency/hr)	nd			
Smoker present (% pop)	nd	32	34	44
Smoker present (min/day)	nd	366	318	245

Sources: Tsang and Klepeis (1996); Klepeis, Tsang, and Behar (1996); Environmental Protection Agency (1997).

Note: nd = no population-based data available.

FIGURE 12.2. DIFFERENTIAL EXPOSURES TO AMBIENT AIR POLLUTANTS FROM MOTOR VEHICLE EXHAUST.



The difference in exposure is due not simply to the difference in ambient versus enclosed space but to the increased respiration rate of the bicycler compared to the passive rider and the closer proximity to the exhaust fumes of the bicycler. With regard to air pollutants, while young children may not smoke, proximity to environmental tobacco smoke (ETS) has been documented to be greatest for infants and toddlers and less for older children because infants and toddlers are more likely to spend time with a parent or adult caretaker. ETS is a trigger for asthma attacks, and its component chemicals are carcinogens and respiratory irritants (Nelson, Conrad, and Kelley, 2000).

For children, soil and house dust can be important exposure pathways because of the increased intimacy of contact children have with these media when they play, the greater frequency and duration of contact with the media, and secondary behaviors such as hand-to-mouth and object-to-mouth activities that may contribute to soil and dust ingestion (Davis and others, 1990; Calabrese and Stanek, 1995; Calabrese, Stanek, James, and Roberts, 1997). The rate of these behaviors and whether the child exhibits pica could potentially expose children to both chronic and acute toxicity. Several studies have measured the amounts of

sediment on the hands and legs of children and adults at the beach and soils on hands and legs of adults and children carrying out age-typical behaviors (Kissel, Richter, and Fenske, 1996; Shoaf and others, 2005a, 2005b). In these studies, children tended to have greater sediment loadings than adults, and the deposition of soils and sediments on the body differed by age and activity. Persistence of dermal loadings may differ across ages due to the moist or sticky conditions of children's skin compared to adults'; however, there are little data to address this issue. In laboratory experiments with adults, Camann and others (1996) and Rodes, Newsome, Vanderpol, and Lewis (2001) found that the condition of the hand—dry, moist, or sticky—and the characteristics of the contact surface influenced dermal loading and adhesion. Similar studies have not been done with children, nor has a systematic assessment of the condition of children's hands been conducted. Contact with contaminants in soil or in house dust is likely to be greater for young children, since they spend more time on the floor than do older children. In addition, mouthing behaviors are more common among infants and toddlers and therefore increase the possibility of nondietary or incidental ingestion.

The synergy between physiological and behavioral influences on children's exposure and potential risk is most clearly shown in children's food-consumption patterns. Children consume more fluids and foods per body weight than adults (Guzelian, Henry, and Olin, 1992). In addition, children tend to have less breadth in choice of diet, thus potentially being exposed to relatively larger quantities of contaminants found in the limited range of foods consumed. If the rate of gut absorption is greater in the child the potential dose may be increased relative to the adult.

Biomarkers of Exposure

Biomarkers are chemicals found in body tissues and fluids that can be used as indicators of an individual's exposure to an environmental chemical, as measures of body burden, changes in function or condition; or they may be indictors of an individual's ability to process an environmental chemical once it has entered the body. For the most part, the biomarkers of exposure are the same for adults and children and are indicators of the amount of the contaminant that has entered the body. In some cases the biomarker is the contaminant itself, while in other cases it is a metabolite. There tends to be less data on biomarkers for children than for adults.

Biomarkers are commonly collected in blood or urine samples. Blood samples are useful for a wide range of chemicals but have the limitation that children don't like blood draws. Urine collection is relatively easy and is especially useful for measuring pesticide metabolites and nonlipophilic substances. Collection of

urine samples for infants and toddlers is more challenging when children are not toilet-trained. However, collection and analysis of urine samples from diapers can be successfully done (Hu and others, 2000; Shalat and others, 2003). Biomarkers in urine are typically corrected for creatinine. High creatinine values suggest that the individual is dehydrated, while very low creatinine levels suggest kidney function anomalies or other factors that may produce dilute urine. The traditional range of acceptable creatinine values used for adjustments on urine samples for adults is not relevant for young children (Barr and others, 2005; O'Rourke and others, 2000). Children's creatinine levels tend to be very low; at the same time a wider range of values is observed in children's urine when compared to that of adults. Creatinine adjustments may not have a normalizing effect on metabolite values for children, while it is assumed to have one for adults. Alternative methods of normalizing urine samples for hydration and dilution such as using specific gravity can be done, but they are not commonly accepted.

Recent work on biomarkers of exposure has focused on cord blood and meconium measures as indicators of contaminants children are exposed to in utero (Whyatt and Barr, 2001; Whyatt and others, 2001; Whyatt and others, 2004; Walker and others, 2003). While these findings are provocative, the integration of data and concepts of in utero exposure into formal EPA risk assessments has not yet been done. Hair can also be used to measure biomarkers of exposure. They provide a historical measure of exposure across the length of the hair strand. However, its utility is limited primarily to metals.

Risk Assessment Paradigms as They Apply to Children

Much of the work of risk assessment has been prompted by the USEPA in its need to uphold the various federal acts developed to regulate chemicals in the environment and protect individuals from contaminant exposure.

USEPA Exposure Models

The general mechanistic model for exposure or potential dose (PD) is

$$\text{PD} = \text{Contaminant concentration} \times \text{exposure pathway} \times \text{contact rate} \times \text{exposure duration}.$$

Exposure models are required for each relevant exposure pathway: inhalation, dermal, dietary ingestion, and nondietary ingestion. While the general model is

applicable to all humans, the differences for children lie in the exposure pathways that are relevant and the actual values used for the contact rates and exposure durations. The EPA *Exposure Factors Handbook* (1997) and the *Child-Specific Exposure Factors Handbook* (2002) provide default values for adults and children that can be used in a variety of risk assessment scenarios. The limitations in the default values and needs for additional data to improve the quality of assessments is well-documented (Needham and Sexton, 2000); however, until such time as better data are available, the default values in the EPA handbooks provide a consistent set of metrics to use. Examples of the differences in exposure metrics used by EPA are obtained from a variety of sources including the National Human Activity Pattern Survey (NHAPS). If we consider soil-based contaminants that have a dermal route of exposure, the metrics of interest would be time spent outdoors, duration of contact with soil, and frequency of contact with soil (Table 12.3). Secondary exposure metrics would be behaviors that contribute to enhancing adhesion or removal of soil contaminants such as water contact, hand washing, or food handling. In addition, factors such as seasonality and age of the child may influence the potential for exposure.

USEPA has funded the development of two lead models, one specific to children and the second carrying through exposures at all life stages. The objectives behind these models are to calculate blood lead distributions based on exposures to lead from multiple sources. As tools in risk assessment, they allow us to estimate risk based on lead in a range of environments without having to collect blood samples from children, and they can help determine if a site's environmental lead levels are high enough to produce an elevated blood-lead estimate.

TABLE 12.3. ACTIVITIES ONE MIGHT CONSIDER IN AN EXPOSURE SCENARIO FOR DERMAL CONTACT WITH SOIL.

Activity	Soil	Water
Time outdoors	Age of child	Pre-soil contact
	Gender of child	Post-soil contact
	Urban/suburban/rural	Post-soil/Pre-food contact
	Time of day	Hand washing
	Day of week	Food contact
	Season of year	
Duration of contact with soil	Minutes/day	
Frequency of contact with soil	Times/minute	

IUBEK Lead Model

The Integrated Exposure Uptake and Biokinetic (IEUBK) Model was developed to predict the probability of elevated blood lead levels in children under age 7 using a three-compartment model. The first compartment includes all the potential sources of lead exposure (air, dust soil, diet, water) through two pathways, inhalation and ingestion. Dermal exposure is not considered an important route for lead, although it can contribute to nondietary ingestion (Freeman and others, 2001). The second compartment takes lead from the respiratory tract and gastrointestinal tract into the bloodstream or through elimination pathways to the feces. The third compartment takes lead from the blood into bone; soft tissues such as skin, hair, and nails; kidneys; elimination through urine; liver; and elimination through feces. In the process it calculates expected blood-lead levels based on the sources, routes, and concentrations of lead in environmental media. The purpose of the model is to provide risk assessors with a means for determining potential exposures to lead. The adequacy of the model is based on the assumptions used in it, such as that the primary source of lead exposure is in the child's home and that the child spends nearly all his or her time in or around the home. Data from NHAPS suggests that for many children this assumption may not be valid. Application of the model to data collected in a dietary lead study suggests that in some circumstances the model may under-estimate children's exposure (Melnyk and others, 2000).

ALLMA Lead Model

More recently (2005) EPA has developed a lead model that carries through all life stages. This model builds on the previous modeling efforts of the Agency, including IEUBK, and extends the exposure scenario to include children older than age 7 and adults up to age 90.

SHEDS Pesticide Model

SHEDS is the Stochastic Human Exposure and Dose Simulation model developed by EPA (Zartarian and others, 2000; Zartarian and others, 2002). As a variant on the SHEDS model, MENTOR/SHEDS-Pesticides, a physically based-probabilistic-population model was developed to help estimate a child's aggregate exposure and dose to pesticides in the residential environment; exposure was via the inhalation, dermal, nondietary, and dietary ingestion exposure pathways using a source-to-dose paradigm for analysis (Georgopoulos and Lioy, 1994; Zartarian and others, 2000). MENTOR/SHEDS-Pesticides is a population-based

model that can estimate exposures and doses for population groups of interest, including age-specific cohorts of children in the general population. Evaluation of the model and its default values with field-based data has been conducted in one study (Hore and others, 2005b). The SHEDS model relies heavily on existing EPA default values, which may not be relevant for specific situations. Systematic validation of this model using environmental and biomarker data is desirable.

Special Case: Lead Exposure

Lead is one of the commonly found metals in most Superfund sites; therefore, Superfund risk assessments are frequently conducted on lead, taking into account the concentrations found on-site, the potential for infiltration of leaded dust offsite into residential areas, and the presence of residences and schools in proximity to the sites. From a toxicological point of view lead is of interest because of the wide range of adverse health outcomes associated with lead exposure and the apparent linear dose curve for noncancer end points (Agency for Toxic Substances and Disease Registry, 2005). Lead is also of interest because it is found in housing, on soil along roadways, and in objects found in homes. The Consumer Product Safety Commission regularly reports about objects and toys containing lead that may pose hazards to children, including toys in which lead-based paints or dyes are used or Venetian blinds (U.S. Consumer Product Safety Commission, 1996, 2003; Jones and others, 1999).

Exposure to lead can be considered either as a "glass is half full" or a "glass is half empty" situation. On the one hand, the average blood lead levels for children under age 6 has declined sharply over the past 25 to 30 years from nearly 78 percent of children having blood lead levels greater than 10 μg/dl to less than 2 percent during the period from 1999 to 2002 (Centers for Disease Control and Prevention, 2005a). This decline has been attributed to removal of lead from gasoline, removal of lead from paint and abatement of homes with lead paint, removal of lead solder from food cans, and a vigorous public health education program throughout the United States. On the other hand, specific subsets of the inner city and minority child population still have elevated blood lead levels relative to the rest of the child population. In addition, the blood lead levels at which adverse health outcomes are observed have continued to decline; while 10 years ago a blood lead level of 10 μg/dl was perceived as acceptable, it is now known to be associated with elevated risks of adverse neurological effects (Lanphear and others, 2005). Provocatively, the greatest impact of lead on IQ may be at the lower levels of exposure.

Issues of Surveillance

The data used by the Centers for Disease Control and Prevention to track blood lead levels in the United States is from the National Health and Nutrition Examination Survey (NHANES), a population-based sample of individuals across the United States (Centers for Disease Control and Prevention, 2005a, 2005b). The CDC also requests reportage of blood lead measures from all states. Based on that reportage, more than 400,000 children under age 5 are estimated to have blood lead levels greater than 10 μg/dl. Using the same data and the uncertainties produced by the different reporting methods used across the states, it may be that as many as 800,000 children under age 5 have elevated blood lead levels.

Role of Nutrition on Lead Absorption and Retention

How lead behaves in the body is highly dependent on the nutritional status of the individual and the individual's age. Young children absorb 40–60 percent of ingested lead, while adults absorb only 10 percent. In addition, blood lead circulates in the child's bloodstream for approximately 10 months, while circulation in the adult bloodstream averages one month. Adult studies suggest that 4 to 15 times more lead is ingested on an empty stomach than on a full one (Maddaloni, Lolacono, and Manton, 1998) and that the type of food consumed also influences lead solubility, absorption, and retention. If the food in the digestive track is high in fat, lead solubility and absorption are enhanced. Therefore, evaluating lead risks to children requires an understanding of the dietary habits of the exposed children.

Lead competes with calcium for sites in bone. If a child is calcium-deficient, lead is more likely to be absorbed and retained in the body. Studies of children with low to moderate blood lead levels showed a negative association between blood lead levels and milk consumption, even when the environmental levels of lead in the home were similar (Freeman, Ettinger, Barry, and Rhoads, 1997). Vitamin C and iron have also been implicated in lead absorption. Vitamin C facilitates iron absorption and the presence of iron inhibits lead absorption (Campbell and Osterhoodt, 2000; Hubbs-Tait, Nation, Krebs, and Bellinger, 2005).

Hazard Assessment

Unlike many other chemicals in which hazard assessment is based on animal toxicological data, the toxicological effects of lead are well-documented in humans. Lead ingestion or inhalation leads to irreversible neurological damage, which is expressed by loss of intelligence as measured on IQ tests, hearing loss, attention deficit, and increased irritability (Table 12.4). Lead ingestion or inhalation can

TABLE 12.4. HEALTH EFFECTS ASSOCIATED WITH ELEVATED BLOOD LEAD LEVELS IN CHILDREN.

Blood Lead Level (μg/dl)	Effect, Sign, or Symptom
1–5 pts/10 μg/dl	IQ loss
< 5	Inhibition of ALAD
< 5	Colic and abdominal distress
< 10	Reproductive development
< 10	Liver dysfunction
< 20	Kidney dysfunction
> 30	Depressed nerve conduction
> 70	Encephalopathy
> 100	Death

Source: Agency for Toxic Substances and Disease Registry (2005).

also lead to permanent kidney damage, which can be expressed in adulthood by hypertension. High exposures to lead can lead to death. Unlike many noncarcinogens, lead does not seem to have a threshold for effect for each of its outcomes. As a neurotoxicant, there seems to be no point at which a measurable adverse outcome cannot be measured (Lanphear and others, 2005).

Exposure Assessment

Lead concentration in blood is the most commonly used biomarker of exposure and is the metric used by health officials for determining health risks to children. From the mid-1970s to 1980s the action level for blood lead was 25 g/dl; it has been reduced to 10 μg/dl as information about adverse effects at lower exposure levels has been obtained. While blood lead is used as an indicator of exposure, it is in fact a biomarker of effect, since the blood lead action levels are determined by the long-term health effects (i.e., cognitive function) found above those levels. Other biomarkers of exposure that are used less often include fecal and urinary levels and bone lead levels (Hu and others, 2000).

Environmental factors considered in lead exposure assessment include dietary lead intake and lead levels in homes and soil. FDA has generated age-specific lead dietary levels and a provisional tolerable-intake level. The age-specific lead levels are based on typical diets for children as calculated from market-basket surveys and the Continuing Survey of Food Intake by Individuals (CSFII). As of 1985, the lead levels found in children's diets averaged 8.5 g/kg for children ages 12 to

24 months and 6.49 g/kg for children ages 25 to 36 months. Because of reduction in use of lead-soldered cans and active efforts to reduce lead contamination during processing, by 1998 the typical diet for children ages 12 to 36 months was 1.4 g/kg food. As of 1998, the provisional tolerable intake level for lead for young children was 6 g/kg. There are few dietary lead measures based on duplicate diets. One study of 54 toddlers living in aging homes in northern New Jersey found that the average dietary lead level was 9.4 g/kg, above the current provisional tolerable intake level for young children and well above the FDA's estimate of typical dietary intakes for young children (Melnyk and others, 2000). In this study, the foods were obtained in the home after preparation as opposed to the methods used by the FDA which assess diet composition based on food samples that have not been prepared in homes.

Risk Characterization

Risk characterization is the basis upon which the risk managers determine if interventions are needed, and upon which regulatory decisions are made. Both EPA and the Department of Housing and Urban Development (HUD) have standards for lead levels in and around homes. The acceptable levels depend on where the lead is found—water, floor dust, window sills, window wells, and soil—and have been evolving over the years with the most recent standards consistent across agencies. Floor-dust levels have the lowest acceptable level because this area is most readily available to children. Table 12.5 shows the levels currently used by USEPA and HUD.

The drinking water standard only addresses community water supplies, not private wells. If less than 10 percent of municipal samples during any screening is greater than 15 ppb, no action or reportage is required. These standards are

TABLE 12.5. LEAD HAZARD STANDARDS FOR HOMES.

Lead Source	EPA/HUD
Water Pb	15 ppb in 10% of municipal samples
Floor dust Pb	40 μg/ft^2
Window sill Pb	250 μg/ft^2
Window well Pb	800 μg/ft^2
Soil Pb (bare soil in play area)	400 ppm
Soil Pb (elsewhere in yard)	1200 ppm

Source: Environmental Protection Agency (2001).

supposed to be protective of children, yet clearly the standard does not protect all children who might have lead in drinking water. Risk models and measurements are used to determine if the standards are being maintained. In several studies of lead-burdened children in New Jersey (Freeman, Ettinger, Barry, and Rhoads, 1997; Adgate and others, 1995) the average dust levels found in children's homes were at or below federal standards, yet the children had elevated blood lead levels. In these studies it became clear that the behaviors of the children were associated with their lead burden (Table 12.6).

TABLE 12.6. COMPARISON OF PERCENTAGE OF CHILDREN WITH REPORTED BEHAVIORS FOR CHILDREN WITH LOW AND MODERATE BLOOD LEAD LEVELS.

Behavior	Low Lead Group	Moderate Lead Group
Hand-to-mouth activities		
Mouths objects	80	85
Eats with fingers	81	80
Eats food from floor**	43	68
Sucks fingers/thumbs**	16	30
Food access		
Fed by siblings*	29	53
Get own food	42	39
Eat snacks everywhere	26	24
Handwashing activities		
Before meals	85	77
After meals	64	70
Before snacks	36	25
After snacks**	42	20
After playing outside***	56	21
Before bed***	52	15
Study characteristics		
Age (months)	25.3 +/– 5.5	25.7 +/– 5.8
Blood lead (µg/dl)***	10.9 +/– 5.5	28.5 +/– 5.5
Gm mean floor lead (µg/ft^2)	43	45
n	60	50

*P < 0.05, **P < 0.01, ***P < 0.001

Special Case: Pesticide Exposure

In 1993 the National Academy of Sciences report on pesticides in the foods of children raised the issue that children may have unusually high exposures to pesticides (National Research Council, 1993). Since many pesticides are either neurotoxicants or endocrine disrupters, they present potential risks to children. Organophosphate pesticides (OP) are commonly used in agriculture and in residential areas. Use in homes has diminished as potentially less hazardous chemicals and attempts at integrative pest management have replaced OP use. The primary consistent source of exposure to OP pesticides for children is through the foods they eat (Fenske and others, 2002; Lu and others, 2005a). In addition, depending on the pesticide usage patterns in homes, schools, and other locations where children spend time, children can be exposed to a range of pesticides in these locations (Savage and others, 1981; Whitmore and others, 1994; Freeman and others, 2004; Landrigan and others, 1999).

Dietary Sources and Surveillance

Surveillance of dietary sources of pesticides is conducted at two federal agencies, the U.S. Department of Agriculture (USDA) and the Food and Drug Administration (FDA). Both agencies collect commodities using variations on a market basket survey. USDA collects and analyzes raw food items. The FDA samples standard food items in four sections of the United States and prepares them according to standardized protocols. Analysis is conducted on the prepared foods. The data collected through these analyses are used in conjunction with dietary intake data collected via interviews such as the Continuing Survey of Food Intake by Individuals (CSFII) and the Supplemental Children's Survey (U.S. Department of Agriculture, 1998), which focused specifically on the eating habits of children. Models are developed that characterize dietary intake of foods for different age groups. The diets from CSFII are matched with the foods used in the market basket survey analyses of pesticide levels and an estimate of dietary intake for the pesticides is calculated. This provides a population-based estimate of dietary exposure rather than a specific individual-based measurement of the pesticides consumed. This indicator of dietary exposure to pesticides does not include contaminants that the food acquires after leaving the store—for example as a result of storage practices in the home. Nor does it include influences of food preparation and handing in the home. It therefore may be an underestimate of the total dietary exposure to pesticides.

Food Quality Protection Act

The Food Quality Protection Act of 1996 (FQPA, 1996) required USEPA to consider all sources and routes of exposure be taken into account when evaluating the potential burden of pesticides to the population. In this effort, the Agency was to use an aggregate exposure model for pesticides that have a common mode of action and to incorporate the aggregate exposure data in a PBPK/PBPD model of cumulative risk. In addition, FQPA identified children as a particularly susceptible population that must be protected either by an addition 10 × safety factor or by provision of enough data that an additional 10 × safety factor would not be required (Charnley and Putzrath, 2001). The FQPA to some extent addressed the deficiencies of the USDA and FDA market basket surveys in that it required some estimate or measurement of sources of exposure within the home to individuals directly or through food contamination to be considered when evaluating pesticide risks to children.

Hazard Assessment

Toxicological data are used to characterize the health outcomes from chronic and acute exposures to pesticides. OP mode of action is as a neurotoxicant-producing cholinesterase suppression. While cholinesterase suppression is considered by EPA to be the indicator effect of OP pesticides, studies of children's exposure to pesticides suggest that there is a wide range of effects including changes in reflexes, problems with memory, attention span, and motor skills (Ruckart, Kakolewski, Bove, and Kay, 2004). Some of these effects appear to be the result of in utero exposure (Eskenazi and others, 2004; Young and others, 2005). What are not known are the significant doses and periods of susceptibility associated with these noncholinesterase effects.

Exposure Assessment

Currently the pesticides primarily used in residences and on foods are organophosphate pesticides and pyrethoid pesticides. Some OPs are still used in agriculture. Biomarkers of pesticide exposure recently have focused on OPs and pyrethroids and have measured metabolites of the pesticides in urine, cord blood, and meconium (Shalat and others, 2003; O'Rourke and others, 2000; Whyatt and Barr, 2001; Whyatt and others, 2004). Urine metabolites are usually an indication of short-term exposure within 24 to 48 hours prior to the void. Both pesticide-specific and nonspecific metabolites can be measured. Meconium metabolite levels may represent cumulative prenatal exposures during the last two trimesters of pregnancy.

Measurement of metabolites in population-based samples of adults and children over age 5 has been conducted as part of the National Health and Nutrition Examination Survey. Data extracted from the Third Report (see Table 12.7) (Centers for Disease Control and Prevention, 2005b) raises issues of potential differences in exposure, perhaps differences in metabolism, and certainly the inadequacy of the database in excluding children under age 6.

The Third Report presents data on six dialkyl phosphate metabolites for organophosphate pesticides as well as on pesticide-specific metabolites for diazinon, malathion, chlorpyrifos, and parathion. The dialkyl phosphate metabolites are dimethylphosphate (DMP), dimethylthiophosphate (DMTP), dimethyldithiophosphate (DMDTP), diethylphosphate (DEP), diethylthiophosphate (DETP), and diethyldithiophosphate (DEDTP). Malathion docarboxylic acid (MDCA) is the primary metabolite for malathion. Para-nitrophenol is the primary metabolite for methyl parathion and parathion ethyl. The trends in levels are consistent for four of the six dialkyl phosphate metabolites for higher levels in younger children. When creatinine corrections are done on the urine samples, the trends are observed for all six dialkyl phosphate metabolites. In terms of assessing risks for children under age 6, we are left with data from studies whose participants may not be representative of the nation's children (Fenske and others, 2002; Whyatt and others, 2004; Shalat and others, 2003; O'Rourke and others, 2000), or we are back to extrapolating from the trends observed in the Third Report (Centers for Disease Control and Prevention, 2005b) or assuming that the metabolite levels of children ages 6 to 11 can be applied to younger children.

Risk Characterization

Dose-response relationships for OPs in children are based not on the metabolite biomarkers of exposure but on cholinesterase suppression. In general, data are lacking on this marker in children unless a child has an acute exposure that has produced an emergency medical situation. Minor influences on the nervous system are typically not assessed, and there is little evidence of cholinesterase suppression at the levels of metabolites found in children's urine.

Initially it was assumed that the pesticide metabolites were found only in urine. Recently however, it has been discovered that a variety of organophosphate metabolites are also found in foods, house dust, and soil (Morgan and others, 2005; Lu and others, 2005b). This makes risk characterization more challenging, since if the metabolite is biologically less active than the parent compound, consumption of the metabolite would carry less risk. It would also be difficult to evaluate exposure when the measure of exposure is the metabolite in urine.

TABLE 12.7. ORGANOPHOSPHATE DIALKYL PHOSPHATE METABOLITE LEVELS (µg/L) IN URINE AT THE 50TH AND 90TH PERCENTILE FOR SELECTED AGE GROUPS FROM THE THIRD REPORT OBTAINED FROM THE NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY.

Pesticide	Metabolite	< 6 years	6–11 Years	12–19 Years	20–59 Years
Azinphos methyl	DMP				
Chlorpyrifos methyl	50th percentile	no data	0.97	0.67	bdl
Malathion					
Phosmet	90th percentile		12.2	9.27	6.89
Dichlorvos					
Fenethion					
Methyl parathion					
Azinphos methyl	DMTP				
Chlorpyrifos methyl	50th percentile	no data	1.44	1.03	bdl
Malathion					
Phosmet	90th percentile		28.2	20.8	13.6
Fenethion					
Methyl parathion					
Azinphos methyl	DMDTP				
Malathion	50th percentile	no data	bdl	bdl	bdl
Phosmet	90th percentile		3.53	2.51	2.32
Chlorpyrifos	DEP		0.29	bdl	bdl
Diazinon	50th percentile	no data	9.56	7.55	5.79
Disulfoton					
Ethion	90th percentile				
Parathion ethyl					
Chlorpyrifos	DETP				
Diazinon	50th percentile	no data	0.54	0.69	0.54
Disulfoton					
Ethion	90th percentile		2.74	2.57	2.46
Parathion ethyl					
Disulfoton	DEDTP				
Ethion	50th percentile	no data	bdl	bdl	bdl
90th percentile			0.63	0.56	0.61

Note: bdl < 0.5 µg/l for DMP, 0.4 µg/l for DMTP, 0.2 µg/l for DEP, and 0.1 µg/l for DMDTP, DETP, DEDTP.

Source: Centers for Disease Control and Prevention (2005).

Issues of uncertainty and variability have made evaluating children's risks a challenge. Limited data or data generated for special populations that may not be representative of all children produce uncertainties in risk assessment when applied to other child populations. Data on the very young, that is, children under age 2, as well as data on adolescents tend to be lacking. We might think that children of farmworkers and children who live in agricultural communities would logically have higher exposures to pesticides than children from other communities, but studies do not necessarily support such an a priori assumption. In the state of Washington, data by Fenske and Lu suggest that while pesticide infiltration and track-in into homes can contribute to children's exposure, diet may be the major driver (Fenske and others, 2000; Lu and others, 2005a). Most of the studies of children's exposure to pesticides have small samples and/or fairly variable measures. Dose estimates calculated by Fenske and others (2000) were based on 109 children, which is one of the larger studies. Without systematic exploration in population-based studies, we do not know if the variability is a result of the small sample size or is indicative of what can be expected with a larger population-based sample.

Web Resources

National Center for Environmental Assessment
http://cfpub.epa.gov/ncea

Risk Assessment Guidelines
http://cfpub.epa.vo/ncea/cfm/recordisplay.cfm?deid=55907

Exposure Factors Handbooks
http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=2056

Superfund Risk Assessment
http://cfpub.epa.gov/oswer/reiskassessment/superfund_hhplanning.htm

IRIS Toxicity Data http://www.epa.gov/iris/

California Toxicity Data
http://www.oehha.ca.gov,risk/ChemicalDB/index.asp

International Toxicity Estimates for Risk Database
http://www.tera.org/iter/

ATSDR Minimum Risk Levels http://www.atsdr.cic.gov/mrls.html

PDP (Pesticide Data Program), 2000, Science and Technology Programs
http://www.ams.usda.gov/science/pdp/download.htm

Thought Questions: Phthalates and Children

1. *Surveillance.* Use the CDC Third Report to determine population-based biological indicators of exposure and dose to phthalates (http://www.cdc.gov/). Identify what further information you would want to collect.
2. *Hazard assessment.* Toxicity of phthalates as evaluated in animal studies is highly variable. Based on surveillance data as to what phthalate metabolites are found, identify two phthalates that might be a concern for children and using ATSDR Toxicological Profiles, EPA IRIS, or primary sources, determine what health outcomes are potentially issues for children. Determine if data is available to address the issue of periods of susceptibility.
3. *Exposure assessment.* Create an exposure scenario that takes into account the information that you have obtained from the surveillance, hazard assessment, and other documents. Determine the source of exposures, media, and routes of concern for children. Are some age groups of children more susceptible? What evidence is available to support your conclusion? What are the issues of uncertainty and variability that need to be addressed?

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CHAPTER THIRTEEN

BIOLOGICAL MONITORING OF EXPOSURE TO ENVIRONMENTAL CHEMICALS THROUGHOUT THE LIFE STAGES

Requirements and Issues to Consider for Birth Cohort Studies

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Learning Objectives

Students who complete this chapter will be able to

1. Understand the behavior of different classes of chemicals in the body after exposure has occurred
2. Recognize the utility of biomonitoring in assessing exposure to environmental toxicants
3. Recognize that different methodologies and techniques may affect the quality and ultimately the utility of selected biomonitoring measurements
4. Learn the appropriate matrices to use for biomonitoring of exposure to selected classes of environmental chemicals
5. Learn about the temporal variability and uncertainties involved with biomonitoring of exposure to chemicals that have short environmental and biological lifetimes

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Exposure assessment is an important component of risk assessment. When examining a population for adverse health impacts that result, in part, from environmental insults, it is essential that we try to link those impacts with exposures to chemical, biological, and physical agents that occur in our daily environment. We consider not only the known toxicity and the concentration of a given chemical to which an individual or a population is exposed but the frequency, duration, pathways, and routes of these exposures. In addition, the developmental life stage of the person(s) exposed is of fundamental importance (Environmental Protection Agency, 2001). For example, many researchers believe that some health end points that manifest themselves at various stages of development are a result of exposures that occurred soon after conception. They also deem the critical or most susceptible time period for environmental exposures to be from in utero through age 2, especially for some neurobehavioral outcomes. Other research suggests that prepubertal exposures are significant; for example, prepubertal males highly exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin later fathered predominantly female children (Mocarelli and others, 2000).

There are various ways to assess children's exposures to environmental agents (Needham and Sexton, 2000). However, before discussing these methods we must examine the pathway of these agents that leads to exposure and ultimately to dose. *Exposure* is defined as contact between an agent and a target; *contact* takes place at an exposure surface over an exposure period (International Programme on Chemical Safety, 2002; World Health Organization, 2004; Zartarian, Ott, and Duan, 1997). For many longitudinal birth cohort studies, the agents of concern are selected environmental chemical, biological, and physical agents; the target is the child; the exposure surfaces are the external surfaces of the child (i.e., skin, mouth, and nasal passage); and the exposure period is the child's lifetime or a defined portion of that lifetime. The continuum (Needham and others, 2005b) often used to describe the human exposure assessment pathway starts with the agent at its origin or its source, which, for example, can be a chemical manufacturing plant, automobile exhaust, or a chemical waste site. The agent can undergo various fates (such as transformation to another chemical) and transport (such as long-range air transport or movement from soil into groundwater) steps in the environment. This may lead to multiple intermediate sources in the pathway for a given agent; eventually, humans may have contact with the environmental media that contain the agent or its environmental transformation products, which is defined as exposure. This exposure may pass through membranes and enter into the body's circulatory system by three routes—ingestion, inhalation, and dermal. Depending on the membrane absorption coefficients and other bioavailability factors, the agent (or its metabolite) can be absorbed into the bloodstream. This absorbed dose of the agent or metabolite [or its reaction product (adduct)] is also known as

the *internal dose*. This internal dose can be either directly eliminated (usually a minor route); distributed within the body to other organs including the target organ(s); metabolized and eliminated (usually in urine); metabolized and distributed within the body to other organs including the target organ; or some combination of these (Needham and others, 2005b). A portion of the dose at the target organ may be biologically effective (*biologically effective dose*) (Needham and others, 1992). The process of estimating or measuring the magnitude, frequency, and duration of exposure to an agent, along with the number and characteristics of the population exposed, is called an *exposure assessment* (International Programme on Chemical Safety, 2002; World Health Organization, 2004; Zartarian, Ott, and Duan, 1997); certainly for health studies the term includes assessing the dose within the body as well as the actual contact with the agent.

Exposure Assessment Methods and Their Uses

A major goal in environmental epidemiology is to determine the association or lack of an association between the exposure assessment for environmental chemicals and morbidity and/or mortality, which will provide a useful piece of information for risk assessment. In health studies we prefer analytical chemistry data to define the biologically effective dose in a target organ, which was sampled at the appropriate period of time, to relate with the outcome of interest. However, measurement of the biologically effective dose is seldom possible because we may not know the target organ; or if we do, the sampling of that organ is generally a quite invasive process. Therefore, the exposure status of an individual in health studies is classified based on his or her internal dose of that agent, its concentration in personal air samples, and/or the concentration of the agent in relevant environmental samples; data from each of these measurements are coupled with questionnaire information to derive each person's exposure index. This index places each individual into an exposure category, such as tertiles, and each category is examined for an association with a health outcome; the data are most powerful when a statistically significant trend between the exposure assessment and outcome is observed. Hence, to accurately link exposure and disease status, we must accurately classify both the exposure and disease status. Other goals of health studies are to utilize exposure assessment information to diagnose disease, to treat disease, to prevent further disease, and to evaluate the effectiveness of each of these goals.

Exposures to the general population of the United States may be very difficult to accurately assess because we are generally exposed to low levels of environmental chemicals and the exposure scenario may be episodic (occurring only occasionally). The exposures may occur through various pathways, including

occupational, and routes (inhalation, ingestion, and dermal contact). For assessing exposures to environmental agents, there is no single method that will capture all of the needed exposure information all of the time. This is true for children and adults but becomes even more relevant when attempting to assess exposures during the in utero and early-childhood life stages. Therefore, a method that is best for assessing exposure to a given chemical at one life stage may not be the best method for assessing exposure to that same chemical at a different life stage.

There are three main methods (questionnaires, environmental monitoring, and biomonitoring) that are used to assess human exposures to chemical and biological agents. They all seek to gain information on the concentrations of the agent(s) to which the person(s) may have been exposed and the duration and frequency of that exposure. From this information, exposure indices are constructed, which are used to further estimate or categorize an individual's exposure and ultimately the dose within a population. Other data that should be factored into the assessment, especially when the human population contains fetuses and children, is the timing of the exposure (when the exposure took place) during those critical susceptible periods of development. The three means of assessing exposures to these agents are discussed below.

Questionnaires. Questionnaires seek information about an individual's demographics, lifestyle activities, medical history, potential exposure history, and environmental and social stressors; they are essential in any study of human exposure to chemical agents. They can be self-administered or interviewer-administered. Both require a high level of expertise in writing the questionnaire and if interviewer-administered, for administering the questionnaire. The questionnaire must acquire the necessary information in a clear, unbiased manner; yet it should not be so lengthy that it presents an undue burden (which leads to boredom and to inaccurate information) on the study participant. With respect to exposure, questionnaires seek to acquire information for developing exposure indices for the studied population; these indices consist of two types of information: (1) the concentrations of the chemical to which individuals in the study population have contact (exposure) and (2) the frequency/duration of that exposure. In general, questionnaires provide more accurate data on the frequency/duration aspect of the index than on the concentration component. In addition to the exposure situation itself, questionnaires can provide much needed information on factors that affect the chemical's pharmacokinetics within an individual (absorption, distribution, metabolism [biotransformation], and elimination) and pharmacodynamics; differences in pharmacokinetics greatly influence the biologically effective dose, and differences in pharmacodynamics greatly influence the health effects. These factors include demographic factors (e.g., age, sex, and race/ethnicity); environ-

mental (e.g., the built environment) and behavioral stressors; nutritional status; and other exposures, including medications and food supplements. Thus, questionnaires have the advantage of yielding information that cannot be gleaned by other methods. However, they suffer from the disadvantage of information bias, especially recall bias, which can lead to inaccurate exposure and outcome classifications. Also, they often provide no actual concentration data for the chemical/biological agent in the environment and in humans.

Information from other indirect methods, such as geographic information systems (GIS) and videotaping, is also limited by not providing actual concentration data for the agent in environmental and human specimens. However, videotaping has the advantages of tracing a given individual throughout his or her activities in daily life and observing potential contacts with the agent of concern and the frequency/duration of these contacts. Videotaping is particularly useful for recording the potential for transferring an agent from the outer surfaces of the body, for example, into the mouth, since it can log such actions as hand-to-mouth activity. GIS uses computerized maps to integrate potential exposure data (e.g., from estimated pollution data) into a spatial form so that the data can be analyzed geographically. GIS data are often used when more direct monitoring data are not available, but we caution that measurements in environmental or biological samples should be performed to validate the exposure assessment derived from GIS.

Environmental Measurements. The measurement of a chemical agent or its transformation product in an environmental medium provides information that can be used to track the chemical from its source throughout the environment, for example, air, water, food, soil, or dust. Consequently, environmental measurements are especially useful in risk management, where we are concerned about interrupting the pathway to exposure and preventing further environmental contamination and human exposure. In addition, they have been used as the metric for risk assessment. For example, reference concentrations/doses and cancer unit risks are expressed as an environmental concentration that can then be compared to an exposure estimate to determine whether an adverse health risk is likely. Environmental data are of most use when there is a single predominant environmental matrix, such as air, involved in the exposure pathway. If there are many environmental pathways, the number of potential measurements (and hence costs) increases dramatically, and the data are more difficult to model for the purpose of predicting human exposures and particularly the internal doses. In the exposure index paradigm, environmental monitoring gives us information about potential routes of exposure and the concentration of the chemical(s) to which humans are potentially exposed, while questionnaire information provides the data on the duration and frequency of exposure and the timing of the exposures.

Thus, this combination of environmental monitoring and questionnaire information provides needed information on the potential dose. However, for health studies, we are most concerned with the biologically effective dose at the target organ of the exposed individual; therefore, models must be developed to estimate the amount of the chemical to which the population is exposed and furthermore absorbed into the body, which become the internal and ultimately the biologically effective dose. These models, if possible, should be calibrated and validated before being used.

Air pollutants may be measured in the air itself or by personal exposure monitors. Depending on several factors, including the chemicals to be monitored, active or passive sampling may be used. *Active sampling* involves drawing the air into the collection unit with a sampling pump, while *passive sampling* relies upon diffusion. In both sampling processes, the collection unit should be located within 30 cm of the nose and mouth (the breathing zone). Personal air monitoring is an important component in estimating exposure concentrations in certain exposure scenarios, but again, the uptake data for the chemical and pharmacokinetic data have to be modeled for the exposed individual. Disadvantages of personal air monitoring and environmental air monitoring include the lack of accounting for differences of breathing rates and volumes of air inhaled among people or within a person, for example, during physical exercise.

A concern in human exposure assessment is the burden on the study population. The use of environmental monitoring plus questionnaire information may present no more burdens on the study population than the questionnaire itself. However, this is usually not the case. For example, if indoor air is monitored, equipment must be installed in the home; if food is monitored, then duplicate diets may be administered; and if personal air monitors are used, they must be installed on the individual. Assessing personal exposures in community health studies often relies upon partial information on measured concentrations of chemicals in various microenvironments of concern for personal exposures. Consequently, the use of limited outdoor or indoor monitoring information can lead to exposure misclassification biases; these in turn may result in loss of statistical power or potential for obtaining a null result when actually an association between exposure and disease exists (Özkaynak and others, 1986; Özkaynak and Spengler, 1996). To minimize errors in estimating personal exposures, researchers identify key sources, media, routes, and pathways of concern for each environmental pollutant and then determine an optimum sampling and analysis plan that will ensure collection of environmental and/or questionnaire information for each of the significant media and routes of exposure. In practice of course, budgetary and technical constraints often limit the extent of an environmental monitoring program. The actual cost of environmental monitoring is dependent on the chemical, the number of ma-

trices, the selection of matrices, the frequency of monitoring, and the cost of the questionnaire.

One often overlooked advantage of environmental monitoring is that certain chemicals are more toxic when they enter the body by a certain route. For example, chemicals such as manganese and polycyclic aromatic hydrocarbons, which are bound to particulate matter, are potentially more toxic when inhaled than when ingested. Therefore, if only biomonitoring (*vide infra*) is used for assessing exposure to these chemicals, the degree of exposure from these two routes cannot be differentiated; thus, the assessment of toxicity resulting from these exposures may be in error.

Biological Monitoring or Biomonitoring. Biological monitoring or biomonitoring provides information on the internal dose integrated across environmental pathways and routes of exposure (Barr, Wang, and Needham, 2005a); thus, an advantage of biomonitoring is that it directly considers the amount of the chemical that is absorbed into the body's systemic circulatory system. For *persistent chemicals*, those that have long half-lives on the order of months or years in the environment and in humans, biomonitoring data provide information as to what chemical and how much actually enters into people and accumulates. These persistent chemicals are generally measured in blood or its components, such as serum and plasma, in adipose tissue, or in human milk. Following exposure to persistent chemicals, differences in pharmacokinetics among various people will affect the internal dose levels to some degree, but not to the extent of misclassification for the purposes of epidemiological studies. Thus, biomonitoring is generally considered to be the gold standard for assessing human exposure to persistent chemicals provided the sample collection medium is feasible. If biomonitoring is not feasible (for example, collection of 100 mL of blood from an infant for a dioxin measurement is not feasible), an exposure index derived by other methods for persistent chemicals, such as environmental sampling combined with questionnaires, should be considered instead.

For chemicals that have short half-lives, biomonitoring data may become much more difficult to interpret. If the exposure situation is continuous or even continual, then the exposure situation (not the chemical) could be deemed persistent and biomonitoring would play a vital role in assessing human exposure (Needham and others, 2005a); however, if the exposure is predominantly from one environmental medium, then environmental monitoring and questionnaire data should also be considered for assessing a person's exposure. Whenever exposures are inconsistent or epidsodic, then biomonitoring, like other techniques such as environmental monitoring, loses much of its ability to track these exposures. In this scenario, the frequency of sampling and hence the comparison of data from these samplings are extremely important issues.

The collection of the biological sample to be analyzed may range from procedures that are invasive, such as the drawing of blood, to those with little intrusion, such as collecting urine samples from older children. If one neglects the burden on the person and the amount of blood that can be collected, blood has inherent advantages for biomonitoring, for regardless of the route of exposure, the chemical must be absorbed into the bloodstream and circulate to the tissues prior to an effect (exceptions would include direct inhalation effects on the lungs and also blistering agents on skin). Blood is also a *regulated matrix*; there is a constant amount of blood so that measurements can be "normalized" to this amount. The other most commonly monitored biological matrix is urine, which serves as a sink for many chemicals, especially the nonpersistent chemicals; the persistent chemicals are often eliminated primarily through the feces. These nonpersistent chemicals are generally found in the urine not only in their original "parent" structure but, more frequently, as metabolites. Measuring these metabolites to assess exposure, however, may be problematic, because (1) multiple chemicals may form the same metabolite and (2) the environmental transformation product (e.g., for organophosphorous pesticides) may be the same chemical as the metabolite, thereby confounding interpretation. Nonetheless, urinary measurements can play a vital role for assessing human exposure to many environmental chemicals. To gain specificity, these nonpersistent chemicals, such as chlorpyrifos and many volatile organic chemicals, have been measured as the parent compound in blood (Needham and others, 2005a; Whyatt and others, 2004). Another way to gain specificity and increase the time window for the exposure assessment for certain nonpersistent chemicals is to measure their reaction products or *adducts,* such as with hemoglobin, albumin, or DNA.

Before leaving this topic, it should be noted that there are some chemicals or physical agents for which we have little or no means for assessing their exposure via biomonitoring. These include particulate matter, asbestos, some of the air criteria pollutants (e.g., oxides of nitrogen), and allergens. Also, for some chemicals the nonspecificity of the metabolite biomarker (depending on the chemical and the biological matrix used) may make it difficult to determine the actual chemical to which the population was exposed. Another important point, especially for inorganic chemicals, is that both environmental and biological monitoring include the biologically active specie(s) of the chemical (e.g., methyl mercury for assessing exposure to mercury following fish consumption) (Needham and others, 2005a).

Biomonitoring and the Toxicokinetic Process of Environmental Chemicals

Following an individual's exposure to a given chemical a proportion of the chemical may be absorbed into the bloodstream, distributed among the bodily tissues, metabolized, and/or excreted. These four complex steps (absorption, distribution, metabolism, and excretion known as *ADME*) make up the toxicokinetic process of

a chemical (reviewed by Rozman and Klaasen, 2001). In order to assess human exposure to a given chemical, biological measurements of the chemical can be made after the absorption step or during each of the subsequent steps of ADME. Biomonitoring of exposure involves the measurement of the concentration of a chemical in a given biological matrix during or after ADME; its concentration level depends on the amount of the chemical that has been absorbed into the body, the pharmacokinetics (ADME) of the chemical, and the exposure scenario, including the time sequence of exposure and time since last exposure (Sexton, Callahan, and Bryan, 1995). Biomonitoring data are independent of the pathway of exposure (Pirkle, Needham, and Sexton, 1995). Ideally, in order to link the dose with adverse health outcomes measurements of the biologically effective dose, the dose at the target site that causes an adverse health effect is preferred (Pirkle, Needham, and Sexton, 1995). However, often we do not know the target organ, and even if we do, it frequently is not available for sampling. In these situations, we measure the level of the chemical in another biological sample to gauge the internal dose.

For longitudinal birth cohort studies, the biological sample can be taken preconceptionally from both parents, from a pregnant woman during each of the three trimesters, during and immediately following childbirth, from the mother postnatally, and from the child as it develops up to age 21. The appropriate sample for monitoring depends upon matrix availability and the different classes of environmental chemicals to be monitored. We developed this chapter as a part of a larger white paper to help provide guidance about which biological samples may be most useful for characterizing exposures of interest in longitudinal birth cohort studies. Although this guide may be applicable to other exposure studies, it was developed with the life stages of interest to the National Children's Study (NCS) and with the recognition that the specimens available for testing may be limited (National Children's Study, 2005; Needham and others, 2005a; Needham and others, 2005b). Unless otherwise stated, we refer to measurements made on biological samples from the parents or the child, but not to the fetus. Further, we focus primarily on chemical measurements made in a biological matrix taken from the participant, a commonly used strategy in human exposure assessment. Although newer methodologies such as imaging techniques and "omics" technology are becoming more readily available (Chaussabel, 2004; Wetmore and Merrick, 2004; Kiechle, Zhang, and Holland-Staley, 2004; de Hoog and Mann, 2004; Dettmer and Hammock, 2004; Olden, 2002), they are not included here.

General Behavior of a Chemical in the Body

Absorption of a chemical into the body occurs when the chemical enters the bloodstream by passing through absorption membrane barriers following contact

of the chemical with an outer boundary (i.e., skin, nostrils, mouth, or eyes). Without absorption there can be no direct internal toxic effect, even if the chemical is toxic, although effects are possible at the absorption barrier (e.g., skin irritation, eye lens irritation). Once the chemical has been absorbed into the bloodstream, it is distributed to the primary deposition sites. Distribution is crucial to toxicity because if the chemical is never distributed to the target site, the toxic effect may be negligible. However, because the concentration of the chemical in the storage depot is in equilibrium with the concentration in the blood, the chemical is slowly released from the storage depot as it is eliminated from the blood and low concentrations may reach the target organ.

Metabolism takes place primarily in the liver. The overall purpose of metabolism is to make the chemical less toxic and more hydrophilic. Phase 1 metabolism of the chemical typically involves inserting or substituting a functional group to make the chemical more water-soluble. Phase 2 metabolism usually links it chemically to a glucuronide or sulfate group, which increases the water solubility and facilitates elimination of the chemical in the urine. However, metabolism does not always render a chemical less toxic.

Metabolized chemicals may be more hydrophilic; they can be excreted in urine or be passed into the feces. If the chemical is not absorbed, it can go straight into the feces. Lipophilic compounds, in particular, are eliminated primarily in the feces. Volatile organic compounds (VOCs) can be excreted through the alveoli or in the expired air through exhalation. Chemicals can also be deposited in certain secretory structures and be excreted as tears, saliva, and sweat, or as milk in lactating women.

In addition to the internal movement of chemicals in the body, a pregnant woman can distribute the chemicals via the bloodstream through the placenta and into the fetal blood supply. Biomonitoring matrices unique to the fetus include amniotic fluid and meconium. In addition, cord blood, the placenta, and the umbilical cord can be collected at birth.

Behavior of Specific Chemical Classes in the Body

Persistent Organic Chemicals

Persistent organic pollutants or chemicals (POPs) include polychlorinated dibenzo-p-dioxins, polychlorinated biphenyls, and organochlorine insecticides (United Nations Environment Program, 2001; Needham, Barr, and Calafat, 2005). Polycyclic aromatic hydrocarbons (PAHs) are also often included in this class because they persist in the environment; however, because PAHs behave more like nonpersis-

tent chemicals in the body, we have chosen to exclude them from POPs (Needham, Barr, and Calafat, 2005). The primary route of exposure to POPs is ingestion. POPs are readily absorbed into the blood supply by passive diffusion. Initially their blood level decays relatively rapidly, representing the alpha decay period (Flesch-Janys and others, 1996). During the alpha decay, the POP is distributed into the fatty portions of tissues, and in lactating women, in breast milk. The concentration of the POP in the fatty portions of tissues is in equilibrium with the concentration in the lipid portion of blood. The fat content of blood serum is 0.5–0.6 percent, milk is ~4 percent lipid, and adipose tissue may be as much as 95 percent lipid. Thus, while the equilibrium concentrations of the chemical in the blood and fatty tissues may differ over orders of magnitude, they may be very similar when matrices are adjusted for lipid content.

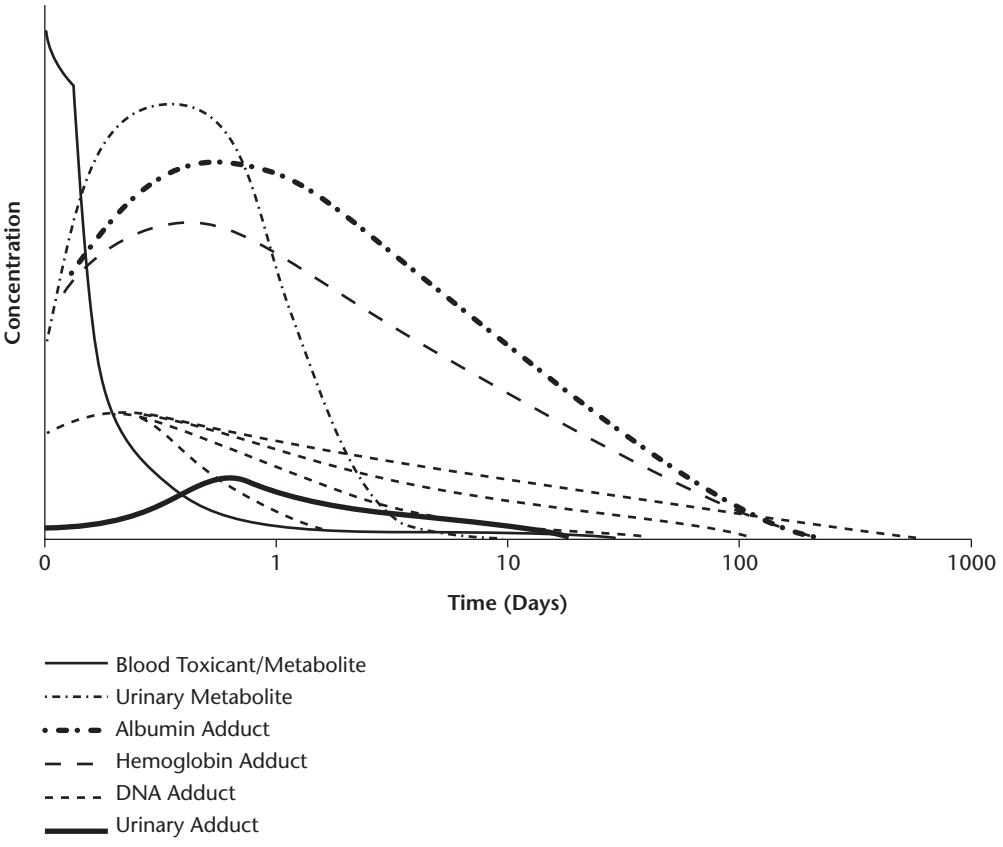
In pregnant women, the POP may also distribute in the fetal compartment; therefore, other matrices such as cord blood or serum may be used for POP measurements. However, the lipid content of cord blood is lower than that of an adult, so the sensitivity of the analytical measurement may play a key role in obtaining a valid measurement. Other fetal matrices, such as meconium, have not been fully explored for their potential in assessing POP exposures in the fetus. Maternal blood or adipose tissue taken before or during pregnancy and maternal blood, milk, or adipose tissue taken soon after parturition (if breast-feeding or taken later if not breast-feeding) are considered the best matrices for estimating fetal exposures to POPs.

Because metabolism and excretion of POPs are very slow, they have a long half-life in the body, usually along the order of years (Phillips and others, 1989b; Michalek and others, 1996). However, because the lipophilic POPs accumulate in the breast milk of lactating women and because the milk is removed from the woman's body, the half-life of POPs in lactating women is about six months (LaKind and others, 2000).

Nonpersistent Organic Chemicals

Nonpersistent organic chemicals, such as current-use pesticides, phthalates, and VOCs (Needham and others, 2005a), can be much more challenging to measure. Depending on the scenario, their primary routes of exposure for the general population are generally ingestion or inhalation. These chemicals are rapidly metabolized and their metabolites are eliminated in urine (Figure 13.1). The deposition matrices are minor matrices for monitoring because only small amounts of the chemical are deposited in the body. The major matrices for assessing exposure are excreta. Blood has also been used as a matrix for biomonitoring. Nonpersistent chemicals tend to have very short half-lives in blood and the concentrations are

FIGURE 13.1. HYPOTHETICAL POSTEXPOSURE FATE OF A NONPERSISTENT TOXICANT IN BLOOD AND URINE.



Source: Used with permission from Needham and Sexton (2000).

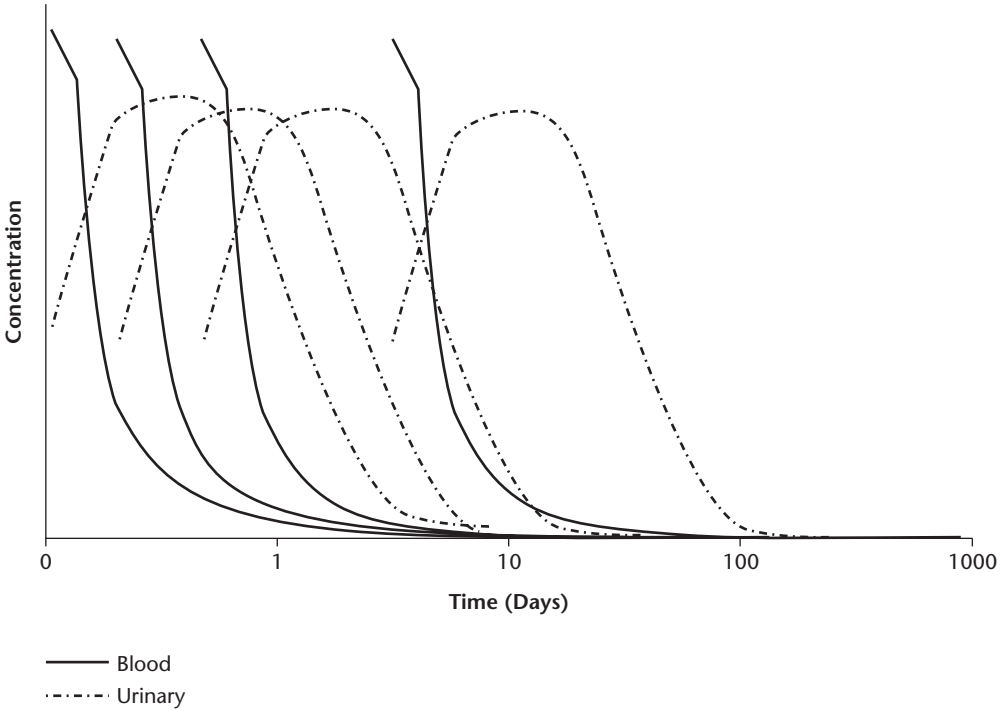
usually about three orders of magnitude lower than urinary metabolite levels (Barr and others, 1999). Thus, if blood is used as a matrix, the sensitivity of the analytical method and the matrix volume available for analysis may become important. Blood can also be a valuable matrix for measuring biomolecular adducts such as hemoglobin, albumin, or DNA adducts such as DNA-PAH adducts.

Saliva has also been explored as a matrix for measuring selected nonpersistent chemicals such as atrazine (Lu, Anderson, Morgan, and Fenske, 1998). The existing data indicate that depending on the degree of protein binding that may occur, saliva levels can be considerably lower than blood levels of a nonpersistent

chemical ; thus, a very sensitive analytical technique is required. Further research on additional chemicals and the relation of these measurements to more commonly used approaches is required before this can routinely be used for analysis.

To evaluate fetal exposures, maternal samples collected throughout pregnancy may be used. However, because these chemicals are, by definition, nonpersistent, urine or blood measurements made at a single point in time during pregnancy will only address the exposures that may have occurred in the previous few days, unless the exposure is continuous (e.g., pervasive air levels of a chemical resulting from smokers in the home) or continual (e.g., eating the same foods daily with measurable levels of pesticides) (Figure 13.2). To circumvent this problem, multiple biological samples can be taken every few days during pregnancy; however, this can be costly, logistically difficult to collect and store, and may present an

FIGURE 13.2. HYPOTHETICAL POSTEXPOSURE FATE FROM CHRONIC EXPOSURE TO A NONPERSISTENT TOXICANT IN BLOOD AND URINE.



Source: Used with permission from Barr, Wang, and Needham (2005a).

undue burden on the participant. An alternative may be to collect multiple samples over particularly vulnerable stages of the pregnancy if such stages can be appropriately identified. Another potential approach is to measure nonpersistent chemicals in fetal matrices such as cord blood or meconium.

Bioaccumulative Metals

Bioaccumulative metals persist in the environment and bioaccumulate in humans. This group of chemicals includes some forms of mercury, lead, and cadmium (Needham and others, 2005a). For example, lead is readily absorbed, particularly in children, with distribution from the blood to its storage depots, bone and teeth (Aufderheide and Wittmers, 1992). Both metabolism and excretion are slow, so monitoring lead levels is more straightforward. The best matrices to use would be blood, bone, and teeth. For general population exposures to mercury, methylmercury is the form of highest concern. Blood, hair, and nails are viable matrices for measuring methylmercury levels.

Nonbioaccumulative Metals

Nonbioaccumulative metals are readily absorbed into the body, and although some proportion may distribute to various tissues, most will pass through the body rapidly. These metals are typically measured in urine (Horng, Tsai, and Lin, 1999). However, to gain a longer-term dosimeter for exposure, arsenic can also be measured in hair (Wilhelm and Idel, 1996) and nails (Lin, Huang, and Wang, 1998).

Criteria Pollutants and Bioallergens

In general, biomonitoring has a limited role in the measurement of criteria pollutants (e.g., CO, NO_X, ozone) and bioallergens (e.g., pollen, endotoxins) (Needham and others, 2005a). Exposure to carbon monoxide can be assessed by measuring the carboxyhemoglobin adduct (Shenoi, Stewart, and Rosenberg, 1998; Smith and others, 1998) or expired CO (Lapostolle and others, 2001; Paredi, Kharitonov, and Barnes, 2002) in blood and breath, respectively. The adduct measurements provide a longer-term dosimeter for the exposure than breath measurements because hemoglobin has a lifetime of about four months.

Bioallergen response can be measured by IgE in maternal, cord, or child blood (Goodman and Leach, 2004; Lee and others, 2004; Carrer and Moscato, 2004). In addition, certain endotoxins or metabolites may be measured in blood or urine samples (Makarananda and others, 1998; Malir and others, 2004). Typically, the endotoxin measurements reflect a more recent exposure, similar to nonpersistent chemical exposures.

Assessing Exposure Throughout the Life Cycle

Biomonitoring measurements have been used for many years to assess exposures in adults (Ashley and others, 1994; Pirkle, Needham, and Sexton, 1995; Blount and others, 2000), and to some extent, in adolescents and children (Fenske and others, 2000; Adgate and others, 2001). Biomonitoring of fetuses, infants, and small children has been performed much less frequently, if at all. Various biological matrices have been used or considered for assessing environmental exposures throughout the life cycle (Table 13.1). The mother or pregnant woman has generally been used as a surrogate to evaluate fetal exposures. However, for many chemicals, their ability to transfer from the mother to the fetus is not known and the relationship between maternal and fetal chemical levels has not been defined. Another potential option to evaluate fetal exposures is the use of meconium as a matrix of measurement since it begins accumulating in the bowels of the infant during the second trimester (Ostrea and others, 1994; Bearer and others, 2003; Bearer, 2003). However, meconium use has many limitations. Meconium measurements are still in their infancy of development, and to date, no reliable way to relate these measurements to measurements in more commonly used matrices (e.g., urine and blood) exists. In addition, no information is gleaned from exposures that occurred in the first trimester. However, many have been show to correlate well with reported maternal exposures to tobacco (Ostrea and others, 1994), drugs of abuse (Ostrea, 1999), and alcohol consumption (Bearer and others, 2003), and this matrix shows promise for other chemical exposures of concern (Whyatt and Barr, 2001).

The period from birth through age one is also very important (Needham and Sexton, 2000; Needham and others, 2005a, 2005b). During this time, the infants may be breast-feeding, so they may be exposed to chemicals via breast milk. In addition, their microenvironments are often close to the floor and substantially different from those of older children or adults. At this age, probably only urinary chemical measurements and breast milk measurements can be made. Urine volume will likely be limited, usually 10 mL or less.

Once children start school, another environment with potential chemical contamination is included in the exposure scenario; however, biological sample collections become easier. At this stage in life, some blood can be collected, but it is often limited to a small amount. Urine and saliva samples can also be readily collected. As children approach adolescence and adulthood, more biological samples and/or a greater quantity of a matrix can be collected. At this life stage, perhaps up to 100 mL of blood can be collected for various measurements; urine is typically plentiful.

TABLE 13.1. IMPORTANCE OF VARIOUS BIOLOGICAL MATRICES FOR MEASURING EXPOSURE DURING THE DIFFERENT LIFE STAGES.

		Fetal Period					
Matrices	**Adult Preconception**	**First**	**Second**	**Third**	**0–1 Year**	**2–3 Years**	**4–11 Years**
			Persistent Organic Pollutants				
Blood (whole)	1	na	na	na	1	1	1
Blood (serum)	1	na	na	na	1	1	1
Blood (plasma)	1	na	na	na	1	1	1
Urine	3	na	na	na	3	3	3
Saliva	3	na	na	na	na	3	3
Hair	3	na	na	na	3	3	3
Nails	3	na	na	na	3	3	3
Adipose tissue	1	na	na	na	na	na	na
Feces	3	na	na	na	3	3	3
Semen	3	na	na	na	na	na	na
Breath	3	na	na	na	na	3	3
Teeth	na	na	na	na	na	na	3
Cord blood	1	1	1	1	3	3	3
Meconium	3	2	2	2	3	3	3
Milk (maternal)	1	1	1	1	1	3	3
Blood (maternal)	1	1	1	1	1	3	3
Urine (maternal)	3	3	3	3	3	3	3
Hair (maternal)	3	3	3	3	3	3	3
Adipose tissue (maternal)	1	1	1	1	1	3	3
			Nonpersistent Organic Chemicals				
Blood (whole)	1	na	na	na	1	1	1
Blood (serum)	1	na	na	na	1	1	1

Blood (plasma)	1	na	na	na	1	1	1
Urine	1	na	na	na	1	1	1
Saliva	2	na	na	na	na	2	2
Hair	3	na	na	na	3	3	3
Nails	3	na	na	na	3	3	3
Adipose tissue	3	na	na	na	na	na	na
Feces	3	na	na	na	3	3	3
Semen	3	na	na	na	na	na	na
Breath	3	na	na	na	na	3	3
Teeth	3	na	na	na	na	na	3
Cord blood	3	3	3	1	3	3	3
Meconium	3	3	2	2	3	3	3
Milk (maternal)	3	3	3	3	2	3	3
Blood (maternal)	3	1	1	1	3	3	3
Urine (maternal)	3	1	1	1	3	3	3
Hair (maternal)	3	3	3	3	3	3	3
Adipose tissue (maternal)	3	3	3	3	3	3	3
Volatile Organic Chemicals							
Blood (whole)	1	na	na	na	1	1	1
Blood (serum)	3	na	na	na	3	3	3
Blood (plasma)	3	na	na	na	3	3	3
Urine	2	na	na	na	2	2	2
Saliva	3	na	na	na	na	3	3
Hair	3	na	na	na	3	3	3
Nails	3	na	na	na	3	3	3
Adipose tissue	2	na	na	na	na	na	na
Feces	3	na	na	na	3	3	3
Semen	3	na	na	na	na	na	na
Breath	1	na	na	na	na	1	1
Teeth	3	na	na	na	na	na	3

TABLE 13.1. IMPORTANCE OF VARIOUS BIOLOGICAL MATRICES FOR MEASURING EXPOSURE DURING THE DIFFERENT LIFE STAGES, Cont'd.

		Fetal Period					
Matrices	**Adult Preconception**	**First**	**Second**	**Third**	**0–1 Year**	**2–3 Years**	**4–11 Years**
Cord blood	3	3	3	1	3	3	3
Meconium	3	3	3	3	3	3	3
Milk (maternal)	3	3	3	3	2	3	3
Blood (maternal)	3	1	1	1	3	3	3
Urine (maternal)	3	3	3	3	3	3	3
Hair (maternal)	3	3	3	3	3	3	3
Adipose tissue (maternal)	3	3	3	3	3	3	3
			Bioaccumulative Inorganic Chemicals				
Blood (whole)	1	na	na	na	1	1	1
Blood (serum)	3	na	na	na	3	3	3
Blood (plasma)	3	na	na	na	3	3	3
Urine	2	na	na	na	2	2	2
Saliva	3	na	na	na	na	3	3
Hair	2	na	na	na	2	2	2
Nails	2	na	na	na	2	2	2
Adipose tissue	3	na	na	na	na	na	na
Feces	3	na	na	na	3	3	3
Semen	3	na	na	na	na	na	na
Breath	3	na	na	na	na	3	3
Teeth	3	na	na	na	na	na	2
Cord blood	2	2	2	1	3	3	3
Meconium	3	2	2	2	3	3	3
Milk (maternal)	3	3	3	3	3	3	3
Blood (maternal)	1	1	1	1	3	3	3
Urine (maternal)	3	2	2	2	3	3	3
Hair (maternal)	2	2	2	2	3	3	3
Adipose tissue (maternal)	3	3	3	3	3	3	3

Nonbioaccumulative Inorganic Chemicals							
Blood (whole)	3	na	na	na	3	3	3
Blood (serum)	3	na	na	na	3	3	3
Blood (plasma)	3	na	na	na	3	3	3
Urine	1	na	na	na	1	1	1
Saliva	3	na	na	na	na	3	3
Hair	2	na	na	na	2	2	2
Nails	2	na	na	na	2	2	2
Adipose tissue	3	na	na	na	na	na	na
Feces	3	na	na	na	3	3	3
Semen	3	na	na	na	na	na	na
Breath	3	na	na	na	na	3	3
Teeth	3	na	na	na	na	na	3
Cord blood	3	3	3	3	3	3	3
Meconium	3	3	3	3	3	3	3
Milk (maternal)	3	3	3	3	3	3	3
Blood (maternal)	3	3	3	3	3	3	3
Urine (maternal)	3	1	1	1	3	3	3
Hair (maternal)	2	2	2	2	3	3	3
Adipose tissue (maternal)	3	3	3	3	3	3	3
Criteria Pollutants (CO only)							
Blood (whole)	1	na	na	na	1	1	1
Blood (serum)	3	na	na	na	3	3	3
Blood (plasma)	3	na	na	na	3	3	3
Urine	3	na	na	na	3	3	3
Saliva	3	na	na	na	na	3	3
Hair	3	na	na	na	3	3	3
Nails	3	na	na	na	3	3	3
Adipose tissue	3	na	na	na	na	na	na
Feces	3	na	na	na	3	3	3
Semen	3	na	na	na	na	na	na
Breath	1	na	na	na	na	1	1

TABLE 13.1. IMPORTANCE OF VARIOUS BIOLOGICAL MATRICES FOR MEASURING EXPOSURE DURING THE DIFFERENT LIFE STAGES, Cont'd.

		Fetal Period					
Matrices	**Adult Preconception**	**First**	**Second**	**Third**	**0–1 Year**	**2–3 Years**	**4–11 Years**
Teeth	3	na	na	na	na	na	3
Meconium	3	3	3	3	3	3	3
Milk (maternal)	3	3	3	3	3	3	3
Blood (maternal)	3	1	1	1	3	3	3
Urine (maternal)	3	3	3	3	3	3	3
Hair (maternal)	3	3	3	3	3	3	3
Adipose tissue (maternal)	3	3	3	3	3	3	3
			Bioallergens				
Blood (whole)	1	na	na	na	1	1	1
Blood (serum)	1	na	na	na	1	1	1
Blood (plasma)	1	na	na	na	1	1	1
Urine	2	na	na	na	2	2	2
Saliva	3	na	na	na	na	3	3
Hair	3	na	na	na	3	3	3
Nails	3	na	na	na	3	3	3
Adipose tissue	3	na	na	na	na	na	na
Feces	3	na	na	na	3	3	3
Semen	3	na	na	na	na	na	na
Breath	3	na	na	na	na	3	3
Teeth	3	na	na	na	na	na	3
Cord Blood	3	1	1	1	3	3	3
Meconium	3	3	3	3	3	3	3
Milk (maternal)	3	3	3	3	3	3	3
Blood (maternal)	3	1	1	1	3	3	3
Urine (maternal)	3	2	2	2	3	3	3
Hair (maternal)	3	3	3	3	3	3	3
Adipose tissue (maternal)	3	3	3	3	3	3	3

	Amount of Matrix Reasonably Obtainable at Each Life Stage						
Blood (whole)	100	0	0	0	9	22	38
Blood (serum)	40	0	0	0	3.6	8.8	15.2
Blood (plasma)	40	0	0	0	3.6	8.8	15.2
Urine	> 100	0	0	0	1–10	10–20	30–50
Saliva	2	0	0	0	0	1–2	1–2
Hair	0.5–4g	0	0	0	< 0.5g	0.5–2g	0.5–4g
Nails	*	0	0	0	*	*	*
Adipose tissue	10g	0	0	0	0	0	0
Feces	10g	0	0	0	3g	5g	10g
Semen	2	0	0	0	0	0	0
Breath	*	0	0	0	*	*	*
Teeth	0	0	0	0	0	0	6–10
Cord blood	30–60	30–60	30–60	30–60	na	na	na
Meconium	2g	2g	2g	2g	na	na	na
Milk (maternal)	> 100	> 100	> 100	> 100	> 100	na	na
Blood (maternal)	100	100	100	100	100	100	100
Urine (maternal)	> 100	> 100	> 100	> 100	> 100	> 100	> 100
Hair (maternal)	*	*	*	*	*	*	*
Adipose tissue (maternal)	10g	10g	10g	10g	0	0	0

Source: Used with permission from Barr, Wang, and Needham (2005).

Note: Matrices available for assessment in 12- to 21-year-olds are similar to that of adults.

1 indicates important matrix for most chemicals in category.

2 indicates important matrix for one or two chemicals in category.

3 indicates not an important matrix for assessing exposure for chemicals in the category.

na = matrix not viable for life stage because it cannot be feasibly collected, the chemical cannot typically be measured in the matrix, or it doesn't represent exposures in a given life stage

* = unknown amount

Biological Matrices for Exposure Assessment

The two primary matrices used to assess human exposure to chemicals are urine and blood (e.g., serum, plasma, and blood cells) (Pirkle, Needham, and Sexton, 1995; Barr and others, 1999; Needham and Sexton, 2000).

Blood or Blood Products

Many persistent and nonpersistent chemicals can be measured in blood (Angerer, 1988; Angerer and Horsch, 1992; Leng, Kuhn, and Idel, 1997; Barr and others, 2002). Although the amount of blood is nearly the same in all adults, the chemical composition of blood, such as lipid content, varies among individuals and within an individual, especially after eating (Phillips and others, 1989a). Blood concentrations of lipophilic chemicals are routinely normalized using blood lipid concentrations; that allows a direct comparison of their concentrations within and among individuals, irrespective of the time of day the blood was collected. However, other chemicals that can be measured in blood may not vary based upon the blood lipid content. For example, fluorinated chemicals in blood are not dependent upon the lipid content; instead they bind to blood albumin (Jones and others, 2003). Therefore, these measurements should not be adjusted on the basis of blood lipid content; however, if deemed appropriate, other adjustments, such as for albumin content, may be required.

Measuring a chemical in blood is inherently advantageous (Barr and others, 1999). Because we know how much blood is in the body, we can calculate the body burden more accurately than if we measure the chemical or its metabolite in urine. However, blood collection is invasive, which may severely limit the ability to collect it from infants and small children. In addition, nonpersistent chemicals are usually found in very low concentrations in blood (Barr and others, 1999, 2002). Also, if testing is not performed soon after sample collection, which will likely be the case in the NCS, long-term storage of blood may be problematic, depending upon what form of blood is being stored. Storage conditions and stability of various matrices and chemicals are shown in Table 13.2.

Urine

One of the major advantages of using urine in biomonitoring is the ease of its collection for spot urine samples (Barr and others, 1999; Needham and others, 2005a); however, the collection of 24-hour urine voids can be very cumbersome and result in nonadherence (Kissel and others, 2005). Therefore, spot urine samples, whether first-morning voids or convenience samplings, are most generally

TABLE 13.2. STORAGE REQUIREMENTS AND CHARACTERISTICS FOR BIOLOGICAL MATRICES AND CHEMICAL CLASSES.

Chemical Class	Chemicals	Storage Temperature	Matrix	Matrix Stability	Chemical Stability	Container	Preservative Requirements
Persistent organic compounds	All	–70°C	milk	years	years	polypropylene NO glass or teflon	na
	All	–70°C	serum/plasma	years	years	polypropylene NO glass or teflon	na
	All	–70°C	adipose tissue	years	years	polypropylene NO glass or teflon	na
Nonpersistent organic compounds	All	–70°C	urine	years	years	polypropylene or glass	na
	Phthalates	–70°C	serum/plasma	years	years	polypropylene or glass	125 µmol H_3PO_4/mL matrix.
	Pesticides	–70°C	serum/plasma	~5years	up to 1 year (less for many of the reactive pesticides)	polypropylene or glass	none
	Others	–70°C	serum/plasma	years	years	polypropylene or glass	na
Volatile organic chemicals		4°C	whole blood	10 weeks	> 10 weeks	heat and vacuum-purged glass gray top vacutainer; restore sterility	NaF/ potassium oxalate
Bioaccumulative metals		4°C	whole blood	indefinitely	indefinitely	Purple top liquid EDTA vacutainer; second or third draw	na
Nonbioaccumulative metals		–20°C	urine	indefinitely	indefinitely	prescreened	for Hg, Triton X 100, sulfamic acid
		room temperature	hair	indefinitely	indefinitely	zipper bag	na

Source: Used with permission from Barr, Wang, and Needham (2005).

used for biomonitoring purposes. The major disadvantages of spot urine samples include the variability of the volume of urine and the concentrations of endogenous and exogenous chemicals from void to void (Barr and others, 1999; Kissel and others, 2004). The issue on how best to adjust the urinary concentrations of environmental chemicals in a manner analogous to the adjustment of the concentrations of lipophilic chemicals in blood is a subject of continued research (Barr and others, 2005b). Adjustment using urinary creatinine concentrations (i.e., dividing the analyte concentration by the creatinine concentration [in g creatinine/L urine]) is the most routinely used method for correcting for dilution. Analyte results are then reported as weight of analyte per gram of creatinine (e.g., μg of analyte/g creatinine). This may work well when comparing analyte levels in a single individual because the intraindividual variation in creatinine excretion is relatively low; however, for diverse populations the interindividual variation is extremely high (Barr and others, 2005).

Breast Milk and Adipose Tissue

Many of the same chemicals measured in blood have been found in breast milk (LaKind, Berlin, and Naiman, 2001) and adipose tissue. Breast milk measurements are unique in that they not only provide data on ingestion exposures for the infant but also are indicators of maternal exposures. Breast milk and adipose tissue are lipid-rich matrices, more so than blood, so similar lipid adjustments are required for reporting concentrations of lipophilic analytes. In general, these lipophilic analytes partition among the lipid stores in blood, breast milk, and adipose tissue on nearly a 1:1:1 basis (Patterson and others, 1987). More laboratory work needs to be done on the partitioning of less bioaccumulative analytes in these matrices.

Alternative Matrices

Chemicals have been successfully measured in alternative matrices such as saliva (Lu, Anderson, Morgan, and Fenske, 1998; Bernert, McGuffey, Morrison, and Pirkle, 2000), meconium (Ostrea and others, 1994; Bearer and others, 1999; Ostrea, 1999; Whyatt and Barr, 2001; Bearer and others, 2003), amniotic fluid (Foster, Chan, Platt, and Hughes, 2002; Bradman and others, 2003), and breath (Pellizzari, Wallace, and Gordon, 1992). Because many of these matrices are not commonly analyzed, the resulting chemical concentration data are more difficult to relate to measurements made in the more commonly used matrices such as urine, blood, or breast milk; consequently, they may be more difficult to relate to exposure. However, because many of these matrices are available and could pro-

vide potentially useful information, we should not discount them. Instead, we should conduct preliminary studies evaluating the partitioning of chemicals in the various matrices to allow for comparison of data among matrices.

Measurement Method Specificity and Sensitivity Requirements

The *specificity* of an analysis method for a particular exposure and *sensitivity,* the ability to measure the chemical at the desired level, are critical parameters for analysis methods, and both must be considered when deciding which matrix to measure. The half-life of a chemical may affect the sensitivity requirement; however, because persistent chemicals have long half-lives, it is not nearly as important as it is for nonpersistent chemicals, which metabolize rapidly. For instance, in adult men, 2,3,7,8-tetrachlorodibenzo-p-dioxin has a half-life of about 7.6 years (Pirkle and others, 1989). Therefore, to assess exposure over a period of time, for example, nine months, the sample could be collected at any time period within the nine months or even afterwards; the biological measurement information would still be useful for accurate exposure classification (e.g., exposure quartiles—people whose exposure is high, medium, low, or none). When measuring exposure to persistent chemicals by analyzing adipose tissue, it does not make much difference which portion of the body the sample is taken from; however, because blood is easy to collect and readily available, blood is an ideal medium in which to measure persistent chemicals. In lactating women, milk is also frequently used.

Nonpersistent chemicals have half-lives of hours or minutes; therefore, the postexposure fate of a nonpersistent chemical is dramatically different (see Figure 13.1) (Needham and Sexton, 2000). After each exposure, the concentration of the chemical in blood declines rapidly. The window of opportunity for measuring nonpersistent chemicals in blood is narrow and requires the use of a very sensitive technique. By measuring these chemicals in blood as the intact, or parent, chemical we gain information on the exact chemical to which someone was exposed. For example, if someone was exposed to chlorpyrifos, we can measure chlorpyrifos in the blood rather than its metabolite, which is formed from more than one parent chemical and is also the same chemical as environmentally degraded chlorpyrifos. In addition to blood, certain nonpersistent chemicals, such as cotinine, have been measured in saliva because cotinine is in equilibrium in blood and saliva.

In urine, we generally measure metabolites of the chemical that may lack the desired specificity for analysis; however, measurements in urine allow a much wider window of opportunity in which to take the sample. Generally, we assess exposure to nonpersistent chemicals by measuring their metabolites in urine, even though this method may not have the specificity of the blood measurement.

When chronic exposure to a nonpersistent chemical occurs, the exposure is continually replenishing the chemical in the blood and urinary elimination may reach a steady state. Therefore, urine becomes a better matrix for measurement because we integrate exposure over a longer period.

Biomolecular Adducts

Persistent and nonpersistent chemicals can also react with biomolecules such as DNA, hemoglobin, or fatty acids to form biomolecular adducts (Angerer, Goen, Kramer, and Kafferlein, 1998; Schettgen, Broding, Angerer, and Drexler, 2002). By measuring these adducts, we are able to increase the amount of time after exposure that we can measure a nonpersistent chemical because the amount of time the adduct remains in the body is largely dependent upon the lifetime of the biomolecule itself (Needham and Sexton, 2000). For example, the average lifespan of a red blood cell is about 120 days. If a chemical formed an adduct with hemoglobin on the day a red blood cell was created, the adduct should remain in the body for about four months, allowing a much longer time after exposure to collect the sample. Other adducts are formed with DNA, albumin, and other prominent proteins. Because an adduct is not formed from every chemical molecule to which one is exposed, adduct measurements must be very sensitive, and usually a large amount of matrix is required. In addition, the measurements are usually cumbersome and time-consuming, so the analytical throughput is very low and the cost is very high.

When measuring persistent chemicals, we do not gain much advantage by measuring them as adducts. Blood is still the matrix of choice because the concentration is higher in blood and we have a wide window of opportunity (Barr and Needham, 2002). To form an adduct, the chemical must have an electrophilic site for the nucleophile on the biomolecule (usually sulfur or nitrogen) to attack, which forms a covalent bond; hence, the adduct is formed.

Sampling Time Frame

For persistent organic chemicals, the time frame for sampling is reasonably straightforward. In general, a blood sample can be taken at any time up to several years after exposure has occurred and the exposure can still be accurately identified; however, we will not have any information about when the exposure occurred. For example, if a PCB concentration of 1,000 ng/g lipid was measured in a blood sample, we do not know if a recent exposure to this amount of PCB occurred or whether a larger exposure occurred many years ago; although a portion of the PCB has been eliminated from the body over time, this amount is still

circulating in the bloodstream. By coupling questionnaire data with these biological measurements, we may be able to gain some information on the timing of the exposure (e.g., breast feeding, subsistence food consumption).

The sampling time frame for nonpersistent chemicals is not straightforward. Because these chemicals have short biological half-lives, the samples, whether blood or urine, must be collected soon after the exposure in order to appropriately assess the exposure. If the primary exposure medium is air and the exposure is continuous, a first-morning void urine sample is probably the best biological sample for measuring the exposure. However, if the exposure is from a source related to personal grooming (e.g., VOCs from showers or phthalates from personal care products), a first-morning void urine sample or an early-morning blood sample (prior to showering) would likely miss the exposure from the following day. Rather, a late-morning or early-afternoon sample would more accurately characterize the daily exposure to these chemicals. Similarly, samples designed to evaluate dietary exposures such as pesticides should be collected several hours after mealtimes so that these exposures can be identified.

In general, sample collection for nonpersistent chemical measurements should reflect the residence time of the chemical in each individual matrix. The half-lives of nonpersistent chemicals in blood are typically much less than in urine samples. Thus, we may need to collect blood samples within minutes or hours after the exposure whereas we may collect urine samples several hours, or in some instances days, after the exposure. Saliva samples will typically mimic blood, whereas meconium samples may provide a longer window for capturing the exposure. Measurements of biomolecular adducts need to consider the lifetime of the biomolecule rather than the lifetime of the chemical in the particular matrix; however, more adduct will likely be present immediately after exposure than several weeks afterward.

Collecting Samples from Infants and Children

We often encounter difficulty when collecting urine samples from infants and children who are not toilet-trained. The traditional approach is similar to that in a clinical setting, using an infant urine collection bag. This technique is rather straightforward; however, it is usually bothersome to the child and often requires that the child be given liquids to encourage urination within a given time frame. Encouraging urination with drinks will usually dilute the urine and make the analytical measurement more difficult. Other approaches for urine collection, primarily from cloth diapers or cotton inserts, have also been investigated (Hu and others, 2000; Calafat, Needham, Silva, and Lambert, 2004). Another approach

of ongoing investigation is the collection of the target analytes directly from the coagulated gel matrix of disposable diapers (Hu, Beach, Raymer, and Gardner, 2004). If proved viable for isolating a broad array of target analytes, this method of collection would be most attractive as it is the least burdensome on the participant and the most logistically practical.

Temporal Variability in Urine and Blood Samples

The variability of nonpersistent target analyte levels in samples collected from an individual over time is of concern whether the sample is biological or environmental. Temporal variability can include the variation of a given chemical in multiple samples collected on a single day or can include variation over days, months, or seasons. For chronic exposures to nonpersistent chemicals, the exposure is repeated. Thus, the amount in a given sample would likely represent the average exposure. However, for episodic exposures, the variability is often greater. For a urine matrix, a 24-hour urine sample is preferred; however, this can be burdensome on the participant and often logistically difficult. If a 24-hour sample cannot be obtained, a first-morning void is often preferred because the urine is more concentrated and the collection represents a longer window of accumulation (usually >8 hr). However, a first-morning collection may not be ideal for certain exposures because the timing for capturing the exposure is off. To evaluate daily, monthly, and/or seasonal variations of analytes in urine, sequential samples are often taken days and weeks apart to evaluate how the intraindividual variation over time compares to the interindividual variation and whether an accurate classification of exposure is possible. These studies are important in interpreting the biomonitoring data and should at some level be considered in the NCS. These data will help to determine whether multiple samples should be taken and at what intervals. In most instances, sampling for nonpersistent chemicals will require multiple samples taken at regular intervals.

Methodology

Organic Chemicals

Most methods for measuring organic chemicals in biological matrices use a sample preparation step to isolate the target chemical(s) from the matrix; it is an analytical technique with a detection system, data processing, and quality assurance processes (Needham, Barr, and Calafat, 2005).

The sample preparation steps are usually the most common source of analytic error, whether systematic or random (Barr and others, 1999). If the chemi-

cal is inherently incompatible with the analytic system that follows, a chemical derivatization or reduction procedure may also be required. The addition of steps into the sample preparation procedure usually increases the overall imprecision of the method.

Common analytical techniques for separation of individual chemicals include gas chromatography, high-performance liquid chromatography, or capillary electrophoresis, which are coupled in-line to a detection system. Common detection systems include mass spectrometry, electron capture, flame photometric, nitrogen phosphorus, fluorescence, and UV absorbance detection. Of the detection systems, mass spectrometers provide the most specificity, whereas UV absorbance detection usually provides the least (Barr and others, 1999). Most mass spectrometry-based methods have limit of detections (LODs) in the pg to ng/g matrix range, typically adequate enough to detect levels in the general population when 1 to 10 g of matrix is used (Table 13.3). The analytical imprecision usually ranges from 10 to 20 percent.

Other analytic techniques that are often employed with organic chemicals are immunoassays and bioassays (Brady, Fleeker, Wilson, and Mumma, 1989; Biagini and others, 1995). For these techniques, a sample preparation step to isolate the chemical from the matrix may or may not be used. Many immunoassays and bioassays are commercially available for selected chemicals. However, developing one for a new chemical is a lengthy process that typically requires first the generation and isolation of antibodies and then the development of the assay itself. Usually, UV, fluorescence, or radioactivity detection is used for the assays. Each one may be very specific for a given chemical or may have a great deal of cross-reactivity that may limit its utility. All of their LODs can vary widely; however, many have adequate sensitivity for measuring levels in the general population.

Because organic chemicals are measured using expensive instrumentation and require highly trained analysts, these measurements are usually costly. The most selective and sensitive methods are usually the most complex and can range in cost from $100 to $1,500 per sample analyzed (see Table 13.3). However, many of the analyses are multianalyte panels, so the cost per analyte per sample is much more reasonable. In general, immunoassays are less specific and less complex; therefore, their cost is usually less than $50 per test, but usually only one chemical can be measured per test, and new chemicals cannot be easily incorporated into the method.

Inorganic Chemicals

The sample preparation process for inorganic chemicals is typically much simpler than for organic chemicals. In some instances, the sample matrix just needs to be diluted with water prior to analysis. However, special precautions must be taken

TABLE 13.3. CHARACTERISTICS OF ANALYTICAL METHODS FOR MEASURING CHEMICAL CLASSES IN BIOLOGICAL MATRICES.

Chemical Class	Most Typical Matrices	Methodology Used	Detection Limits	Relative Standard Deviations	Throughput per Day	Volume for Analysis	Cost
Persistent Organic Chemicals	Blood (serum or plasma)	GC-HRMS	fg/g–pg/g	15–25%	20	2–30mL	H
	Milk	GC-HRMS	fg/g–pg/g	15–25%	20	2–30mL	H
	Adipose tissue	GC-HRMS	fg/g–pg/g	15–25%	10	1–2g	H
Nonpersistent Organic Chemicals	Blood (serum or plasma)	GC-HRMS; HPLC-MS/MS	pg/g–ng/g	10–20%	30	2–10mL	H
	Urine	GC-MS/MS; HPLC-MS/MS; immunoassay	pg/g–ng/g	10–15%	50	1–4mL	H
	Saliva	GC-HRMS; GC-MS/MS; HPLC-MS/MS	pg/g–ng/g	10–15%	30	1–4mL	H
	Milk	GC-HRMS; GC-MS/MS; HPLC-MS/MS	pg/g–ng/g	10–15%	40	1–10mL	H
Volatile Organic Chemicals	Blood (whole)	GC-MSD;GC-HRMS	pg/g	10–20%	10–20	5–10mL	M
	Breath	GC-MSD	ng/g	10–20%	20	10–20mL	M
Bioaccumulative Metals	Blood (whole)	ICP-MS	ng/g	10–15%	40	1–2mL	M
	Hair	ICP-MS	ng/g	10–15%	40		M
Nonbioaccumulative Metals	Blood (whole)	ICP-MS	ng/g	10–15%	40	1–2mL	M
	Urine	ICP-MS	ng/g	10–15%	40	1–5mL	M
	Hair	ICP-MS	ng/g	10–15%	40		M
Cost Categories	Low (L)	$0–100					
	Medium (M)	$100–500					
	High (H)	> $500					

Source: Used with permission from Barr and Needham (2002).

Note: GC = gas chromatography; HRMS = high resolution mass spectrometry; MS = mass spectrometry; ICP = inductively coupled plasma; MS/MS = tandem mass spectrometry; MSD = mass selective detector; HPLC = high performance liquid chromatography.

to avoid contamination, both preanalytically and in the analytic system. For example, prescreened collection materials should be used for sample collection, all analytic supplies should be appropriately free of the target chemicals, and special clean rooms may be required for analysis.

Inorganic chemicals are usually measured using atomic absorption spectrometry (AAS) or inductively coupled plasma-mass spectrometry (ICP-MS). In some instances, a dynamic collision cell may also be used to eliminate potentially interfering salts from the system. When various forms of inorganic chemicals are speciated, such as for arsenic or mercury, the AAS or ICP-MS will be preceded in-line by a chromatographic unit. For lead screening, an efficient portable lead analyzer can be used for in-field measurements.

Similar to organic chemicals, since expensive instrumentation is used, the analyses are usually costly, ranging from $50 for single chemicals to $250 for multichemical panels (see Table 13.3). The LODs are comparable to those of organic chemicals and are suitable for general population studies. Because the handling of the sample is usually minimal, the precision is usually better, within 5 to 10 percent.

Quality Assurance and Control

A vital component of all biomonitoring methodology is a sound quality assurance/control program (QA/QC). QA/QC programs typically require strict adherence to protocols and multiple testing procedures that easily allow the detection of systematic failures in the methodology. The requirements for QA/QC are described in detail in Needham and others (2005a). The general requirement for an analytical laboratory performing a method must be that it is able to demonstrate the method's accuracy, precision, specificity, linearity and range, limit of detection, and ruggedness/robustness. Once demonstrated, a quality assurance/quality control program must be established and enforced to easily allow the detection of systematic failures in the methodology and ensure that these defined requirements are being maintained over time and among laboratories (Needham, Ryan, and Fürst, 2002). The utilized testing procedures can include proficiency testing to ensure accuracy as measured against a known reference material; repeat measurements of known materials to confirm the validity of an analytical run and measure analytical precision; "round robin" or interlaboratory studies to confirm reproducible measurement values among laboratories; regular verification of instrument calibration; daily assurance of minimal laboratory contamination by analyzing "blank" samples; and cross-validations to ensure that multiple analysts and instruments obtain similar analytical values. In addition, some public health laboratories in the United States have been certified by the Health Care Finance

Administration (HCFA) to comply with all QA/QC parameters outlined in the Clinical Laboratories Improvement Amendment (1988). Quality assurance/quality control measures are applicable not just to the analytical method but to all aspects of the measurement process—from sampling design, sample collection (need to ensure no or a defined amount of contamination), transport and storage of samples, analytical method, and data reporting. Therefore, all aspects of the measurement process must be subject to a stringent QA/QC protocol. Also, any new analytical method or any change in the measurement process must be documented and validated against the method being used. Many parameters for implementing or improving a quality assurance program have been published (Taylor, 1990; Schaller, Angerer, and Lehnert, 1991).

Conclusions

As a part of the National Children's Study, many researchers will be competing for the matrices available for biological measurements. We should refine existing methodology to include as many chemicals as possible using as little blood or urine as possible. In addition, we should investigate ways of using more readily available, less-invasive matrices. We must consider all matrices and analytes that integrate exposure over longer periods in order to maximize the exposure information gained on an individual using the matrices available during a particular life stage.

Another consideration is the quality and cost of analyses. We should evaluate low-cost techniques such as immunoassays for some applications. In addition to requiring smaller volumes of samples, these analyses are often less expensive and require less training to effectively perform the analyses. Before using these less-costly techniques, they should be compared to more commonly used techniques to confirm that quality exposure assessment information, as rated by the method sensitivity, accuracy, specificity, and precision, can be obtained and that the resulting data will be comparable to data existing in the literature.

In general, persistent organic chemicals are more readily measured in blood-based matrices or other lipid-rich matrices. Maternal measurements serve as good surrogates for fetal exposures—and even early-childhood exposures if levels are not reduced by breast-feeding. Assessment of exposure to nonpersistent chemicals is the most challenging, but it can be measured in multiple matrix types. Urine is the most commonly used matrix for measurement of these chemicals, but interpretation of the information obtained is often complicated by coexposures, urine dilution, specificity issues, and the temporality of the measurement. To date, no ideal way exists to interpret many of these measurements without the use of additional measures, for example, repeat measurements or environmental

measurements. Measurements of metals have been performed in many matrices over the years and are, in general, well-understood. Biomonitoring will likely have limited utility in the assessment of exposure to criteria pollutants and bioallergens.

Thought Questions

1. If you wanted to measure fetal exposure to a persistent organic pollutant, what biological matrix would you choose?
2. How would you go about assessing dietary (chronic) exposures to pesticides? How would you account for household use (acute exposures)?
3. Why would you want to assess exposures at different life stages using different techniques or matrices?
4. How do fetal, infant, toddler, and early childhood exposures differ?

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CHAPTER FOURTEEN

OVERVIEW OF ENVIRONMENTAL PUBLIC HEALTH LAWS AND THEIR RELATION TO RISK

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Learning Objectives

Students who complete this chapter will be able to

1. Gain an introduction to the U.S. government and legal system, as a backdrop for studying environmental law
2. Understand how laws, and environmental law in particular, are developed, implemented, and enforced
3. Familiarize themselves with the goals, strategies, and requirements of some of the major federal environmental health laws
4. Know about various approaches for assessing and managing risk in major federal environmental health laws

The goal of this chapter is to provide an overview of laws and legal processes related to environmental health risk. The chapter is specifically aimed at public health students and others interested in the subject. We focus particularly on the portions of those laws that are involved in assessing those risks.

We should caution that this chapter is not intended to be a guide to lawyers or to those contemplating legal action. Nor is it a compendium of environmental laws. Although we subscribe to the idea that human health in the broadest sense is inextricably linked to a healthy environment, we do not include laws that are aimed primarily at protecting ecosystems. Nor do we consider provisions of

laws related to ecological risk assessment. Similarly, sections of environmental laws devoted to control technology and administrative procedural issues are largely omitted. Another caution is that we usually omit the exceptions that are specified within the law. (Some exceptions are understandable—such as the exclusion of chemicals developed for research purposes from many of the provisions of the Toxic Substance Control Act, and the allowance of NASA rockets to exceed the EPA noise standards. But other exclusions or special provisions are in the fine print because of the effectiveness of industry lobbyists, which may or may not be anticipated.)

Overview of the U.S. Governmental Structure

The Founders of this country, having recently won independence from England, were suspicious of too much power concentrated in the same hands. As a result, the government they created is characterized by checks and balances. First, power is divided between the federal government on the one hand and the individual state governments on the other. Second, within the federal government, as within each of the state governments, power is divided among three separate branches of government: legislative, executive, and judicial. Third, protections of individual liberties, such as speech and religion, create further restrictions on governmental powers. The purpose of this section is to outline our governmental structure and legal system, as a background for understanding U.S. environmental law.

United States Constitution and the Federal System

The founding document of the federal government, and the supreme law of the land, is the Constitution of the United States. The Constitution enumerates specific powers that are delegated to the federal government. All other powers remain with the states and the people. Accordingly, the federal government is often described as a government of limited or enumerated powers. This division of powers between the national and sovereign state governments is a *federal* system. By contrast, most European countries have a centralized system of government where all or most powers reside in the national government; the states or provinces have only such powers as the national government chooses to delegate.

Federal Supremacy in the American System

The line between enumerated federal powers and retained state powers is often unclear and subject to debate. But the theory is clear: outside its enumerated powers, the federal government has no authority; within the enumerated powers, its authority is supreme. The concept of *federal supremacy* refers to the fact that the

federal government has supreme authority within the area of its enumerated powers.[1] It does not mean that the states are totally prohibited from acting within the arena of enumerated federal powers. On the contrary, state laws often overlap the arena of federal powers, but there are certain restrictions. Most important, a state may not adopt a law that conflicts or interferes with federal law. In addition, states may not adopt laws in an area where Congress has fully "occupied the field," meaning that federal laws are so thorough and detailed as to leave no room for state laws. Whether a particular state law runs afoul of either of these restrictions is often disputed and must be decided by the courts.

Branches of Government

As another safeguard against concentrated power, the U.S. Constitution divides the federal government into three independent branches—legislative, executive, and judicial—and divides the major governmental powers among them. Congress is vested with the legislative (lawmaking) power (see below). The executive branch, consisting of the president, vice president, and various departments and agencies, has the power and responsibility for carrying out the laws passed by Congress. The federal courts, led by the U.S. Supreme Court, have the power and responsibility to decide disputes and interpret federal law, including the Constitution.

The individual states generally follow this same model of three independent branches. The terminology may vary—for example, the head of a state's executive branch is called *governor* rather than *president*—but our description of the federal government is generally also true of the individual state governments.

Sources of American Law, Including Environmental Law

When most people think about "law" they think of federal or state legislation. Certainly the most familiar environmental laws are the major federal Acts such as the Clean Air Act and the Clean Water Act. But Congress and the state legislatures are not the only sources of American law. The purpose of this section is to give a brief introduction to the multiple sources of law, including environmental law, in the United States.

U.S. Constitution

The U.S. Constitution does not explicitly give the federal government the authority to protect the environment or regulate environmental impacts. Rather, the federal government relies on the Commerce Clause as the constitutional foundation

for most environmental laws. This clause simply states that "the Congress shall have Power . . . to regulate Commerce with foreign Nations, and among the several States . . . ."[2]

Like many sections of the Constitution, the Commerce Clause has language that is elastic; it can be read narrowly or broadly. In our nation's early years, consistent with the Founders' suspicion of centralized federal power, the clause was interpreted narrowly to give Congress authority to regulate only very basic functions such as interstate shipping of goods. As Americans became more comfortable with their federal government, the interpretation of interstate commerce gradually expanded. Today, Congress can regulate pollution in a lake that is entirely within the borders of a single state if, for example, that lake attracts tourists from other states or if fish from the lake are shipped to other states for sale. Connections such as these are now deemed a sufficient nexus with interstate commerce to fall within the federal government's enumerated powers.

State Constitutions

Each state has its own constitution, which establishes the structure and powers of the state government and the rights of citizens. Unlike the U.S. Constitution, some state constitutions have explicit provisions related to environmental protection.[3] While not essential to *authorize* state environmental protection, a constitutional provision serves as a statement of state policy and may help influence laws and governmental action. Such a provision may add support to a legal challenge by environmental advocates to a particular governmental action, such as the issuance of an emission permit or the construction of a dam.

Legislation

Legislative power encompasses both the power to make laws and the power to set the agenda. Congress has the power to decide which problems or goals it wants to address and then to enact laws in those selected areas, provided only that the matter be within its constitutionally enumerated powers.

A legislative *Act* is a systematic group of statutes addressing a particular subject, such as the Clean Air Act or the Safe Drinking Water Act. Typically, Congress establishes goals and programs in broad outline and directs a particular executive department or agency to implement them. For example, in the Clean Air Act, Congress directs the U.S. Environmental Protection Agency (the EPA) to establish ambient air quality standards "the attainment and maintenance of which in the judgment of the [EPA] Administrator, . . . allowing an adequate margin of safety, are requisite to protect the public health."[4] Some of the major federal environmental Acts are summarized below.

State legislation is another major source of law, including environmental law. Like Congress, state legislatures set their own agendas and priorities for legislation. The existence of 50 sovereign states is sometimes viewed as offering multiple laboratories trying different legislative approaches to common problems.[5] If a particular state approach proves successful or commands respect, it can influence legislation in other states and in Congress. Once a particular environmental act is adopted by Congress, state legislatures often follow the federal model.

In almost every major federal environmental act, Congress explicitly authorizes, and even encourages, the states to enact legislation on the subject. Thus, air pollution, water pollution, and other environmental issues are generally subject to statutory regulation at both federal and state levels. Even though state intervention is explicitly authorized, the concept of federal supremacy is still relevant. With respect to antipollution and other environmental standards, the supremacy rule generally means that states may impose standards that are as strict as, or stricter than, federal standards. But state legislatures may not undermine federal legislation by allowing standards that are less strict than federal standards.

Local governments, such as cities and counties, are also a source of environmental law. They are not sovereign; they derive their powers from the state. But their legislation, often referred to as *ordinances* or *codes,* can have a significant impact on the local environment, for example, zoning and health codes. Moreover, successful local ordinances can influence state and federal law. For example, measures adopted in the 1940s by Allegheny County, Pennsylvania, to control steel mill emissions in the Pittsburgh area were a model for part of the 1970 federal Clean Air Act.

Executive Branch

Agency Regulations. Whereas Congress derives its legislative power from the Constitution, executive agencies derive their regulatory authority from Congress. Accordingly, the law-making authority of the agencies is more limited in scope. Agencies, unlike Congress, do not have the authority to set their own agendas. Rather, agencies have only such regulatory authority as Congress delegates to them. But because the authority delegated by Congress is often broad in outline, the agencies exercise considerable discretion. (See Table 14.1 for a list of major federal agencies and statutes related to environmental health.)

For example, as noted above, the Clean Air Act directs the EPA to establish ambient air quality standards which "in the judgment of the [EPA] Administrator, . . . allowing an adequate margin of safety, are requisite to protect the public health." This is both a mandate and a delegation of authority to the EPA, to issue regulations reasonable and necessary to carry out this provision. It is up to the EPA to flesh out this broad mandate, in large part by developing quantitative limits and

TABLE 14.1. MAJOR ENVIRONMENTAL LAWS AND REGULATIONS ENFORCED BY FEDERAL AGENCIES.

Agency	Regulation
Consumer Product Safety Commission (CPSC)	Consumer Product Safety Act Flammable Fabrics Act Poison Prevention Packaging Act
Environmental Protection Agency (EPA)	Asbestos Hazard Emergency Response Act Asbestos School Hazard Abatement Act Asbestos School Hazard Detection and Control Act Chemical Safety Information, Site Security and Fuels Regulatory Relief Act Clean Air Act Clean Water Act Coastal Zone Management Act Comprehensive Environmental Response, Compensation, and Liability Act Emergency Planning & Community Right-To-Know Act Endangered Species Act Federal Insecticide, Fungicide, and Rodenticide Act Federal Food, Drug, and Cosmetic Act (with FDA) Food Quality Protection Act (with FDA) Hazardous Materials Transportation Act Indoor Radon Abatement Act Lead Contamination Control Act Lead-Based Paint Poisoning Prevention Act (with OSHA) Marine Protection, Research, and Sanctuaries Act Medical Waste Tracking Act National Environmental Education Act National Environmental Policy Act Nuclear Waste Policy Act Ocean Dumping Act Ocean Dumping Ban Act Oil Pollution Act Pollution Prevention Act Pollution Prevention Packaging Act Resource Conservation and Recovery Act Resource Recovery Act Safe Drinking Water Act Shore Protection Act Shoreline Erosion Protection Act Solid Waste Disposal Act Superfund Amendments and Reauthorization Act Surface Mining Control and Reclamation Act Toxic Substances Control Act Uranium Mill-Tailings Radiation Control Act

TABLE 14.1. MAJOR ENVIRONMENTAL LAWS AND REGULATIONS ENFORCED BY FEDERAL AGENCIES, Cont'd.

Agency	Regulation
Food and Drug Administration (FDA)	Animal Drug Availability Act Animal Medicinal Drug Use Clarification Act Best Pharmaceuticals for Children Act Dietary Supplement Health and Education Act Federal Food, Drug, and Cosmetic Act Food and Drug Administration Modernization Act Food Quality Protection Act Infant Formula Act Medical Device Amendments Medical Device User Fee and Modernization Act Minor Use and Minor Species Animal Health Act Nutrition Labeling and Education Act Orphan Drug Act Pediatric Research Equity Act Prescription Drug Marketing Act Safe Medical Devices Act
Mine Safety and Health Administration	Mine Safety and Health Act
Occupational Safety and Health Administration (OSHA)	Contract Work Hours and Safety Standards Act Hazardous Materials Transportation Uniform Safety Act Lead-Based Paint Poisoning Prevention Act (with EPA) Occupational Safety and Health Act Vocational Rehabilitation Act Amendments

other concrete requirements that can be understood by and enforced against regulated entities.

An agency has broad discretion to make policy decisions consistent with its mandate. Thus, the EPA has discretion here to determine what degree of public health protection is requisite, and to determine what margin of safety is adequate.

In addition to policy judgments, an agency also has considerable discretion in making judgments involving its areas of expertise. This is particularly significant with respect to environmental regulation, where there is often scientific uncertainty about relevant data. For example, the EPA must make judgments about exposure and health effects, often in the face of incomplete or conflicting data, in assessing whether, or at what ambient level, a particular pollutant poses a threat

to public health. So long as there is reasonable support, a court will uphold the agency's scientific judgment against challenge. For example, even if there are other reasonable interpretations of the data, a court will not second-guess the agency's choice of which reasonable interpretation to rely on. This deference to agency judgment is important because in the face of scientific uncertainty an agency could be hamstrung in court forever if it had the burden of proving that every judgment it made was the best possible judgment.

Much of the EPA's work consists of developing numerical standards in accordance with the mandates of various environmental Acts. But there are some important distinctions among numeric standards that the reader should be alert to. One important distinction is that some of the EPA's numeric standards pertain to allowable ambient concentrations of contaminants, whereas others pertain to allowable concentrations in emissions or effluents. A second distinction is that some numeric standards are derived from risk-based legislative criteria, whereas others are derived from technology-based legislative criteria. The Clean Air Act's mandate for ambient air quality standards requisite to protect public health with an adequate margin of safety is an example of a risk-based, ambient standard. Another provision of the Clean Air Act mandates emission limits reflecting the maximum achievable control technology, an example of a technology-based standard for emissions. Risk-based standard setting usually involves risk assessment based on the best available science. Science is less influential in technology-based standard-setting, which depends more on engineering and is more subject to industry influence. A third distinction is that most standards the EPA is required to develop have the force of law, but some standards do not. The latter are most commonly guidelines for states.

The above discussion pertains to substantive requirements and limits imposed on agencies. There are also important procedural requirements for agencies designed to promote transparency and public participation. These are often referred to as *notice and comment procedures.* The basic requirements for adopting new agency regulations are:

> Notice to the public: The agency must publish[6] proposed regulations in advance, so interested individuals and groups will have notice.
>
> Comment: Interested parties are allowed a period of time to file written comments and objections to proposed regulations. For high-profile issues, the agency may hold public hearings where interested parties can testify in person. Agencies sometimes revise proposed regulations in response to the comments received. Objections to the proposed regulation must be raised during the comment period in order to be preserved. A court will not listen to a challenge

to final regulations unless it was first raised at this stage, and the agency given the opportunity to cure the asserted deficiency.

Final regulations and record: The agency must publish the final regulations,[7] along with a formal record documenting the rule-making proceedings. The record includes at least a summary of comments received, with the agency's analysis and response—for example, why an objection did or did not warrant modification of the proposed regulation. The record is essential for judicial review, as well as promoting transparency in government.

After publication, there is a fixed period of time during which interested parties may challenge final regulations in court, that is, seek judicial review. A regulation may be challenged on the ground that the agency did not comply with procedural requirements, or that the regulation is inconsistent with the authorizing statute, or on constitutional grounds. The evidence considered by the reviewing court is usually limited to the published record, and that is why the record must carefully document the rule-making proceeding. A court will show considerable deference to agency decisions provided the agency has followed and documented proper procedures.

Executive Orders. The President has authority to issue executive orders. These are generally limited to establishing advisory boards or procedural directives to the executive branch.[8] An executive order is trumped by laws and rules passed by Congress; moreover, it may be countermanded by the next President.

Like the federal executive branch, the executive branch of each state makes law applicable within its jurisdiction. Thus, the student wishing to investigate "the law" applicable to a given environmental issue must consider the agency regulations of the state involved as well as the other layers of law already discussed.

Common Law

Historically, there was no statutory law governing some major subject areas, notably contracts, torts, and property rights. When disputes arose in those areas, a court would decide the case by applying precedents from previous cases to the facts of the new case. Each decision added to the storehouse of precedents that could be useful in deciding future cases. This body of judicial precedential law is called *common law*. Its keystone is *stare decisis*, the judicial doctrine of standing by that which has already been decided. This respect for precedent tends to promote fairness, as well as providing the predictability needed in an orderly society. Common law remains important today, although it is subordinate to statutes that have been enacted on many issues that were traditionally covered only by common law.

Common law varies from state to state, but there are more similarities than differences. There is essentially no federal common law. To the extent the federal government seeks to regulate the relevant subject areas, it is done through legislation, not judicial law making.

Before there was environmental statutory law, some protection was available under common law. For example, the tort theory of trespass could be used to protect private property from such invasions as pollution of a stream by an upstream neighbor or ash from an upwind incinerator. Even more significant for the environment and public health, a tort theory called *public nuisance* could be invoked to protect a public right, for example, to restrict pollution from a local factory that fouls a public lake or a community's ambient air. A public nuisance lawsuit may be filed by public authorities or by any private individual who has standing. To have *standing,* a private individual must generally suffer some harm greater than the public in general, for example, a rancher whose sheep were watered at the public lake and became sickened by the contamination. Today the same goal might be achieved by a citizen's enforcement suit under the Clean Water Act. But the common law, long the only avenue of redress, is still available as a backup to statutory law.

In recent decades, toxic tort litigation has become a major source of the common law's impact on the public health arena. A *toxic tort lawsuit* seeks to bar a toxic exposure or, more commonly, to obtain compensation for attributed harm. The toxic exposure might be anything from an oil spill to ingestion of a pharmaceutical. The harm might be anything from property damage to lung cancer. As in any tort lawsuit, the plaintiff has the burden of proof that his or her injury was more likely than not caused by the exposure. This is a difficult hurdle in many lawsuits, due in large part to scientific uncertainty as to whether a particular substance is capable of causing a particular disease (*general causation*), and whether a particular individual's disease was caused by a particular exposure (*specific causation*). Proof of causation is especially difficult in cases involving latent diseases such as cancer that take years or even decades to develop.

An interesting risk-related issue raised in a number toxic tort cases is whether the plaintiff's "more likely than not" burden of proof can be analogized to a relative risk greater than two (RR > 2.0) in a published epidemiological study. Some courts, seeking a brightline rule to dispose of daunting scientific complexity, have ruled that RR > 2.0 is required to establish general causation. Other courts have given more nuanced consideration to the role of relative risk is establishing a causal relationship.[9]

The goals of the common law tort system are not only to fairly compensate injured individuals but to discourage behaviors that cause harm. As applied to

toxic torts, the theory is that the threat of liability will motivate those who manufacture and handle dangerous substances to exercise greater care. In practice, the impact on public health is subject to debate. In some instances there is broad agreement that the impact of toxic tort litigation, for example, eliminating the use of asbestos as a construction and insulating material, has been beneficial. In other instances, it is argued that the threat of liability, or even the threat of litigation costs, has deprived society of beneficial products, such as the pharmaceutical agent Bendectin.[10]

Enforcement of Federal Environmental Laws

There are several enforcement approaches available when environmental laws are violated, for example, when an industrial source exceeds emission limits promulgated under the Clean Air Act. The federal agency can impose an administrative fine, or it can prosecute the violator in court. The most common penalty imposed by a court is a civil fine.[11] In certain circumstances, a court will issue an *injunction*, which is a court order requiring a party to do, or to stop doing, some particular act. An extreme example would be an order for a violator to close down a factory.[12] The federal agency may also ask a court to impose criminal penalties, consisting of criminal fines or even incarceration, for very egregious violations.

Most federal environmental acts allow individual states to take over implementation of the federal law, provided they enact a *state implementation plan* (SIP) approved by the EPA. In any state with an approved SIP, the appropriate state agency can exercise the same enforcement powers as a federal agency.

Most federal environmental acts also provide for *citizen actions*, a unique enforcement mechanism that allows a private citizen to file an enforcement action in court against a violator. Such actions are usually filed not by individuals but by public interest groups such as the Environmental Defense Fund or the American Lung Association. Any fines awarded by the court are paid to the general treasury, not to the plaintiff. Allowing for such *private prosecutors* serves the purposes of environmental acts because government agencies do not have adequate resources to prosecute all violators.

The Precautionary Principle

The *precautionary principle* (discussed in Chapter 15) is a variously defined and controversial approach to environmental regulation. Some of the regulatory actions under this principle can be described as a more stringent approach to risk-based standards such as the additional safety factor of 10 for infants and children in the

Food Quality Protection Act. Other regulatory actions consistent with the precautionary principle fit under the heading of primary prevention, including shifting the burden of proof for safety of a new chemical to industry. In our discussion of individual laws, we point out some of the precautionary approaches that have been taken, many of which have been very valuable to protecting health and the environment.

We tend to take a more cautionary approach to the precautionary principle than many of its advocates, particularly when this ill-defined principle is used as a basis for environmental law.[13] Our concern in part is raised by the precautionary principle being abused by the European Community to protect its agriculture,[14] and in part by the precautionary principle being used as a rationale to replace careful scientific evaluation of the potential risks and benefits of chemicals.

Clean Air Act

The 1970 Clean Air Act (CAA) was the first comprehensive attempt to regulate air pollution at the national level. Clean air was a central goal of the growing environmental movement, and Congress sought to achieve that goal through the CAA. The Act set unrealistically short deadlines for the EPA to achieve the clean air mandates, for example, controlling all major air pollutants to healthy levels by 1975, and the EPA fell far behind.

The 1990 Clean Air Act Amendments (CAAA) reflected growing Congressional impatience with the EPA's progress in meeting clean air goals. They also reflected newly recognized problems such as acid rain. The 1990 CAA amendments deal with a wide variety of issues directly or indirectly related to clean air. The distinction made in the 1970 Clean Air Act between stationary and mobile sources (e.g., automobiles) is maintained, although it is currently recognized that many air pollutants of concern require control measures for both types of sources. For example, particulates come from both diesel exhaust and power plant emissions; nitrogen dioxide similarly comes from both stationary and mobile sources.

Through its complex approaches to different types of sources and pollutants, the CAA provides almost a textbook of alternative ways to regulate environmental pollutants. Changes invoked in the 1990 CAA amendments, particularly concerning Hazardous Air Pollutants (HAPs), further illustrate the role and perceived limitations of risk assessment in assessing and controlling environmental pollution. The CAA encompasses a wide array of programs and provisions.[15] For this chapter we will focus on standard setting for National Ambient Air Quality Pollutants and Hazardous Air Pollutants.

National Ambient Air Quality Standards

Impetus for the original 1970 National Ambient Air Quality Standards (NAAQS) program came from air pollution disasters in London and in Donora, Pennsylvania, as well as from the fouling of previously pristine areas such as Southern California by oxidant smog from increased automobile use. The goal of the NAAQS provisions is to protect public health by controlling levels of harmful ambient *air pollutants.* Congress defined these as pollutants that may reasonably be anticipated to endanger public health and that are emitted from numerous or diverse sources, mobile or stationary. Thus, the NAAQS program is aimed at pollutants that have been identified with reasonable confidence as causing adverse health effects in exposed populations at ambient levels.

The EPA's mandate is to identify which pollutants fit the definition and then to set uniform national ambient standards. Currently, six pollutants are regulated under the NAAQS program: sulfur dioxide, ozone, particulates, lead, carbon monoxide, and nitrogen dioxide. For each pollutant, the EPA must establish ambient limits at the level that, in the administrator's judgment, will "protect the public health," including sensitive populations, from "known or anticipated adverse effects" and do so with an "adequate margin of safety." All of these terms are subject to interpretation, and disputes have often led to time-consuming litigation. Unlike standard setting under most environmental Acts, the EPA is not required or even permitted to consider cost or technological feasibility in setting NAAQS standards.[16]

Implicit in setting an ambient standard that meets these criteria is the assumption that there is a pollutant level below which it is reasonable to anticipate no adverse effects in a sensitive population. This is equivalent to establishing a threshold, or more properly, *a no-observed effect level* (NOEL). The process includes a recommendation from the Congressionally established EPA Clean Air Scientific Advisory Committee (CASAC). To establish a NOEL, CASAC uses a weight-of-evidence approach, based initially on a thorough review of the extensive literature for each of these pollutants, prepared by the EPA's Office of Research and Development.

What constitutes an "adequate margin of safety" is a policy decision within the discretion of the EPA administrator. This is in contrast to other statutes for which a margin of safety is established through a more formal use of assigned safety factors based upon scientific and technical considerations.[17] The large database for NAAQS, including human data, obviates the need for classic "factors of ten" in establishing the margin of safety. Rather than a technical decision by scientists, which is the case when extrapolation is performed through standard safety factors, the extent of the margin of safety often reflects the policy values of the EPA administrator.

Determination of what constitutes an adverse effect can be controversial. For example, modern pulmonary research techniques can readily demonstrate very small changes in airway diameter in individuals experimentally exposed to defined levels of an air pollutant. Industry can be expected to argue that these small changes are less than what occurs when an individual walks outdoors into cold air. On the other side, environmental advocates emphasize that to an asthmatic even a very small increase in bronchoconstriction can be serious.

The CAA requires a review of each NAAQS ambient standard every five years. The need to revisit an ambient standard has led to ongoing research to clarify uncertainties. This is in contrast to much other standard setting for which the establishment of a standard often leads to cessation of research.

Most public attention is given to the level of an ambient standard. However, public health impact is often greatly affected by the form of a standard, for example, the time period over which it is averaged, the number of allowable exceedences, and measurement techniques. For example, the EPA originally set an ambient limit on ozone averaged over a one-hour period. It later revised the standard to set a limit averaged over an eight-hour period, to recognize ozone's daylight-long presence and longer-term effects. Similarly, the NAAQS standard for particulates was changed from a measure of particles less than 10 microns to those less than 2.5 microns in diameter, reflecting the health importance of fine particulates that can be breathed deeply into the lung.

To achieve NAAQS, it is necessary to control emissions of pollutants to the ambient air. These emissions come from stationary sources, for example, factories, power plants, and incinerators, and from mobile sources, for example, cars, trucks, and airplanes. For stationary sources, the general regulatory approach is to set emission limits, then let individual emitters choose how to meet their limits, for example, through antipollution equipment, processing methods, and quality of raw materials. Emission limits are stricter for new sources than for existing sources, reflecting the reality that it is more economical to build in control technology during construction than to retrofit an older plant. Some areas, especially densely populated urban areas, have not been able to achieve required ambient levels for one or more NAAQS pollutants. In these areas, called *non-attainment* areas, there are even stricter emission limits, as well as other hurdles, on new construction, to avoid making the problem even worse. In areas where ambient standards are met, called *attainment* areas, there are also rules for new construction designed to prevent significant deterioration of the ambient air. For mobile sources, control regulations include limits on new-car tailpipe emissions, gasoline additives and formulation, and vehicle inspection and maintenance programs.

Regulating emissions involves efforts at both the federal and state levels. Ultimately, each state is responsible for achieving NAAQS within its borders. If a

NAAQS standard is exceeded, a state is required to provide to the EPA a State Implementation Plan (SIP) detailing its plans to achieve the standard. Air emissions, of course, do not respect state borders, and each state is also responsible for avoiding undue pollution of its downwind neighbors.

Hazardous Air Pollutants

The NAAQS program was designed to control those air pollutants that are a threat to public health at ambient levels. Another group of air pollutants is regulated under the CAA's Hazardous Air Pollutants (HAPs) program. The HAPs program (also called *air toxics*) is intended to regulate air pollutants that can endanger human health or the environment not just due to ambient concentrations but also through emissions, bioaccumulation, deposition, or otherwise.[18]

The original 1970 Clean Air Act gave a risk-based definition of "hazardous air pollutants." The Act directed the EPA to identify the air pollutants that met that definition and to issue emission standards that would protect public health with an ample margin of safety. This approach placed the burden of proof on the EPA, if challenged, to show that a pollutant met the HAPs definition, and to show that the emission standard imposed was indeed necessary to protect public health. The EPA marshalled the available science and applied risk assessment methodology to its task.[19] But, tripped up by litigation and by gaps in the relevant science, the EPA managed to issue final regulations for only seven substances[20] in the next 20 years, although those seven were the pollutants with the greatest known risk.

By 1990 Congress and the public were impatient with this lack of progress. The Toxic Release Inventory (TRI), required by the Emergency Planning and Right to Know Act of 1986, gave average citizens knowledge of how many tons of pollutants were emitted into the air not only nationally but in their own neighborhoods. This heightened awareness led to public demand for more vigorous control of hazardous air pollutants.

The resulting 1990 Clean Air Act amendments completely changed the approach to regulating HAPs in a way that removed the burden of proof from the EPA in most respects. Rather than relying on an abstract definition, Congress actually made a list of 189 substances and defined "hazardous air pollutants" as any substance on that list. The EPA is to review this list every five years and add to it as appropriate. Specifically, it may add

> pollutants which present, *or may present*, through inhalation or other routes of exposure, a threat of adverse human health effects (including, but not limited to, substances which are known to be, *or may reasonably be anticipated to be*, carcinogenic, mutagenic, teratogenic, neurotoxic, which cause reproductive dysfunction,

> or which are acutely or chronically toxic) or adverse environmental effects whether through ambient concentrations, bioaccumulation, deposition, or otherwise. . . .[21]

This provision for designating additional HAPs still places a burden of proof on the EPA in the event of a court challenge, but the language clearly gives the EPA significant latitude for erring on the side of caution in its risk assessment when faced with scientific uncertainty.

There is also a provision in the amended program for *delisting* a substance, that is, removing the HAPs designation. For delisting, the burden of proof is on the petitioner, invariably industry, to show that the substance cannot reasonably be expected to cause any adverse effects to human health or the environment, whether from emissions, ambient concentrations, bioaccumulation, or deposition. This showing must be based on adequate data. Hence, the onus of gaps in available science falls not on the EPA but on the petitioner seeking to avoid regulation.

The 1990 Clean Air Act Amendments changed not only how HAPs are defined, but also how they are regulated. The Act now requires that the EPA set emission limits reflecting the *maximum available control technology* (MACT), defined by Congress to mean the emission levels achieved by the best-performing 88th percentile of HAPs emitters within each industrial category. The rationale is essentially that if the available technology enables 12 percent of emitters to keep emissions down to a certain level, then all similar sources should be required to match that performance.[22] Under the amended Act, MACT is applied across the board, irrespective of risk considerations. This same strict technology-based standard applies regardless of the size of population exposed, for example, whether a source sits in the middle of Los Angeles or in the middle of the Mojave Desert. Further, MACT is applied with equal force to all substances on the HAPs list, even though some of those substances are far more toxic than others.

In maximizing the degree of control without regard to magnitude of the exposure or hazard, the 1990 HAPs amendments exemplify concepts advocated under the precautionary principle rubric.[23] Risk assessment still has a secondary role in a backup provision, commonly called the *residual risk* provision. Essentially, the Act requires follow-up investigation by the EPA to determine if MACT emission limits are succeeding in protecting public health with "an ample margin of safety" and to impose more stringent regulation if necessary to accomplish this. For noncarcinogens, "ample margin of safety" is not defined, leaving the EPA to conduct its risk assessment and exercise its policy judgment. However, for HAPs that are classified as carcinogens (known, probable, or even possible carcinogens), Congress is more explicit: lifetime excess cancer risk to the most exposed individual must be reduced to less than one in a million. This mandated focus on the

maximally exposed individual, rather than a population-based risk assessment, is at odds with standard public health practice.[24]

Proponents expected the 1990 amendments to result in more efficient regulation of HAPs. Fifteen years later, however, the EPA has not completed its task of developing standards, and the process continues to be dogged by litigation. Moreover, there are a number of concerns about the amended program's effectiveness for protecting public health. First, industry may have little, if any, incentive to substitute a less toxic agent for a more toxic agent if both are on the HAPs list and therefore subject equally to MACT.[25] Second, industry will have an incentive to resort to new, untested chemicals that are not on the HAPs list and therefore not subject to MACT. Given the almost inevitable slow pace of the regulatory process, it may take years to add new chemicals to the list, even those with relatively high potential for toxicity. Third, while MACT emission standards are based on the best technology in existence when they are established, there seems to be no incentive for any improvement in control technology after the standards are set.

Issues Related to Cancer Risk

There are no known human carcinogens in the list of NAAQS air pollutants for which ambient standards are set.[26] Using emissions standards for known human carcinogens rather than setting an ambient standard is politically convenient. The usual presumption about known human carcinogens is that there is no threshold for an effect; every molecule carries with it the possibility that it will cause the specific unrepaired mutation that leads to cancer. Therefore, setting an ambient standard for such compounds would in essence allow a permitted level for a human carcinogen. No matter how small the risk, it could not be said to be risk-free. As concern about cancer from air pollution is a major driving force in the control of hazardous air pollutants, having a permissible level in the air of a known carcinogen is politically unacceptable.[27]

For certain carcinogenic volatile organic compounds such as benzene and formaldehyde exposure and risk are highest indoors. The EPA has almost no regulatory authority over the indoor environment, Congress being notoriously loathe to regulate the American home. In some instances the EPA has issued guidelines that, while not federally enforceable, have had major impact on the extent of human exposures to carcinogens, for example, through influence on state law, market forces, or voluntary private behaviors. Two examples are the EPA guidelines for wood stoves, which, through greater efficiency, have led to a reduction of polycyclic aromatic hydrocarbons emitted within the homes and to the outdoors; and the EPA guidelines on radon that have been followed in many instances by state laws requiring testing and notification if the guideline is exceeded.

Safe Drinking Water Act

Federal Standards

The Safe Drinking Water Act (SDWA),[28] administered by the EPA, is the main federal statute protecting drinking water. While the Act has some provisions aimed at preventing pollution at the source, its main approach is to require treatment by suppliers to remove or reduce contaminants so that the water delivered to consumers will be safe for human consumption.

The suppliers regulated under the SDWA are referred to in the Act as public water systems (PWS). The word *public* in this designation refers to who is served, not who owns the system. A water utility is deemed a PWS if it has at least 15 service connections or regularly serves at least 25 people. Whether owned by a private company or by a municipality or other governmental entity, every PWS is subject to regulation under the SDWA. Smaller multiuser systems and individual private wells are not regulated under the SDWA.

A contaminant is to be regulated under SDWA if the EPA administrator determines that it meets all three of the following criteria:

1. It "may have an adverse effect on the health of persons."
2. It occurs "with a frequency and at levels of public health concern."
3. Regulation "presents a meaningful opportunity for health risk reduction. . . ."[29]

Unlike most environmental health regulation, the SDWA targets harmful substances regardless of whether they occur naturally or as a result of human activity.[30] There are currently 88 contaminants regulated, which include microorganisms, disinfection byproducts, disinfectants, inorganic chemicals, organic chemicals, and radionuclides.

The EPA must initiate a review at least every five years to determine if additional contaminants should be regulated under SDWA. After consultation with the Science Advisory Board and other scientists, and after seeking public input, the EPA publishes a list of priority candidates for regulation. In compiling this list, the EPA is to select contaminants "that present the greatest public health concern," taking into consideration, "among other factors of public health concern, the effect of such contaminants upon subgroups that comprise a meaningful portion of the general population (such as infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other subpopulations) that are identifiable as being at greater risk."[31] After further evaluation of each new contaminant on the list, the EPA either proceeds to issue a regulation or makes a decision not to regulate it. A decision by the EPA not to regulate a particular contaminant may be challenged in court, just as a new regulation may be challenged.

For every regulated contaminant, the EPA sets a *maximum contaminant level goal* (MCLG), defined in the SDWA as the level at which there are "no known or anticipated adverse effects on the health of persons" and which "allows an adequate margin of safety."[32] The MCLG is thus a risk-based public health goal. For carcinogens and microbial contaminants, the EPA's policy is to set the MCLG at zero. For noncarcinogenic chemicals, the EPA calculates the MCLG based on a reference dose, which is the estimated dose a person can be exposed to on a daily basis over his or her lifetime without adverse health effects. MCLGs per se are not enforceable, but they serve as the basis for enforceable regulations.

The enforceable regulations promulgated by the EPA to protect human health are called National Primary Drinking Water Regulations (NPDWRs).[33] For most regulated contaminants, the EPA sets a technology-based standard called a maximum contaminant limit (MCL). The SDWA mandates that the MCL be set at the level "which is as close to the maximum contaminant level goal as is feasible." The SDWA defines this to mean the level that can be achieved with the use of the best available technology, treatment techniques, and other means which the EPA finds are available, taking cost into consideration.[34] For noncarcinogenic organic chemicals, the MCL and MCLG are virtually identical; while for carcinogenic organic chemicals, the MCLG is set at zero.

For certain contaminants the NPDWR prescribes treatment techniques in lieu of setting an MCL. This alternative form of rule is authorized if the EPA finds it is "not economically or technologically feasible" to determine the level of the particular contaminant in a public water system.[35] As is often the case, this statutory language is subject to dispute. The EPA applied the "feasibility" exception to prescribe a corrosion control technique for lead, in lieu of an MCL.[36] The EPA's rationale was that compliance with an MCL would require aggressive corrosion control techniques that, while they might successfully reduce the level of lead leached from water pipes, would result in increased levels of other contaminants. The court upheld the EPA's reasoning that an MCL is not "feasible" if it would have an adverse public health impact, contrary to the very purpose of the Act.[37]

Risk Considerations

The 1996 SDWA amendments provided the EPA with more flexibility to use risk-based approaches to prioritize which contaminants it would choose for regulation. The previous rule under the 1986 SDWA, which required an additional 25 contaminants to be regulated every three years, was eliminated. Instead, the EPA is now required to review at least five additional contaminants every five years. The EPA uses risk-based criteria to select compounds for review and to decide whether those compounds will meet the criteria for regulation. The increased reliance on risk assessment embodied in the 1996 SDWA amendments is in marked contrast

to the direction taken by Congress in the 1990 amendments to the Clean Air Act provisions for Hazardous Air Pollutants (HAP), which eliminated much of the EPA's flexibility to use risk-based criteria. In part, this may reflect a difference in Congressional attitude toward the respective regulated entities: public water systems, often owned by municipalities, as opposed to industrial polluters.

Another risk-related difference between SDWA and the CAA HAP provisions is the approach taken to setting standards for known or probable human carcinogens. The basic issue is the reluctance of Congress and of regulators to approve any exposure to a carcinogen. In the SDWA, the approach used is to set a goal of zero but then set a feasible level above zero as the enforceable standard. In contrast, for HAPs, rather than setting any ambient standard, the law requires a maximum available control technology and permits additional actions if the residual risk after MACT is above one in a million to the maximally exposed individual. This focus on the maximally exposed individual also distinguishes the HAP provisions from the SDWA, the latter primarily considering population risk.

The SDWA monitoring requirements provide the EPA with additional tools for exposure assessment. There is also a requirement for risk analysis related to provisions concerning source water assessment by states. The 1996 amendments included new approaches to protecting sources of drinking water, including watersheds and groundwater, and provided incentives for states to perform risk analyses aimed at source-water protection. In addition, provisions for the education of system operators and for release of information to the public were added to the Act. There is also an antiterrorist provision requiring contingency assessment and planning by states.

A resurgent area of emphasis within the SDWA amendments is that of microbial contaminants. Increasing recognition of the importance of microbial contamination of water and of food has led to much work on microbial risk assessment being done at both the EPA and FDA. The SDWA particularly directs the EPA to evaluate the costs and benefits of different approaches to disinfecting water supplies, including the lingering issue of cancer risk due to the by-products of chlorination.

Clean Water Act

The Clean Water Act (CWA) (more formally referred to as the Federal Water Pollution Control Act) addresses water pollution prevention and control. The CWA applies mainly to surface waters, and its objective is to restore and maintain the chemical, physical, and biological integrity of those waters. Ideally, Congress in the CWA calls for the elimination of all pollution discharges into navigable wa-

ters. As a more practical interim goal, the Act seeks to achieve water quality that provides for the protection and propagation of fish, shellfish, and wildlife and for recreation in and on the water.

While not primarily a public health act, the CWA has public health implications. This is because surface water pollution can contaminate fish and other aquatic food consumed by humans and because swimming and other recreational activities expose humans to water contamination through ingestion, dermal absorption, or inhalation of vapors. Ecological risk issues relevant to this act are considered in Chapter 13.

The pollutants regulated by the CWA are broadly defined. In addition to chemical waste and other substances commonly regarded as pollutants, the CWA also includes things such as dredged spoil, munitions, heat, rock, and sand. The CWA is directed specifically at pollutants discharged from industrial point sources. Typically a *point source* is a pipe or ditch, although it can be any "discernable, confined and discrete conveyance," such as a well, discrete fissure, container, rolling stock, concentrated animal feeding operation, or vessel.

The regulatory approach of the CWA is to begin with a blanket prohibition of all effluent discharges from industrial point sources except discharges made in compliance with a permit, called a National Pollutant Discharge Elimination System (NPDES) permit. In practice this means that every industrial source must obtain such a permit. Each permit spells out the type and amount of pollutants the individual permit holder is allowed to discharge. This system places the burden of proof on the discharger to prove that a discharge is allowed under its permit, rather than on the EPA (or the corresponding state agency) to prove that a particular discharge is unlawful. Permit holders are required to monitor and report their discharges, including any violations of their permit limits, thus aiding enforcement of the Act.

The permit limits are based on effluent standards adopted by the EPA, which prescribe the concentration or amount of pollutants that can be discharged from a point source. In the CWA, Congress directs the EPA to establish effluent standards based not on risk but on technological feasibility. Specifically, the Act directs the EPA to set effluent standards at levels reflecting the "best available technology economically achievable" (BAT). The EPA sets standards by industrial category, and the statutory language means that the standard must be economically achievable by that industrial category, not necessarily by every individual discharger. Indeed, it is anticipated that marginal plants may close because they cannot economically undertake adequate antipollution measures.[38]

Point source discharges are measured at the end of the pipe, but their ultimate purpose is to protect water quality, which is determined by measuring concentrations of contaminants in the ambient water. The CWA requires the EPA to

set ambient water quality standards, prescribing the allowable concentration of contaminants that will "protect the public health or welfare, enhance the quality of water and serve the purposes of [the CWA]."[39] Water quality standards are set by each state, generally based on guidelines published by the EPA. The quality standards vary according to what the water body is used for. For example, limits on ambient pollutants are more stringent in waters used for swimming or fishing than for industrial use. Limitations on point source discharges are not always adequate for maintaining ambient water quality standards, especially when there are multiple facilities discharging into a single body of water. When that happens, the state is responsible for imposing stricter discharge limitations in the permits of those dischargers in order to bring the water body into compliance with water quality standards.

Food, Drug, and Cosmetic Act

The Federal Food, Drug and Cosmetic Act[40] seeks to protect consumers from health risks, misinformation, and other pitfalls with respect to food, drugs, cosmetics, and dietary supplements. The Act in substantially its present form was enacted by Congress in 1988, but the roots of federal protection of food and drugs stretch back to the mid-nineteenth century. Congress has made several important changes to the Act since passage in 1988, and presumably will continue to do so in the future.[41] The Act is administered by the Food and Drug Administration (FDA), which is part of the Department of Health and Human Services (HHS). Congress did not authorize joint implementation of the Act by states, which is a departure from most of the acts discussed here. On the other hand, the Act does not preempt states from adopting their own laws in this field so long as state laws do not conflict with the federal law.

The Act's regulatory approach is characterized by science-based risk management, including the balancing of risks and benefits. But among the different categories of products, there are significant differences in the legislative standards and the regulatory authority granted to the FDA. Accordingly, we separately examine the regulation of food, drugs and devices, dietary supplements,[42] and cosmetics.

Food

The Act is intended to protect public health by ensuring that foods are safe, wholesome, and properly labeled. Protection of our food supply has traditionally relied on precaution and science-based risk analysis, and these approaches are written into food safety statutes and regulations.

The "food" subject to FDA regulation is broadly defined, the major exceptions being meat and poultry, which are regulated by the United States Department of Agriculture.[43] FDA food regulation runs from the point of manufacture or import through the point of sale to the consumer. Thus, the regulated community includes manufacturers, importers, processors, and sellers.[44] The Act has two main food safety approaches: (1) prohibiting the sale of "adulterated" food and (2) certain labeling requirements, including prohibition of "misbranding."

Prohibition of Sale of Adulterated Foods. The Act prohibits the sale in interstate commerce of adulterated foods, which covers a wide variety of threats to health. Most obviously, the term *adulterated* applies to the actual contents of food.[45] Food may not contain any "poisonous or deleterious substance which *may render* it injurious to health," including unsafe levels of pesticide residues.[46] The italicized wording reflects a precautionary approach. The law does not require actual harm to a person, or even demonstrated toxicity of the foodstuff, only that the contents create an unreasonable risk of harm. The precautionary approach is further reflected in the pre-marketing approval requirements pertaining to food additives and pesticides. The burden is on producers to demonstrate safety to the satisfaction of the agency before the products are allowed on the market.

Besides food content, the term *adulterated* also applies to the conditions under which food is prepared, packed, or held. If those conditions are unsanitary or otherwise may render the food injurious to health, the food is deemed adulterated under the Act. Here again, the Act is precautionary, aiming at preventing risk of harm rather than requiring proof that the food is actually harmful.

Certain things that might compromise the wholesomeness of food, even without making it potentially injurious, also fall within the Act's definition of adulterated food. Food is deemed adulterated, for example, if valuable constituents are omitted. The term also applies if something is mixed in to increase bulk, reduce quality, or otherwise make a food appear better than it is.

For many years, food safety regulation was aimed primarily at chemical hazards, but in recent years microbial pathogens have become a major focus. For example, salmonella enteritidis in eggs and Bovine Spongiform Encephalopathy have been the subjects of risk analyses.[47]

Labeling: Prohibition of Misbranding. For the safety and education of the consumer the Act imposes strict labeling requirements for prepared foods. Recognizing that the educational goal would be undermined by advertising "spin" or by relegating required information to the fine print, FDA regulations prescribe the content and format of required labeling in great detail, including placement, wording, and size of type. The information required on labels has evolved over

the years as our health concerns have evolved. In addition to such basics as ingredients and volume/quantity, package labels must also disclose such information as artificial flavoring, coloring, or chemical preservatives. The label must include a nutrition panel that shows in an easy-to-read format information such as calories, dietary fiber, sugar, carbohydrates, and certain vitamin and mineral content. Among the newest requirements, the nutritional panel must disclose trans-fat content, as well as certain ingredients strongly associated with food allergies such as peanuts, cow's milk, shellfish, and wheat.

The Act prohibits the sale of food that is *misbranded,* a term that is broadly defined. The omission of required label information constitutes misbranding. The term also encompasses such wrongs as false or misleading statements, unauthorized health benefit claims, imitation, and misleading containers.

Drugs

A major part of the FDA's mission is to ensure that therapeutic drugs and medical devices are safe and effective. One of the major tools for achieving drug safety and efficacy is the Act's requirement that all new drugs be approved in advance by FDA before they can be legally marketed. This premarketing approval can be granted only if FDA makes a formal determination, based on substantial scientific evidence, that the drug is safe and effective for its intended use. The manufacturer has the burden of proving safety and efficacy, so scientific uncertainty cuts against approval. Even if the available science is promising, if it is inadequate to demonstrate safety and efficacy to FDA's satisfaction, the drug will not be approved. There is an inherent tension between the desire to make promising drugs available as quickly as possible and the desire to make sure that the scientific testing has been adequate to demonstrate safety and efficacy.

Advisory panels are an important part of the process of approving new drugs and medical devices. These include external experts as well as members of consumer or patient groups. FDA need not accept the recommendations of their advisory groups—but it almost always does.

The Act prohibits the sale of "adulterated" or "misbranded" drugs. These are the same prohibitions applied to foods, and for the most part the definitions are similar, with some additions and adaptations. Any of the following would be deemed to constitute adulteration in a drug, so that its sale would be a violation:

- Poisonous or unsanitary ingredients
- Unsanitary manufacturing conditions that present undue risk of contamination
- Differences in actual strength, quality, or purity from product representations or from the official compendium

- Container composition that is toxic or unsafe
- Unsafe color additives

Any of the following would be deemed to constitute misbranding of a drug so that its sale would be a violation of the Act:

- False or misleading label
- Health-endangering when used as prescribed or recommended
- Lacking adequate directions or warnings
- Manufacturer is not properly registered under the Act
- Dispensation without a prescription (for drugs that can safely be used only under professional care)

The drug provisions of the Act apply to both prescription and over-the-counter drugs, and there are similar provisions applicable to medical devices. The primary definition of *drugs* to which the Act applies encompasses all articles recognized in the official *U.S. Pharmacopoeia* and similar references. However, the FDA's reach does not stop there because the Act adds a functional definition that encompasses substances that might otherwise fly below the radar and which the manufacturer might prefer not to have recognized as drugs. Specifically, any article intended to affect the structure or any function of the body, or any article intended to treat or mitigate disease, is by definition a "drug" subject to FDA regulation under the Act.[48] In a hotly disputed test of this functional definition, FDA tried and failed in recent years to regulate tobacco products.

Dietary Supplements

Dietary supplements include products containing, for example, vitamins, botanicals, or amino acids. They are classified under the Act as foods, not as drugs. As a result, they are not subject to the rigorous requirements governing drugs. The Act prohibits adulteration or misbranding of dietary supplements, but these prohibitions lack the teeth of the Act's drug provisions.

Most notably, for dietary supplements there is no requirement of premarketing approval, and manufacturers do not have the burden of demonstrating that their products are safe and effective. For new dietary ingredients, manufacturers are required under the Act to have adequate information on file to provide reasonable assurance of safety. However, there is no requirement that this information be routinely submitted for FDA scrutiny,[49] so it is the manufacturer rather than FDA that judges whether the scientific evidence is adequate. Moreover, if FDA challenges the manufacturer, FDA has the burden of proof that the article

is unsafe. By contrast, the manufacturer of a drug has the burden of affirmatively proving its product is safe by rigorous scientific evidence. Whereas for drugs, scientific uncertainty is grounds for keeping a product off the market, for dietary supplements, scientific uncertainty defeats regulatory action. This is the opposite of the precautionary approach that characterizes other parts of the Act.

Health-related claims, for example, on product labels or in advertising, are also less rigorously policed for dietary supplements than for drugs. For general claims of health benefits, the manufacturer is required by the Act to have substantiation that the claim is truthful and not misleading. The manufacturer is not required to routinely submit this substantiating evidence for FDA scrutiny, nor even to notify FDA of general health claims. Notice to FDA is required only for specific claims about disease diagnosis, mitigation, treatment, or the like. Even for these claims, the notification is not required before marketing, and scientific support need not be routinely submitted to FDA. Here again, if FDA disputes the manufacturer's claims, the burden of proof is on FDA.

The Act requires that good manufacturing practice (GMP) be followed in the preparation of dietary supplements. But GMP regulations must be based on generally available analytical methodology. If there is none, FDA cannot impose standards. Here again, uncertainty defeats restrictions rather than leading to precautionary restrictions.

Cosmetics

With respect to cosmetics FDA's mission is to ensure that products are safe. The Act gives FDA the authority to prevent the marketing of adulterated or misbranded cosmetics, but otherwise little else. In contrast to drugs, FDA does not have the authority to require premarketing approval for cosmetics, but it can take action when safety issues are reported. FDA actions and litigation have largely led to replacement of cosmetics that posed significant chemical risks, such as white lead used for millennia in Europe and which is now limited almost totally to personal imports from the Near and Far East. Much of FDA's current activities about cosmetics are related to education to prevent errors or accidents that could harm consumers, such as the potential for ocular damage if mascara is applied while driving an automobile. In 1975 FDA's attempts to control the use of the term *hypoallergenic* in labeling were thrown out by the U.S. Court of Appeals for the District of Columbia. Similarly, it has no ability to control the use of the term *natural*.

FDA does not have the authority to directly require animal testing for new cosmetics, a controversial issue. The agency does advise cosmetic manufacturers to employ appropriate and effective testing for substantiating the safety of their products. Of note, there have been attempts by FDA to develop and validate re-

placements for the standard Draize test in which compounds are instilled in the eyes of rabbits.

Congress has put into the Cosmetics portion of the Act a variety of limitations seeming to represent special interests. For instance, while FDA has the authority to regulate hair-color additives, Congress specifically forbids FDA to regulate coal tar hair dyes, and FDA can take no action against the manufacturer or distributor of such dyes as long as they contain a specified cautionary statement on the label that includes a warning about blindness if used on eyebrows or eyelids. Despite this warning statement, and the lack of FDA approval for any color additive on eyebrows or eyelids, ocular damage from such dying and tinting continues to occur.[50]

Occupational Safety and Health Act

The Occupational Safety and Health Act created within the Department of Labor the Occupational Safety and Health Administration (OSHA). The Act imposed two duties on employers, a general duty for a safe workplace, free from recognized hazards that are causing or are likely to cause death or serious physical harm to its employees, and a specific duty to comply with specific OSH standards promulgated under the Act. The details of this Act are discussed in Chapter 9.

Mine Safety and Health Act

The Mine Safety and Health Act is administered by the Department of Labor. The Act was passed in 1977 and the Mine Safety and Health Administration (MSHA) was formed in 1978. Its goal is to prevent death, serious physical harm, and occupational diseases among miners. Specific programs address safety issues, respirable coal dust, respirable silicas, and noise. Mine owners are required to inform miners about chemical hazards.

The standard-setting criterion is to "most adequately assure on the basis of the best available evidence that no miner will suffer material impairment of health or functional capacity even if such miner has regular exposure to the hazards . . . for the period of his working life." For respirable dust the key risk issues are related to the average concentration measurements, the allowable levels, and the specific presence of quartz or other hazardous agents. As for any occupational regulatory situation, there is the need to find the optimum balance between general workplace control measures and the use of personal protective equipment such as respirators. A longstanding issue is the extent to which lung dysfunction

is due to pneumoconiosis in cigarette smokers, and the resultant eligibility for the black lung compensation insurance fund. Risk issues also include definitions of imminent danger and the use of emergency temporary standards for toxic exposures.

National Environmental Policy Act

The goal of the National Environmental Policy Act (NEPA) is to ensure that federal officials make informed decisions based on an understanding of the environmental consequences of their decisions and of reasonable alternatives that might have lesser impact. The Act establishes a Council on Environmental Quality which, depending upon the Administration, has had a greater or lesser impact on coordination of environmental activities within federal agencies. Its official role is to oversee the procedural aspects of NEPA and to report annually to Congress on the state of the environment.

NEPA requires that all federal agencies integrate environmental values into their decision making by considering the environmental impacts of their proposed actions and reasonable alternatives to those actions. To meet this requirement, federal agencies prepare an Environmental Impact Statement (EIS) for any proposed legislation and in advance of other major federal actions that are likely to affect the quality of the human environment. NEPA requirements apply not just to direct federal actions, for example, construction of a dam by the Army Corps of Engineers, but to any action over which a federal agency has control, for example, state or private projects that require a federal permit or involve federal funding. The EPA reviews and comments on EISs prepared by other federal agencies, maintains a national filing system for all EISs, and has the role of ensuring that its own actions comply with NEPA.

Risk analysis is a tool commonly used in evaluating options under NEPA. The use of environmental impact assessment by U.S. states and internationally has grown in recent years, often with the addition of a health impact analysis that focuses on the public health impact of decisions.

NEPA regulates process, not outcome. A federal agency must go through a science-based analysis of environmental risks, but it is not required to select the course of action that would minimize that risk. There are often competing considerations—for example, social and economic—and NEPA does not compel subordination of such considerations to environmental risks. Agency actions have been successfully challenged in court for not following the required analytic process, but if proper procedures are followed a court will not overturn a decision simply because it disagrees with the agency. NEPA merely prohibits uninformed rather than unwise agency actions.

Toxic Substances Control Act

The Toxic Substances Control Act (TSCA) was enacted in 1976 in response to national concern over the threat of synthetic chemicals. In contrast to most other laws related to human health and the environment, TSCA was initiated by congressional committees responsible for commerce and trade rather than committees involved in public health. Recognition of the value of chemicals and of technological innovation to our society, as balanced against the associated risks, is evident in this law. The Act states: "It is the intent of Congress that the Administrator shall carry out this chapter in a reasonable and prudent manner, and that the Administrator shall consider the environmental, economic, and social impact of any action the Administrator takes or proposes to take."[51]

TSCA empowers and directs the EPA to evaluate and regulate chemical substances[52] in order to protect against unreasonable risk of injury to human health or the environment. Thus, the EPA need not find actual harm before it can act; an unreasonable risk of harm is sufficient. This unreasonable risk standard contemplates risk of injury throughout the life cycle of toxic chemicals—manufacture, distribution in commerce, use, and disposal.[53] The Act does not define *unreasonable risk*. The EPA must make that determination on a case-by-case basis, balancing the likelihood and severity of harm against the benefits of the chemical and the cost of risk-avoiding regulation. Thus, the Act gives the EPA broad discretion and scant guidance in deciding what constitutes an unreasonable risk. It is, however, well-established that the Act is not intended to protect against *de minimis* risks or to provide a risk-free society.[54]

Under TSCA, new chemicals are subject to EPA review before they are manufactured and placed in the stream of commerce. Manufacturers must submit a premanufacturing notice informing the EPA of the identity of the chemical, its categories of use, the amount to be manufactured, both health and environmental risk assessments, and a risk management program including communication and labeling. For existing chemicals, manufacturers must notify the EPA if new information is developed about potential toxicity, or when a significant new use is anticipated. A *significant new use* is one that, for example, will result in substantially increased production volume, greater exposure, or a different disposal method.

For new or existing chemicals,[55] TSCA empowers the EPA to require testing by manufacturers and to impose regulations if the EPA determines the chemical may present an unreasonable risk of harm. The EPA considers both the type of hazard and the degree of exposure in assessing risk. Testing may be triggered by evidence of toxicity, for example the physical and chemical properties of a chemical or its structure-activity relationships.[56] Testing is also triggered if there is

substantial production, release, and exposure.[57] The EPA can prescribe what risks are to be tested for, for example, acute, subchronic, and chronic toxicity, oncogenicity, teratogenicity, mutagenicity, neurotoxicity, and environmental effects. Depending on the risks disclosed by testing, the EPA may impose specific regulations for a chemical, such as warnings and labels. If the risks warrant, the EPA may limit or even prohibit the manufacture, distribution, use, and disposal of a chemical.

TSCA created an Interagency Advisory Committee consisting of representatives from several federal agencies with relevant expertise.[58] The committee makes recommendations to the EPA regarding testing needs and priorities. In formulating its recommendations, the committee considers such factors as quantity manufactured or entering the environment, extent and duration of human exposure, whether the chemical or mixture is closely related to known substances, existence of data, and whether testing may help predict health or environmental effects. Generally, priority is given to substances causing cancer, gene mutations, or birth defects.

TSCA contains programs related to asbestos, indoor radon, and lead-based paint. These programs focus on provisions such as research, public education, and training and certification of contractors.

There is speculation as to whether, in light of anticipated action by the European Union, Congress may revamp TSCA within the next few years. The EU is considering a major new proposal for the regulation of chemicals known as the Registration, Evaluation and Authorization of Chemicals (REACH). In contrast to TSCA, which relies heavily on risk assessment, REACH reflects the European predisposition to the precautionary principle. Compared to TSCA, REACH imposes a much higher burden of premarket testing for new chemicals, as well as a more rigorous review of existing chemicals. Further, REACH places less emphasis on balancing the potential value of new chemicals against their risks.[59]

Resource Conservation and Recovery Act

The Resource Conservation and Recovery Act (RCRA), enacted in 1976, addresses the management and disposal of waste in an effort to reduce risk to the environment and public health. Although RCRA expressly refers to *solid waste*, that term is broadly defined to include liquids and containerized gases as well as solids. Thus, it encompasses almost everything we typically think of as waste, but not, for example, smokestack emissions. The Act divides solid waste into hazardous waste and nonhazardous waste. Hazardous waste is the Act's main focus; responsibility for nonhazardous waste is delegated to the states. RCRA is imple-

mented by the EPA and by states with approved state implementation plans (SIPs). The complex RCRA rules focus to a large extent upon volume and days in storage and on the regulation of how wastes are handled, but very little upon risk.

Hazardous Waste

Hazardous waste is broadly defined by the Act as any solid waste that, because of quantity, concentration, or physical, chemical, or infectious characteristics, may either (1) cause an increase in mortality, serious irreversible illness, or incapacitating reversible illness or (2) pose a substantial threat to human health or the environment when improperly treated, stored, transported, or disposed of. The EPA has translated this narrative legislative definition to a more concrete regulatory definition that has two parts: listed wastes and characteristic wastes. *Listed* hazardous wastes include wastes on three different lists maintained by the EPA and accessible on its web site.[60] *Characteristic* hazardous wastes include any waste that is ignitable, corrosive, reactive, or toxic. The EPA describes standard methods for analyzing the wastes, including a leaching procedure that assays for the mobility of chemicals within wastes.

One of the goals of RCRA is to minimize the creation of hazardous waste, both in terms of volume and toxicity. The Act requires generators of hazardous waste to undertake and report on efforts to reduce wastes generated. Generators are also required to report what and how much waste they generate.

Another goal of RCRA is the proper handling and disposal of hazardous waste, to minimize the risk that wastes will be released into the environment. The Act establishes cradle-to-grave regulation and tracking in an effort to achieve this goal. RCRA regulates not only generators of hazardous waste but transporters and *TSD facilities,* which include any entity that treats, stores, or disposes of such waste. Each regulated entity must be registered and have an identification number. When a generator has hazardous waste to dispose of, it must use only registered transporters and TSD facilities. The generator must prepare a tracking document, called a *manifest,* to accompany the wastes. Each entity that deals with a load of waste must sign the manifest, and the final disposal facility must contact the generator to confirm that the wastes are received and properly disposed of. If that confirmation is not received within 45 days, the generator must notify the EPA and/or state officials.

RCRA requires generators to properly containerize and label hazardous wastes, including the specific identity of the contents. When each regulated facility signs the tracking manifest, it is certifying that the containers and labels meet RCRA requirements and match what is listed on the manifest. Thus, RCRA has

built-in redundancy. Lest a generator be tempted to avoid these requirements simply by holding the waste itself, RCRA places strict limits—55 gallons or 90 days—on accumulation of hazardous wastes by anyone other than a registered disposal facility.

Disposal facilities are necessarily the most heavily regulated in the chain of entities dealing with hazardous waste. RCRA imposes treatment standards, depending on the type of facility, for example, landfill or incinerator. Other requirements include contingency planning and preparation, training of personnel, security systems against unauthorized entry, and limitation of air and water emissions. Disposal facilities must inspect the waste they accept, and they must keep permanent records and file detailed periodic reports with such information as type and quantity of waste, date and method of disposal, and (for landfills) location within the facility where the waste was placed. Another category of regulations addresses the fact that the hazard of these wastes will outlive the company running the disposal facility. Each disposal facility must have a closure plan that provides for care of the facility for 30 years after closure. Further, each disposal facility must post a bond or other guaranty of financial responsibility to cover postclosure care, as well as liability claims.

Land disposal of hazardous waste—for example in landfills or injection wells—is strongly discouraged under RCRA. The Act requires the EPA to strictly regulate land disposal to protect human health and the environment, taking account of the characteristics of the waste and the long-term uncertainties associated with land disposal. In general, land disposal of untreated waste may be approved by the EPA only if the applicant has demonstrated to a reasonable degree of certainty that there will be no migration of hazardous constituents for as long as the wastes remain hazardous. If this strict standard cannot be met, the hazardous waste must be pretreated to "substantially diminish the toxicity of the waste or to substantially reduce the likelihood of migration of hazardous constituents . . ."[61]

Any time that hazardous waste may present an imminent and substantial endangerment to health or the environment, RCRA authorizes the EPA to seek emergency injunctive relief in federal court. The risk may arise at any stage in the cradle-to-grave progression of the waste, including leaks. The Act has been interpreted to mean that the EPA need not establish actual harm; it is enough to prove that an existing dangerous condition creates a risk of harm to the environment or human health. A court's injunction may require action tailored to address the specific risk, including cleaning up a leak or reimbursing the government for doing so. The injunction may be directed against any appropriate person, including past or present generators, transporters, and disposal facilities, and it does not require a showing of fault. In these broad liability provisions, RCRA overlaps

CERCLA, discussed below. Because RCRA provides for citizen action, a private citizen could bring such a suit in lieu of the EPA or the state.

Nonhazardous Waste

RCRA explicitly leaves to the states the responsibility for regulating nonhazardous waste. Federal involvement is limited to grant programs and recommended standards. Laws vary from state to state, but typically address such matters as siting and operation of facilities, protection of surface and groundwater, and promotion of recycling. More specifically, regulation may address such issues as leacheate treatment and control, air emission controls and gas venting, rodent and insect control, minimizing odors, unsightliness, public nuisances, and special handling of medical wastes. Actual collection, treatment, and disposal of waste is typically handled at the local level by or under the direction of local governments within the state law framework.

Although the Act clearly gives states authority to regulate nonhazardous waste, that authority is limited by the Interstate Commerce Clause of the U.S. Constitution, as demonstrated by two landmark U.S. Supreme Court decisions. The first ruled that a state cannot refuse to let garbage in. The second ruled that a state cannot refuse to let garbage out.

The first case, which arose in New Jersey, dealt with banning the importation of waste. New Jersey had an environmental problem in that its volume of waste was increasing but available landfill sites were diminishing. The state legislature's solution was to enact a law prohibiting the importation of out-of-state waste into New Jersey. In 1978, in the case of *Philadelphia* v. *New Jersey,*[62] the U.S. Supreme Court ruled the ban unconstitutional. The rationale was that the law discriminated against out-of-state waste generators by placing on them the entire burden of conserving New Jersey's landfill space.

In response to the decision in *Philadelphia* v. *New Jersey,* some state and local governments began looking for alternatives to landfills for dealing with waste, such as incinerators and increased recycling. The problem was that, due to high construction costs and the resulting necessity to charge high tipping fees, these alternative facilities could not compete with landfills. The solution adopted by some localities was a *flow control ordinance,* which essentially guaranteed the local alternative facility a monopoly over locally generated waste. Local waste generators were effectively barred from exporting their waste to a neighboring state, where it could be disposed of more cheaply in a landfill. In the case of *Carbone* v. *Clarkstown,* decided in 1994, the U.S. Supreme Court said that this was unconstitutional.[63] The rationale was that the law favored one local service provider against all out-of-state service

providers. Having twice run afoul of the Interstate Commerce Clause, populous states with diminishing landfill capacity are still searching for ways to dispose of waste without undue risk to the environment.

Comprehensive Environmental Response Compensation and Liability Act

The Comprehensive Environmental Response Compensation and Liability Act (CERCLA, also known as the Superfund Act), which is implemented by the EPA and the states, governs response and cleanup of hazardous wastes from the environment. Any release of hazardous waste into the environment triggers CERCLA, for example, the leaching of hazardous waste from an authorized disposal facility or the unauthorized dumping of hazardous waste. Hazardous nonwaste also triggers CERCLA if it is released into the environment, for example, if a tank truck of valuable chemicals overturns and spills. Accordingly, the definition of "hazardous substances" subject to CERCLA includes, but is broader than, RCRA's "hazardous waste" definition. The most notable omission from CERCLA's definition of "hazardous substance" is petroleum, which is covered under other Acts.

Releases, whether new or old, must be reported to the EPA as soon as they are discovered. The EPA evaluates every release under a hazard ranking system, considering such risk factors as how many people are exposed, how hazardous is the substance, and whether there is potential for contaminating drinking water supplies or ambient air. High-scoring sites are placed on the National Priorities List, which affects both how soon and how aggressive the response will be.

The National Contingency Plan (NCP) establishes procedures and standards for responding to releases of hazardous substances. Depending on its evaluation of a release, the EPA prescribes cleanup requirements consistent with the NCP. The EPA may require responsible parties to clean up the contamination; alternatively, the EPA may undertake the cleanup itself and seek reimbursement from the responsible parties.

CERCLA makes a broad array of "potentially responsible parties" (PRPs) liable for cleanup of a hazardous waste site. The liability provisions are sometimes quite onerous, as suggested by these illustrations:

Owners and operators. These can include both past and present owners, regardless of fault. For example, if property is contaminated by hazardous chemicals that leaked from an underground storage tank many years ago,

the current owners are PRPs, even if they were unaware of the tank's existence. Purchasers of property cannot avoid liability unless they have exercised due diligence in investigating in advance, which generally means a professional environmental inspection of the physical property and of records of prior ownership and uses.

Generators of hazardous waste. If waste is released from a disposal facility, all generators who contributed waste to the site are PRPs, regardless of whose waste is actually released.

Transporters. The transporter is a PRP if the release occurs while being transported, for example, the overturned tank truck mentioned above. Further, if hazardous waste is released from a disposal facility, any transporter who delivered to that facility is a PRP if it played any part in helping select the disposal site.

There are clear benefits to this broad distribution of liability for releases from hazardous waste disposal facilities. It discourages generators and transporters of hazardous waste from selecting a cut-rate, unreliable disposal facility. Further, it can be difficult, if not impossible, to trace leacheate back to the particular source containers; enforcement would be undermined if the EPA had the burden of proving that a particular generator was at fault. Another provision that facilitates enforcement is that all PRPs are jointly liable. This means that the EPA does not have the burden of identifying and pursuing every PRP; it can choose one or a few easy targets to clean up the site (or reimburse the EPA for doing so). Another important provision is that liability is *no-fault*. This means that the EPA does not have the burden of proving that a PRP was negligent or otherwise did anything wrong.

While these provisions are beneficial for enforcement, they seem draconian from the viewpoint of the PRP. However, a PRP that has been compelled to pay more than its fair share has a remedy: it can sue other PRPs for contribution. In a contribution action, a court has broad discretion to allocate costs among PRPs on an equitable basis, considering such factors as volume contributed to the site, relative toxicity, exercise of care, and extent of involvement in the release. One of the biggest controversies is how to allocate *orphan shares*, that is, the shares of any PRP that is insolvent or otherwise unreachable.

The Superfund, from which the Act gets its nickname, is more formally called the Hazardous Substances Trust Fund. This fund is used primarily to pay for cleanup activities that the EPA undertakes directly. When reimbursement is collected from PRPs, the recovered costs help replenish the trust fund. But cost recovery is not sufficient to keep the Superfund at the level needed. Originally, the source of funding for this trust was a special tax primarily on the petroleum and

chemical industries. The rationale was to place the burden on those industries that profit from the activities that give rise eventually to toxic waste sites. But Congress failed to reauthorize that special tax, so now the burden falls on all taxpayers.

Recommendations for Further Reading

For those nonlawyers interested in further information about the subject, we recommend the web sites of the federal agencies involved. They often have very informative, although bland, overviews of the specific laws they administer. We also recommend J. P. Dwyer, and M. F. Bergsund, *Environmental Laws Annotated* (Thomson West, 2005), which contains the full text of most federal environmental laws, annotated overviews, and references to law review articles or specific judicial decisions. For a recent overview of RCRA and CERCLA we recommend J. S. Applegate and J. G. Laitos, *Environmental Law: RCRA, CERCLA, and the Management of Hazardous Waste* (Foundation Press, 2006). There is also a series of paperbacks known as *In a Nutshell*, which includes R. W. Findley and D. A. Farber, *Environmental Law in a Nutshell* (Thomson West, 2004), and J. G. Sprankling and G. S. Weber, *The Law of Hazardous Wastes and Toxic Substances in a Nutshell* (Thomson West, 1997). The Government Institute publishes summaries of federal and state environmental laws. Their web site is http://www.govinst.com. The Society for Risk Analysis has a Risk Policy and Law Specialty Section, and articles related to environmental law and risk are sometimes found in the society's journal, *Risk Analysis.*

Thought Questions

1. The EPA uses a greater variety of approaches to risk assessment and risk management than do other agencies. In contrast to most other federal agencies in the field, the EPA was established by administrative fiat and has no single organic act. Does the absence of the equivalent of a Food and Drug Act or an Occupational Safety and Health Act account for the greater variety of approaches to risk assessment used by EPA; or is this greater variety due to the wider range of environmental threats under the purview of the EPA?
2. The precautionary principle is described in Chapter 15. Should U.S. environmental laws be amended to include provisions more in keeping with the precautionary principle? How could this be done effectively?
3. Both the EPA and FDA are empowered and funded by Congress to have their own research activities that directly support the agency's mission. In contrast, Congress has placed research activities to support OSHA in the National Institute of Occupational Safety and Health. OSHA is part of the Depart-

ment of Labor, while NIOSH is part of the Centers for Disease Control and Prevention in the Department of Health and Human Services. Does this difference in the organizational location of its scientific and technical strengths have any impact on OSHA's risk-based regulatory activities?

Notes

1. "This Constitution, and the Laws of the United States which shall be made in Pursuance thereof . . . shall be the supreme Law of the Land." Constitution of the United States, Article VI.
2. Constitution of the United States, Article I, Section 8.
3. Examples include Hawaii ("The State shall have the power to promote and maintain a healthful environment . . ."; "Each person has the right to a clean and healthful environment." Const. of the State of Hawaii, Art. IX, Sec. 8, and Art. XI, Sec. 9); Illinois ("Each person has the right to a healthful environment." Const. of the State of Illinois, Art. XI, Sec. 2); Massachusetts ("The people shall have the right to clean air and water." Const. of the State of Massachusetts, Art. XLIX); Pennsylvania ("The people have a right to clean air, pure water, and to the preservation of the natural, scenic, historic and esthetic values of the environment." Const. of the Commonwealth of Pennsylvania, Art. I, Sec. 27).
4. Clean Air Act, 42 U.S.C. §7409 (b)(1).
5. California has laws that change the behavior of nationwide industries that want to sell their products in this most populous state. An example of a significant risk-based state law is California's Safe Drinking Water and Toxic Enforcement Act of 1986, often known as Proposition 65. The focus of this law is on warning the public about environmental risks prior to exposure, usually through labeling of products or of the exposure location. Chemicals are listed through a formal process involving expert groups. Risk assessment can be used to provide an exemption for a known hazard: for a carcinogen if the lifetime cancer risk is less than 1 in 100,000; and for a reproductive or developmental toxin, if the exposure is less than one thousand times as high as the No-Observed-Adverse-Effect level (i.e., a thousandfold safety factor). These calculations can be based on reasonably anticipated rather than worst-case exposure scenarios.
6. Official notice is published in the *Federal Register.* Matters of particular interest are often reported in the popular press or private newsletters. Information about draft and newly published regulations is also commonly available on an agency's web site. Twice yearly, a comprehensive report that describes all the regulations an agency is working on or has recently finished is published in the *Federal Register* as the Unified Agenda of Federal and Regulatory and Deregulatory Actions.
7. After publication in the *Federal Register* as a final rule, the regulation is added to the Code of Federal Regulations (CFR). Title 40 of the CFR, which contains most environmental regulations, is revised every July 1 and is available in PDF format at http:// www.epa.gov/epahome/cfr40.htm.
8. For example, President Clinton issued an executive order on environmental justice that stated "To the greatest extent practicable and permitted by law . . . each Federal agency shall make achieving environmental justice part of its mission by identifying and addressing, as appropriate, disproportionately high and adverse human health or environmental

effects of its programs, policies, and activities on minority populations and low-income populations." This executive order also set forth specific task groups and reporting requirements related to environmental justice for federal agencies.

9. Carruth, R. S., and Goldstein, B. D. "Relative Risk Greater than Two in Proof of Causation in Toxic Tort Litigation." *Jurimetrics,* 2001, *41,* 195–209.
10. Brent, R. "Commentary: Bendectin and Birth Defects: Hopefully the Final Chapter. Birth Defects Research Part A." *Clinical and Molecular Teratology,* 2003, *67,* 79–87.
11. Although an administrative action is quicker, a judicial action provides the possibility of stiffer fines, as well as follow-up enforcement if the violator fails to comply.
12. Injunctions are issued sparingly, and minimum requirements generally include a risk of imminent serious harm for which monetary compensation would not be an adequate remedy.
13. Goldstein, B. D., and Carruth, R. S. "Implications of the Precautionary Principle: Is It a Threat to Science?" *European Journal of Oncology,* 2003, *2,* 193–202; Goldstein, B. D., and Carruth, R. S. "Implications of the Precautionary Principle to Environmental Regulation in the United States: Examples from the Control of Hazardous Air Pollutants in the 1990 Clean Air Act Amendments." *Law & Contemporary Problems,* 2003, *66,* 247–261; Goldstein, B. D. "The Precautionary Principle, Toxicological Science, and European-U.S. Scientific Cooperation." *Drug Metabolism Reviews,* 2004, *36,* 487–495.
14. G. Majone ("The Precautionary Principle and Its Policy Implications," *Journal of Common Market Studies,* 2002, *40,* 89–110) has pointed out a particularly egregious abuse related to a new European Union aflatoxin standard that, based upon the precautionary principle, is by far the most stringent in the world. Its effect is to protect European agricultural interests while excluding about $700 million per year in agricultural produce from sub-Saharan African nations, arguably the poorest in the world. The health benefit, under a worst-case risk assessment, is one case of liver cancer every two years among half a billion Europeans.
15. These include, for example, matters as diverse as acid deposition, wood stoves, consumer products affecting the ozone layer, and trading of pollution allowances.
16. Cost and technological feasibility may, however, be considered in deciding on regulatory strategies to achieve the ambient standards.
17. See Chapter 9 for discussion of the use of standard safety factors in environmental management.
18. The term *hazardous air pollutants* is a loose one, which often gives rise to confusion. To a toxicologist, all chemicals have intrinsic hazards; it is only the question of dose that determines whether and to what extent risk is imposed. There is a further confusion in that by definition under the Clean Air Act the term is not applied to the NAAQS pollutants, even though it is the latter that are known to have the greatest effect at ambient concentrations.
19. For example, in a 1984 decision on benzene, EPA administrator Ruckelshaus included risk to the population, risk to the maximally exposed individual, needed capital investment, and annual emission control costs as among his considerations as to which industrial sources to regulate.
20. Asbestos, beryllium, mercury, radionuclides, inorganic arsenic, benzene, and vinyl chloride.
21. 42 U.S.C. §7412(b)(2), emphasis added.
22. The emission limits are set separately for each industrial category, based on the best-controlled 12 percent within the category. If EPA considers that all emitters within the category have been too lax to serve as role models, it can look outside the industrial category to determine what is achievable.
23. Goldstein, B. D., and Carruth, R. S. "Implications of the Precautionary Principle to Environmental Regulation in the United States: Examples from the Control of Hazardous Air

Pollutants in the 1990 Clean Air Act Amendments." *Law & Contemporary Problems,* 2003, *66,* 247–261.

24. Goldstein, B. D. "The Maximally Exposed Individual: An Inappropriate Basis for Public Health Decisionmaking." *The Environmental Forum,* 1989, *6,* 13–16.
25. For example, both benzene, a known human carcinogen, and toluene, a noncarcinogen with similar solvent properties, are listed.
26. However, there is some evidence suggesting the potential carcinogenicity of lead.
27. An alternative approach under the Safe Drinking Water Act is to set the health goal at zero but to allow a permissible level above zero.
28. Information about EPA's regulation of drinking water under SDWA can be found at http;//www.epa.gov/safewater.
29. 42 U.S.C. §300g-1(b)(1)(A).
30. Arsenic, for example, occurs both naturally and from human activity. Treatment requirements are the same, regardless of origin.
31. 42 U.S.C. § 300g-1(b)(1)(C).
32. 42 U.S.C. § 300g-1(b)(4)(A).
33. Not discussed here are National Secondary Drinking Water Regulations which relate to aesthetics (taste, odor, etc.) rather than health risks. These are recommended but not enforced by EPA, although states may use these recommendations as a basis for their own standards.
34. 42 U.S.C. § 300g-1(b)(4)(B) and (D). In certain exceptional circumstances, EPA may set a more stringent MCL if the defined "feasible" level does not adequately address human health risk. 42 U.S.C. § 300g-1(b)(5)(A). In any event, a cost-benefit analysis is required for every new NPDWR. 42 U.S.C. § 300g-1(b)(4)(C).
35. 42 U.S.C. § 300g-1(b)(7)(A).
36. Beginning in 1986, the SDWA prohibited the installation of lead pipes in public water systems. The lead contamination addressed by this rule comes from pipes in situ before that prohibition went into effect.
37. *American Water Works Ass'n* v. *EPA,* 40 F.3d 1266 (USDC 1994).
38. Like the Clean Air Act, the CWA has more stringent effluent standards for new sources because better antipollution measures can be economically incorporated in new construction. In addition, the CWA requires more stringent effluent standards for toxic pollutants.
39. 33 U.S.C. § 1313(c)(2)(A).
40. For additional information, see the FDA web site at http://www.fda.gov.
41. In terms of risk-based regulation, an important addition is the Food Quality Protection Act of 1996, which recognizes the risk issues of infants and children. This is discussed in Chapters 4 and 14.
42. Health supplements are classified as foods under the Act, but their regulation is sufficiently distinct and significant to warrant separate treatment here.
43. *Food* as defined in the Act includes food components. Notable exceptions to FDA jurisdiction (besides meat and poultry) are alcoholic beverages and restaurant food and sanitation. Although FDA does not regulate pesticides, it does regulate pesticide contamination of food products. FDA also regulates animal feed to minimize the risks to animals and to people consuming the products; for example, aflatoxin in dairy cattle feed is regulated on the basis of the hepatic cancer risk to milk drinkers. Dietary supplements, also classified as food, are discussed separately in this section.
44. FDA estimates that it regulates $240 billion worth of domestic food and $15 billion worth of imported food per year, involving about fifty thousand food establishments.

45. The Center for Food Safety and Applied Nutrition (CFSAN, the FDA office responsible for food and cosmetics) lists among its primary responsibilities the policing of food additives (including ionizing radiation and color additives), chemical and biological contaminants, and the safety of foods and ingredients developed through biotechnology.
46. Even naturally occurring (i.e., nonadditive) contents are treated as adulteration if of sufficient quantity to be injurious to health. Moreover, food is deemed "adulterated" if it has any "filthy, putrid, or decomposed substance," or if it is otherwise unfit for food.
47. FDA regulates eggs in the shell. The Department of Agriculture is responsible for eggs in liquid or other forms, as well as for beef.
48. The definition regarding disease is broader, for example, "any article intended to diagnose . . ."
49. FDA may obtain the supporting evidence, but only by expressly requesting it.
50. http://www.cfsan.fda.gov/~dms/fdahdye.html.
51. Toxic Substances Control Act, 15 U.S.C. §2601(c).
52. The main chemicals excluded from TSCA are drugs, covered under the Federal Food, Drug and Cosmetic Act, and pesticides, covered under the Federal Insecticide, Fungicide, and Rodenticide Act.
53. In regulating the manufacture and distribution of chemicals, TSCA can be viewed as a front-end effort to minimize the problem of hazardous waste.
54. For an interesting and informative discussion of the unreasonable risk standard as it applies in TSCA, FIFRA and other Acts, see Applegate, J. S., "The Perils of Unreasonable Risk: Information, Regulatory Policy, and Toxic Substances Control," *Columbia Law Review*, March 1991, *261*.
55. The large number of relatively untested chemicals in commerce has led to an agreement to test "high production volume" chemicals (http://www.epa.gov/chemrtk/volchall.htm), although it remains unclear whether sufficient investment has been made in improving the ability of the testing approaches to detect potential adverse effects.
56. Using structure-activity relationships to predict the toxicity of a new chemical is a useful but limited tool. An example is that the central nervous system toxicity shared by benzene and alkyl benzenes is readily predictable from chemical structure; yet it is only benzene that causes hematological effects due to its specific metabolites. Similarly, because of a specific biological niche, of the related straight chain hydrocarbons n-pentane, n-hexane, n-heptane, and n-octane, it is only n-hexane that produces peripheral neuropathy.
57. One million pounds per year is deemed to be "substantial" exposure or release. The criteria for substantial human exposure consists of either one hundred persons in the general population, or of ten thousand consumers of a product, or of one thousand workers.
58. The agencies represented are the EPA, the Occupational Safety and Health Administration (OSHA), the National Institute of Occupational Safety and Health (NIOSH), the National Institute of Environmental Health Science (NIEHS), the National Cancer Institute (NCI), the Council on Environmental Quality (CEQ), the National Science Foundation (NSF), and the Department of Commerce.
59. REACH is still under consideration by the EU parliament. Depending on its final wording, it may have a significant effect on the harmonization among nations of risk-based procedures for assessing new and existing chemicals.
60. http://www.epa.gov.
61. 42 U.S.C. 6924(m)(1).
62. 98 S.Ct. 2531 (United States Supreme Court, 1978).
63. 114 S.Ct. 1677 (United States Supreme Court, 1994).

CHAPTER FIFTEEN

WHY RISK ASSESSMENT IS NOT ENOUGH TO PROTECT HEALTH

Rationale for a Precautionary Approach to Science and Policy

Joel A. Tickner

Learning Objectives

Students who complete this chapter will be able to

1. Understand some of the critiques and limitations of risk assessment and its use in public health decision making
2. Understand the precautionary principle and approaches for its application in public health decision making
3. Understand the role of risk assessment and other tools in a more precautionary approach to decision making

The enormous growth of synthetic chemistry following World War II signaled the beginnings of a new industrial era, one of great prosperity, improved health, and new conveniences for society. The explosive production, use, and emission of these substances has also resulted in a large-scale experiment on human and ecosystem health, the full impacts of which are still unknown and may never be well-understood. Little information exists on the toxicology, health effects, or exposures for the vast majority of some seventy thousand industrial chemicals currently in commerce (although this situation is improving). Even less is known about the cumulative impacts of long-term exposures to mixtures of chemicals or exposures at particularly sensitive points in development. Yet, there is strong evidence that many

of these chemicals are found in house dust, food, air, water, and our bodies (including cord blood and breast milk).

Uncertainty pervades our attempts to understand these impacts of toxic substances for two reasons: (1) scientific tools are limited in their ability to identify, measure, and anticipate harm to human health and the environment and (2) we live in complex, dynamic, heterogeneous systems. Uncertainty complicates decision making, can undermine the authority of regulatory agencies, and leads to contentious debates about causal links, relative harm, and risk-benefit tradeoffs. These debates are amplified when the potential victim or the type of impact is unknown or unidentifiable.

During the past 25 years government agencies in the United States have responded to these environmental hazards and uncertainty by developing various decision-making instruments and structures. They have built what can be termed a *risk-based* decision framework in which decisions are frequently made on the basis of unilateral, agency-developed "reasonable" or "acceptable" levels of risk. Under this framework, permissible environmental exposures are deduced through a heavy reliance on quantitative risk assessment, a method for combining uncertain scientific information on hazards and exposures into similarly uncertain probabilistic health risk data, through the incorporation of numerous simplifying assumptions.

Although this structure has been successfully used to control certain hazards, in practice it suffers from numerous constraints. First, the "acceptable" risk-based framework generally determines how much exposure is safe or acceptable, even though safe levels may be impossible to establish. (Acceptability of risk is a politically and culturally determined phenomenon, not a scientific one.) By asking such questions, the risk-based approach limits consideration of the magnitude or distribution of potential harm from activities and fails to recognize options for prevention. Second, by incorporating narrow hypotheses and disciplines, it often results in an oversimplification of complex causal relationship and hides any resulting uncertainty and ignorance involved in examining such problems. Third, the quantitative evidence of causal links often required by administrative and legal agencies generally places the burden of demonstrating harm on those exposed to toxic chemicals. In sum, by implicitly acknowledging that chemical exposure is inevitable, the current approach to environmental decision making can endanger long-term public health and limit industrial innovation toward sustainable production and consumption.

The precautionary principle, a guiding principle for public health policy derived from the age-old tradition of "first, do no harm," provides an alternative framework for addressing uncertain health risks. It is underscored by the notion that government agencies have an obligation to take anticipatory, preventive ac-

tion even when the nature or magnitude of harm is not well-understood. A precautionary framework for decision making explicitly acknowledges uncertainties and ignorance, and recognizes that environmental decisions cannot be based on science alone. Under a precautionary approach, uncertainty is viewed as a reason to take action to prevent harm rather than as a reason to postpone action. Such an approach incorporates a greater range of information from multiple disciplines and constituencies than does current decision making. By asking a different set of questions—"How much harm can be avoided?" "What are the alternatives to this activity?"—a precautionary framework for decision making can better protect human and environmental health.

Other chapters in this book outline the history and practice of risk assessment in the science and policy of public health, which has been advanced as the *sound science* method of decision making for environmental health. Unfortunately, the elevation of risk assessment as the primary tool for decision making has occurred in an uncritical fashion, with little attention paid to the limitations of risk assessment and risk-based policy in the prevention of complex and uncertain risks.

In this chapter we explore the limitations of the current use of risk assessment in public health policy. Following an examination of the limitations of risk assessment and risk-based policy, we present an alternative framework underscored by the precautionary principle. While some have characterized risk assessment and the precautionary principle as opposing concepts, we view them as being quite different, yet complementary, in many respects. We analyze how the precautionary principle can be implemented in practice and present some of the limitations of a precautionary approach to policy.

Limitations of Risk Assessment and Risk-Based Policy

Since the early 1980s the United States regulatory and scientific response to environmental degradation and uncertainty has focused heavily on the development of quantitative assessment methods. Tools such as risk assessment and cost-benefit analysis were developed in the United States to assist decision makers in making complex decisions about industrial activities and their impacts. These methods presuppose the ability to objectively and adequately characterize and quantify complex hazards and their probability of occurrence. These predictions are then incorporated into decisions that are based on agency-established (or sometimes court or congressional) levels of reasonable or acceptable risks and, often, economic feasibility. Risk assessment was originally developed for mechanical problems such as

bridge construction, where the technical process and parameters are well-defined and can be analyzed. Wynne (1993) notes that by definition, risk indicates that probabilities of occurrence are fairly well-understood, whereas in most environmental health decision making, available information and uncertainties do not allow for such precision. However, risk assessment has taken on the role of predictor of extremely uncertain and highly variable events.

Defined by the National Research Council in 1983, quantitative risk assessment has become a central element of environmental and health decision making in the United States. The technique of risk assessment has evolved over the years to address different disease end points and to incorporate broader notions of exposure and greater analysis of uncertainty. But the general framework for conducting risk assessments remains the same: hazard identification, dose-response assessment, exposure assessment, and risk characterization (National Research Council, 1983). Risk assessment (science) is also generally separated from risk management (policy).

The development of risk assessment has brought substantial advances in the scientific understanding of exposure and disease and our ability to predict adverse outcomes from hazardous activities. Risk assessment is a useful tool for predicting outcomes in data-rich circumstances when the nature of the harm is specific and well-characterized and probabilities are well-established. It provides a standardized, structured methodology for decision making that has its foundations in science.

Nearly all decisions involve some weighing of risks, either qualitatively or quantitatively. However, the reliance on risk assessment as the sole analytical technique in environmental and health decision making has significant disadvantages. We discuss specific criticisms of quantitative risk assessment and its use as a central, singular tool in regulatory decision making in the following sections (O'Brien, 2000; Tickner, 1996).

Limiting Broader Understanding of Risks and Stakeholders

Risk assessment tends to limit the amount of information and disciplines used in examining environmental and health hazards. It should be noted that *numerical determinations crumple a lot of information (but sometimes very little information) into a single value, losing track of nuances and qualitative details about that information.* This may inhibit a holistic understanding of complex systems and interactions. It can limit consideration of uncertainties, multiple exposures, cumulative effects, sensitive populations, or less-studied end points (such as developmental toxicity) and alternatives to a dangerous substance or activity.

Limiting Interdisciplinary Perspectives

In a risk assessment approach, scientists tend to study risks from a single disciplinary perspective, even though it might take an interdisciplinary approach to synthesize sufficient evidence to characterize a problem. Multidisciplinary teams may be more likely to find new ways to frame hypotheses that lead to insights not possible from narrow disciplinary viewpoints. The recognition of the problem of endocrine disruption provides an example. A review of many different types of evidence on the effects of persistent pollutants on wildlife in the Great Lakes led to the hypothesis that a common mechanism of action might be causing a variety of reproductive and developmental effects (Colborn and Clement, 1992). Because of the fragmentation of scientific disciplines, no single researcher was able to develop a coherent hypothesis. An interdisciplinary conference provided the opportunity for scientists from many different fields to meet and share insights.

Devaluing Qualitative Information

Scientists tend to devalue qualitative information, viewing it as of lesser quality than quantitative evidence (Funtowicz and Ravetz, 1992). But in the face of great uncertainty such information may be the highest-quality information on which to base decisions. For example, parents of children in the farming regions of Sonora, Mexico, raised concerns about the impacts of pesticides on their children's health and development. Dr. Elizabeth Guillette set out to study similar communities of native Mexican farmers—one community that used pesticides and one community that did not. She was able to identify subtle but real differences in neurological development caused by pesticides by comparing the drawings of children in pesticide- and nonpesticide-exposed communities (Guillette, 2003). These results were supported by other laboratory and human evidence of the impacts of pesticides on neurological development. Yet the differential effects seen in these communities would not have been captured through traditional study designs.

Limiting Consideration of Uncertainties

Uncertainty is frequently considered as a temporary lack of data that can be quantified, modeled, and controlled through additional scientific inquiry (Barrett and Raffensperger, 1999). Yet the formal evaluation of uncertainty in risk assessment is generally limited to a narrow discussion of errors in main results, such as p-values or confidence intervals that indicate the magnitude of error in the outcome variable. Sometimes more comprehensive probabilistic or quantitative uncertainty analyses are undertaken to present a distribution of uncertainties for various

independent variables and the outcome variable. But these may leave out potentially more important sources of uncertainty, such as errors in the model used to analyze and interpret data, variability and susceptibility of specific populations, systemic uncertainties such as the impacts of poverty on health, interactions of variables, and biases from limitations in the conduct of the study (Kriebel and others, 2001; Bailar and Bailer, 1999). Further, current forms of uncertainty analysis leave out critical qualitative uncertainty information such as interpretations of what is and is not known, and what is suspected. While discussion of these issues is increasing among environmental scientists and policy makers, there is little consensus on how uncertainty should be characterized.

Attempts to Get Overly Precise Estimates of Risk

Because of the challenges that uncertainty poses in decision making, agencies tend to focus efforts on characterizing only limited, quantifiable aspects of problems, such as the relationship between a single chemical and a single disease, without examining the potentially more important but more-difficult-to-prove aspects of disease, such as exposure to multiple toxic substances. The attempt to translate problems into manageable, defensible research and policy questions means that we may get extremely precise answers to incomplete or incorrect questions—a *Type III error* (Schwartz and Carpenter, 1999). A related tendency is to refine understanding and increase detail about specific substances or hazards rather than explore new questions. While such increased understanding is interesting from a scientific perspective, it often slows down preventive actions (Cranor, 1993). In these cases, the search for more detailed understanding may be misinterpreted as insufficient knowledge to act and may mask what is already known about a hazard.

Failing to Study Cumulative Exposures

Scientists generally study the direct effects of single exposures rather than exposures to multiple chemicals and other stressors—our everyday reality. For example, there is increasing evidence that pharmaceuticals and personal care products are building up in surface waters and may present an exposure hazard to humans. These include a broad range of products that could cause effects via multiple mechanisms of action, including all drugs (human and veterinary and prescription or over-the-counter, including proteinaceous biologics); diagnostic agents (X-ray contrast media); nutraceuticals; bioactive food supplements (huperzine A); fragrances (musks); and sun-screen agents (methylbenzylidene camphor) (Daughton and Ternes, 1999). While exposures to these substances are arguably low, given the complexity of the exposures, quantitative risk assessment would be virtually impossible. In part due to this complexity, the problem is only now beginning to receive attention.

Limitations of Risk Assessment to Address Cumulative Risks: The Case of Massachusetts

Efforts have been under way for nearly a decade to define methods for cumulative risk assessment. Cumulative impacts assessment has been required for years for new federal activities that may impact health or the environment under the National Environmental Policy Act. But only recently has the Environmental Protection Agency developed guidelines for cumulative risk assessment (Environmental Protection Agency, 2003). Much of this work is focused on the cumulative risk of toxicants acting via a similar mechanism (called *aggregate risk*), but less so on the impacts of diverse stressors such as diet, poverty, or physical hazards. Unfortunately, the use of cumulative risk assessment is limited and controversial as this example shows:

In the Merrimack Valley of Massachusetts, local residents were concerned about exposure from several surrounding incinerators. The state's Department of Environmental Protection (DEP) studied each one individually and told community residents that the risk was acceptable without studying the cumulative effects of five incinerators in a several-mile radius; other industrial exposures in the area; or the compounding impacts of local poverty (Massachusetts Department of Environmental Protection, 1999). In trying to develop a defensible analysis of risk, the agency neglected the multiple interacting exposures of residents in the valley, such as poverty and exposures from lead-based paint, that jointly contribute to residents' risk of adverse health effects. While DEP found that the risks posed by area incinerators were quite low, there was no way to know whether those risks, when combined with others, would be much greater. Due to public pressure, DEP did conduct a second assessment, which focused on aggregating air emissions from the five facilities, but it neglected other factors, including food-based exposures.

In a second effort, the DEP established a scientific advisory committee to determine ways to evaluate the cumulative risks to surrounding communities from solid waste facility siting. Despite concerns that DEP should at least consider how to include cumulative impact considerations in risk assessments given limitations in existing methodologies, DEP concluded: "Currently, tools and methodologies have not been adequately developed for use in a regulatory context." This conclusion assumes need for more data before action can occur and creates a false impression that no cumulative effects are occurring when the real problem is a lack of defensible methodologies to consider them (Massachusetts Department of Environmental Protection, 2002).

Failing to Examine the Unique Characteristics of Vulnerable Populations

Risk assessments tend to focus on the "average" individual even though there might be populations or individuals at much higher risk due to their higher exposures, genetic susceptibility, or developmental vulnerability, such as children. For example, scientists know that some chemicals, such as diethylhexyl phthalate, cause minimal effects in adult laboratory animals but cause substantial effects at much lower doses in developing animals (Tickner and others, 2001). The areas of children's environmental health and environmental justice have arisen, in part, because of the lack of science and policy to address the impacts of exposures on vulnerable subpopulations.

The Use of Multiple, Often Nontransparent Assumptions

Risk assessments are based on numerous assumptions about exposures, human behavior, chemical effects, and chemical fate that may or may not be explicit. While these assumptions are often scientifically based, many times they are political or based on uncertain information. What is clear is that two different risk assessments, conducted on the same problem (even a simple one where data are shared between research groups) will almost always come up with different answers. In a European Union risk assessment exercise in which 11 different risk assessment groups came up with 11 different conclusions that differed by a millionfold the organizers found that "at any step of a risk analysis, many assumptions are introduced by the analyst and it must be recognized that the numerical results are strongly dependent on these assumptions" (Contini, Amendola, and Ziomas, 1991).

Excluding Those Affected

Risk assessment processes often exclude those potentially harmed by environmental degradation. Traditionally they do not include public perceptions, priorities, or needs. As risk assessments become more complex (using more mechanistic tools and pharmokinetic models), they can increasingly exclude public participation; only those with advanced training in modeling, toxicology, and quantitative analysis have the ability to understand the nuances of the analyses and critique their methods.

Limiting Preventive Actions

Risk assessments are generally used for quantifying and analyzing problems rather than trying to solve or prevent them. Quantitative risk assessments are generally

used to set "safe" levels of exposure rather than to identify and compare alternative actions that can prevent a risk in the first place. They also assume particular technologies, actions, and chemicals as inevitable. The necessity of a risk is rarely considered. For example, despite little evidence as to their efficacy and their potential risks to consumers and ecosystems, antimicrobials are widely used in hand soaps, cutting boards, toothpaste, and clothing (Levy, 2001).

Risk assessments can also be expensive and time-consuming, tying up limited agency resources in developing detailed understanding about risk, while similar resource investments could be used to develop and implement safer processes, materials, and products. For example, while a typical two-year cancer bioassay for a single chemical may cost several million dollars, currently the entire federal government budget for green chemistry—the design of safer and cleaner chemicals—is about the same. In the case of dioxins, for which a risk assessment by the EPA initiated in the 1990s has yet to be finalized, hundreds of millions of dollars have likely been spent studying detailed nuances of risk for a chemical that scientists have known for more than thirty years to be extremely toxic. This disproportional investment in risk assessment is not only costly and slows actions to protect health, it is inefficient and can be a hindrance to innovation in safer chemicals and products.

Problems When Risk Assessment Is Applied in Policy

The regulatory system in the United States and in many other countries perpetuates these limitations in risk assessment due in part to the constant challenges that regulators face from the regulated community, politicians, and others. To make their jobs easier and decisions more defensible, decision makers prefer to release seemingly precise estimates of risk and not talk about the uncertainties underlying the numbers. In addition, they often avoid studying problems if their tools or methods are not fully developed or might be challenged by regulated parties or others (Applegate, 2000).

Unfortunately, the limitations in risk assessment to quantify risks are often misinterpreted as proof of safety. For example, when initially responding to concerns about the health impacts of phthalates used in PVC medical devices on children and chronically ill adults, the U.S. Food and Drug Administration and the medical device industry stated that these substances had been used safely for 40 years without any evidence of human impacts (Phthalate Information Center, 2003). It may be that the reason there was no evidence linking health effects to these devices is that no large studies have been done looking for them, despite

toxicological evidence of effects (Tickner and others, 2001). Biologist John Cairns has noted that scientists and policy makers often discount highly uncertain risks, while concluding that "unrecognized risks are still risks, uncertain risks are still risks, and denied risks are still risks" (Cairns, 1999). Lack of evidence is certainly not proof of safety.

Uncertainty is often viewed by regulators and the regulated community as a negative aspect of science, one that can weaken agency authority (Funtowicz and Ravetz, 1992). Reluctance to acknowledge uncertainty pushes agencies to use numbers as a facade to cover up what are often political decisions. The potential for challenges from regulated parties forces agencies to create certainty where it does not exist, to avoid addressing complex risk (such as cumulative effects), and to wait for more defensible proof of harm before acting, in order to avoid conflict (Brickman, Jasanoff, and Ilgen, 1985; Clark and Majone, 1995). In addition, with regard to uncertainty, it is in the interest of those fighting regulation to convert political questions into technical/scientific ones so as to delay regulation, also called *manufactured* or *smokescreen uncertainty* (Michaels, 2005). Thus, uncertainty is often used strategically by the regulated community as a reason to justify inaction and as a tool to minimize the importance of risk (Clarke, 1989; Abraham, 1994).

There are two particular areas in risk assessment that appear problematic from a manufactured uncertainty perspective:

1. *Mechanisms of action and pharmokinetics.* Over the past 20 years, regulated entities have argued that mechanisms of toxicity for substances must be demonstrated as relevant to humans before regulation occurs, despite evidence that carcinogens identified in laboratory experiments are often ultimately identified as human carcinogens (Fagin and Lavelle, 1996; Huff, 1999; Tomatis, 2002). This pressure can result in policies that "discount" carcinogens based on mechanism and direct agency resources toward developing complex models to understand mechanisms before taking action.

2. *Hormesis.* Research on the concept of hormesis—that low doses of harmful exposures might result in beneficial effects—is increasingly being advocated by regulated industries and others concerned about regulation, despite evidence of problems in its application in risk assessment and policy (Calabrese and Baldwin, 2002). A 1999 U.S. District court, for example, ruled that agencies must not only demonstrate the harmful effects of pollution but show that the beneficial effects of pollution do not outweigh the potential risks (*American Trucking*, 1999).

The problem here is that while the fine points of the evidence on risk uncertainties are debated, nothing is done about the potential hazards.

Using Risk to Forestall Preventive Actions: The Case of Methylene Chloride

Even when data are available, uncertainties raised about the nuances of the risk can stall action. For example, it took the Occupational Safety and Health Administration (OSHA) nearly a decade to finalize a standard for methylene chloride. Many of those years of debate—over a chemical known to be problematic—were focused on minutiae about how the chemical was transported through the human body and caused its toxic effects (U.S. Occupational Safety and Health Administration, 1997). While these debates occurred, workers continued to be exposed to what has now been deemed a potential carcinogen. This approach to environmental science is not only inefficient, but harmful to human health and ecosystems. Indeed, if scientific research had been focused on analyzing alternatives to methylene chloride in various industrial operations while simultaneously exploring the substance's mechanism of action, these debates over toxicologic mechanism might have been avoided and workers would have been better protected sooner because debates over toxicologic mechanism would not have been the only focus of research (Roelofs and Ellenbecker, 2003).

Responding to Risk Assessment Critiques

Government agencies have recognized and are responding to criticisms about risk assessment and its use. They are developing recommendations to improve, but they still rely heavily on, the process. Many academic and nonprofit research and outreach centers are undertaking innovative cumulative risk assessment and community-based comparative risk assessment projects, but these tend to be few and far between. Reports in the mid-1990s by the National Research Council (1994; Stern and Fineberg, 1996) and the Presidential/Congressional Commission on Risk Assessment and Risk Management (1997) recommended changes to the process of risk assessment as follows:

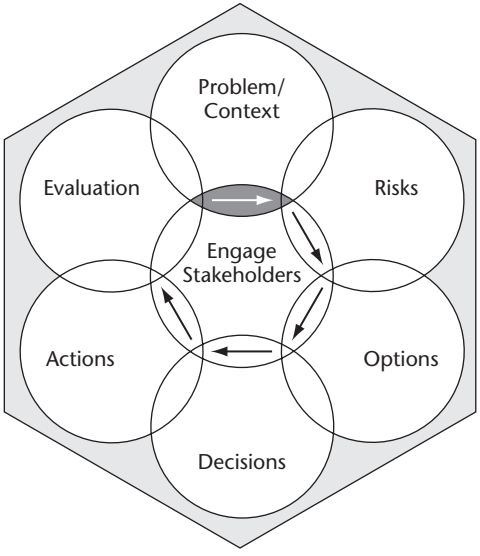
1. Better and more comprehensively examine uncertainty and variability.
2. Include affected publics throughout the risk assessment and management process (from problem definition through risk management).
3. Increase consideration of prevention and options in the risk assessment process.
4. Provide more holistic problem definition.

5. Include greater consideration of cumulative and interactive effects and sensitive subpopulations.
6. Undertake greater evaluation of actions taken:

Figure 15.1 shows a diagram outlining a framework for improving risk assessment processes.

While these recommendations point in the right direction, momentum to put them into practice on a broad scale has been missing. In fact, a growing reductionism in risk assessments (toward mechanistic analyses) does not bode well for such positive changes. In addition, some analysts are proposing that all risk decisions fully consider and quantify "risk-risk" tradeoffs of regulations, for example, natural versus chemical carcinogens and the beneficial aspects of pollution. While it is important to consider potential risk tradeoff from decisions and account for them through flexible decision-making structures, such a requirement would create additional burdens that could halt preventive public policies (Graham and Wiener, 1995).

FIGURE 15.1. THE PRESIDENTIAL/CONGRESSIONAL COMMISSION FRAMEWORK FOR RISK ASSESSMENT AND RISK MANAGEMENT.



Introducing the Precautionary Principle

Put simply, the need for precaution arises from uncertainty. If all potential hazards could be quantitatively assessed with minimal error, then it would be relatively easy to base policy decisions on quantitative risk assessments, and little else. But in a world in which global weather, aquifers, and growing children still hold many mysteries, we believe that the best environmental policies will be informed by the best available science; but they will also be guided by a principle of erring on the side of caution.

In a broad sense, the precautionary principle is not a new concept. Precaution, like prevention, is firmly rooted in centuries of medical and public health theory and practice. Public health practitioners study the famous story of John Snow, who, through observation and informed judgment, and an incomplete understanding of the illness, removed the handle from a Broad Street pump and stopped a cholera epidemic.

Roots of the Precautionary Principle

As a principle of environmental and health decision making, the precautionary principle has its roots in the German word *Vorsorgeprinzip.* A more correct translation of this word is "forecaring or foresight principle," which emphasizes anticipatory action; it is a proactive idea with a connotation slightly different from *precaution,* which to many sounds reactive and even negative. The *Vorsorgeprinzip* was established to deal with serious emerging, but not proven, risks to ecosystems and health. It is based on the concept that society should seek to avoid environmental damage by careful social planning that can stimulate innovation, job creation, and sustainable development. Over the past 25 years the principle has served as a guiding element in international treaties addressing marine pollution, ozone-depleting chemicals, genetically modified organisms, fisheries, climate change, and sustainable development (Raffensperger and Tickner, 1999; Kriebel and others, 2001; O'Riordan, Cameron, and Jordan, 2001).

The 1994 Maastricht Treaty forming the European Union established precaution as a central element of European environmental health policy, and the Rio Declaration of the United Nations Conference on Environment and Development established precaution as a central element of sustainable development (Raffensperger and Tickner, 1999). Although not explicitly mentioned, precaution underscores many worldwide health and environmental policies designed to

protect health and the environment when knowledge of risks is incomplete. These include policies pertaining to food safety, water and air quality, and occupational health and chemical substitution. For example, drug regulation throughout much of the world is based on the precautionary notion that pharmaceuticals should be demonstrated safe and effective before people are exposed to them and that manufacturers have a responsibility to act on knowledge of unintended impacts. In the late 1970s the OSHA Generic Cancer Clause (which was never fully implemented) called for elimination of workplace exposure to carcinogens because of the difficulties in establishing "safe" levels of exposure (Tickner, 2000).

Even early court decisions regarding occupational and environmental laws called for agencies to act despite imperfect information. In a case about regulation of lead as a gasoline additive under the Clean Air Act (*Ethyl Corp.* v. *Environmental Protection Agency,* 1976), the D.C. Circuit Court found the following:

> Case law and dictionary definition agree that endanger means something less than actual harm. . . . Where a statute is precautionary in nature, the evidence difficult to come by, uncertain, or conflicting because it is on the frontiers of scientific knowledge, the regulations designed to protect the public health, and the decision that of an expert administrator, we will not demand rigorous step-by-step proof of cause and effect. Such proof may be impossible to obtain if the precautionary purpose of the statute is to be served.

Unfortunately, this precautionary trend in court interpretations abruptly ended with the decision in a judicial case regarding the establishment of an occupational health standard for benzene (*Industrial Union Department, AFL-CIO* v. *American Petroleum Institute,* 1980). The Supreme Court struck down the OSHA standard on the grounds that the agency had not demonstrated significant risk with substantial evidence, stating that "Congress was concerned, not with absolute safety, but with the elimination of significant harm." The case ushered in requirements for agencies to conduct detailed risk assessments before issuing standards (Cranor, 1999; Applegate, 2000).

Definitions and Elements of the Precautionary Principle

A widely cited definition of the precautionary principle is the 1998 Wingspread Statement on the Precautionary Principle: "When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically" (Raffensperger and Tickner, 1999).

While definitions differ (as is often the case in international policy), they all have similar elements: if there is uncertainty, yet credible scientific evidence or concern of threats to health, precautionary measures should be taken. In other words, preventive action should be taken on early warnings even though the nature and magnitude of the risk are not fully understood.

Implementing the precautionary principle requires new approaches to environmental science and public policy to make them more effective at anticipating risks and promoting cost-effective alternatives to risky activities, products, and processes. This includes the following:

Shifting the questions asked in environmental and health policy. One fundamental change the precautionary principle encourages is that scientists and policy makers begin to ask a different set of questions about activities and potential hazards as a priority. Instead of asking, "What level of risk is acceptable?" or "How much contamination can a human or ecosystem assimilate before demonstrable harm?" we must ask, "How much contamination can we avoid while still achieving our goals?" "What are the alternatives or opportunities for prevention?" and "Is this activity needed in the first place?"

*Shifting presumption*s. In addition to switching the questions decision makers ask about risks, the precautionary principle shifts the presumptions used in decision making. Rather than presume that specific substances or activities are safe until proven dangerous, the precautionary principle establishes a presumption in favor of protecting public and environmental health in the face of uncertain risks. This places the responsibility for developing information, regular monitoring, demonstrating relative safety, analyzing alternatives, and preventing harm on those undertaking potentially harmful activities.

Transparent and inclusive decision-making processes. Decisions under uncertainty are essentially policy decisions, informed by science and values. Thus, involving more stakeholders could improve the ability of decision makers to anticipate and prevent harm. A more democratic decision-making process would allow nonexperts who think more broadly without disciplinary constraints to see problems, issues, and solutions that experts miss. Lay judgments reflect a sensitivity to social and political values and common sense that experts' models often do not acknowledge, and the lay public may have a better capacity than experts alone for accommodating uncertainty and correcting errors. Finally, broader public participation may increase the quality, legitimacy, and accountability of complex decisions (Fiorino, 1990; Tickner, 2001).

Risk-Based Versus Precaution-Based Science and Policy: The Case of Phthalates in Baby Toys

An example of redefining when we know enough to act in environmental health is the approach taken by the Danish government with the use of phthalate plasticizers in children's toys. Phthalates are used to make PVC toys flexible and are also used as solvents in cosmetics (e.g., nail polish). They are among the most widely dispersed chemicals in the environment and are widely found in human blood and urine as well as in household dust. The most commonly used phthalate, diethylhexyl phthalate, is an animal carcinogen and adversely affects the kidneys and respiratory system (Tickner and others, 2001). Of greatest concern is the fetal and neonatal reproductive toxicity of the phthalates, which can affect the testes, sperm production, and development and cause defects in developing embryos.

When concerns were raised about these chemicals being used in children's teething toys, the Danish government weighed the clear evidence of exposure and uncertain toxicity of the chemical, the unique vulnerability of children to environmental insults, the existing availability of alternatives, and the need for such toys and determined that precaution should be applied to phase these chemicals out of toys used by small children.

In contrast, in the United States, the Consumer Product Safety Commission (CPSC), which must quantitatively demonstrate harm before acting, undertook expensive and somewhat unrealistic research using adult volunteers to measure children's exposure. The CSPC came to the conclusion that the risk to children was likely low but that there was a great deal of uncertainty about the risk and that companies should voluntarily remove phthalates from toys. The ultimate result in the United States and Denmark were the same—the chemicals were removed from the toys—but the costs in time, resources, and additional exposure to achieve that result was much greater in the United States.

Source: Kriebel and others (2001).

Precaution and Science

The precautionary principle has many implications for environmental science: what we study, how we study it, and how we summarize and communicate results. As environmental science faces the increasing challenges of more complex risks with greater uncertainty and ignorance, the nexus between science and preventive policy becomes even more important. In this context, there is no contradiction be-

Acting on the Basis of Uncertain Knowledge: The Case of Polybrominated Diphenyl Ethers

Under a more cautious approach, often evidence of exposure along with basic toxicological data on a substance—but without clear evidence of risk or harm to humans—will be enough to set basic policies to prevent or reduce exposure. For example, substances called polybrominated diphenyl ethers (PBDEs), used as flame retardants in plastics and foams, can be found in human body fluids. They are found in places where they should not be: in breast milk and in umbilical cord blood of newborns (and PBDE levels have greatly increased in breast milk over the past 20 years) (Päpke and others, 2001; Birnbaum and Staskal, 2004). These substances are strikingly similar in structure to PCBs, a class of compounds we know to be dangerous to human health. Based on concerns regarding their persistence and bioaccumulation in humans, several Scandinavian countries took action to restrict certain PBDEs, which resulted in their decreased levels in breast milk. Debate about the human health risk and fate of an additional PBDE (the deca congener used in textiles and electronics) has stalled similar action in many countries while risk assessments are conducted.

Following these international actions, in late 2003 the EPA entered into a voluntary agreement with one manufacturer to stop production of two of these substances, and has initiated efforts to identify safer alternatives to them. The potential of these substances to do harm, even if based on limited evidence, combined with documentation of their presence in breast milk and cord blood, should be sufficient to trigger a search for alternative ways to obtain the flame-retarding properties of these chemicals. If safer alternative ways of providing the same flame-retarding function can be found, the substitution should not have to wait for quantitative evidence showing that the estimated risk of potential health outcome exceeds an acceptable risk threshold.

tween good science and precaution. Rather than demand less science, the precautionary principle demands more rigorous and transparent science that provides insights into how health and ecosystems are disrupted by technologies, identifies and assesses opportunities for prevention and restoration, and makes clear the gaps in our current understanding of risks (Kriebel and others, 2001).

A shift to more precautionary policies creates opportunities and challenges for scientists to think differently about the way they conduct studies and communicate results. The 2001 Lowell Statement on Science and the Precautionary Principle, drafted by 85 scientists from 17 countries, outlines changes in science and science policy that would more effectively address uncertain, complex risks, including:

- A more effective linkage between research on hazards and expanded research on primary prevention, safer technological options, and restoration
- Increased use of interdisciplinary approaches to science and policy, including better integration of qualitative and quantitative data
- Innovative research methods for analyzing (1) the cumulative and interactive effects of various hazards to which ecosystems and people are exposed, (2) impacts on populations and systems, and (3) the impacts of hazards on vulnerable subpopulations and disproportionately affected communities
- Systems for continuous monitoring and surveillance to avoid unintended consequences of actions, and to identify early warnings of risks
- More comprehensive techniques for analyzing and communicating potential hazards and uncertainties (what is known, not known, and can be known) (Tickner, 2003)

In risk assessment efforts, scientists and policy makers often refer to the concept of *sound science*, a term often used to represent the standard methods of quantitative risk assessment. But risk assessment is not a scientific discipline per se. It is a formalized, systematic tool used to integrate and communicate scientific information. Yet it is just one tool in a big scientific and policy toolbox.

A quantitative risk assessment may not be the most appropriate scientific method for many uncertain risks; the type of evidence reviewed is too rigid and does not consider that alternative methodologies can shift the very concept of acceptable risk. A more precautionary approach should be informed by the most *appropriate science*, which can be understood as a framework for choosing methods and tools to fit the nature and complexity of the problem (Kriebel, Tickner, and Crumbley, 2003). Critical to this framework is the flexibility to integrate a variety of research methods and data sources into problem evaluation. Also critical is an ability to consult many constituencies to understand the diversity of views on a problem and seek input on alternative solutions. Complex environmental problems that arise in poorly understood systems also require new approaches to examining evidence as a whole rather than as its separate parts. Appropriate science is solutions-based, focused on broadly understanding risks but also on finding ways to prevent their inception. With this approach, the limitations of science to fully characterize complex risks are openly acknowledged, making it harder to use incomplete knowledge to justify preventive actions.

Sir Bradford Hill, the often misquoted father of modern epidemiology, recognized the need to act on the basis of limited scientific knowledge, informed judgment, and common sense when he said,

> All scientific work is incomplete—whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing

> knowledge. That does not confer upon us a freedom to ignore the knowledge we already have or to postpone the action that it appears to demand at a given time (Hill, 1965).

The critical question for decision makers under an appropriate science and precautionary approach (and in environmental and health policy in general) is not causality or "safe" exposures but rather whether there is enough evidence to act to prevent a particular risk. In this respect environmental science, being an applied science, serves the purpose of informing policy, of helping decision makers understand when and if there is enough evidence to act. When there is enough evidence to act (in essence whether a risk is "acceptable") is not simply a numerical determination; it must depend on the nature of the problem and be a function of (1) the available knowledge and accumulated understanding; (2) the complexity, magnitude, and uncertainty of the risk; (3) the presence of high-risk populations; (4) the availability of options to prevent the risk; (5) the potential implications of not acting to prevent the risk; and (6) social and public values.

Alternatives Assessment: A Prevention-Oriented Approach to Weighing Scientific Information

The vast majority of environmental science used to support government environmental policy has focused on understanding and characterizing environmental and public health problems. Millions of dollars are invested annually in investigating issues ranging from the mechanism of action of a small number of toxic compounds and the fate and transport of substances in environmental media to the effects of contaminants on environmental resources and the technologies for measuring, monitoring, and managing those pollutants. While much of this work is important and valuable, it focuses on problems often at the expense of investigations that focus on solutions. To explicate problems without a proportionate effort to find solutions sharply diminishes the efficacy of environmental policy. A precautionary approach to protecting public and environmental health requires a solutions-oriented policy framework that seeks to identify, assess, and implement alternatives to high-risk materials and activities. Such a policy must be a holistic, integrated policy designed to prevent risks at their source, avoid risk shifting, establish far-reaching long-term environmental goals, and stimulate innovation in safer and cleaner forms of production, products, and activities.

There are several reasons why examining alternatives is such a critical part of precautionary policies (Tickner and Geiser, 2004).

Focus on Solutions Rather Than Problems

The most important aspect of alternatives or options analysis is that it reorients environmental protection discussions from problems to solutions. Rather than examine the risks of one bad option, alternatives assessment focuses on choices and opportunities: it draws attention to what a government agency or proponent of an activity *could be* doing rather than to determining the acceptability of a potentially harmful activity. For example, chlorinated solvents provide a service of degreasing and cleaning. Once we understand this service, it is possible to think of a range of alternatives such as ultrasonic cleaning or less toxic aqueous cleaners—or even redesigning a metal part so that the need for cleaning is eliminated altogether.

Examining choices permits a broader range of questions and considerations about activities, including the need for them. Further, focusing on seeking safer alternatives may also allow decision makers to partially bypass contentious and costly debates over proof of harm and causality and instead dedicate scarce public health resources to solutions.

Stimulating Innovation and Prevention

Research has shown that in terms of health benefits, strong regulation and options analysis requirements can drive innovation and produce substantial cost savings for firms as well as for society (Ashford and Caldart, 1997). Alternatives assessment calls attention to current and on-the-horizon alternatives and focuses resources on them that might otherwise be directed solely to the expensive and time-consuming process of characterizing problems. It allows different parties to identify and recognize a wider range of hazards.

Multirisk Reduction

Alternatives assessment can be a more efficient means of reducing risks in the long term. Problem-based approaches generally examine one risk or problem at a time and are met with one solution at a time. These solutions are often inflexible (e.g., pollution control equipment) and require successive investments of technology to meet each new problem and standard. Alternatives assessment exercises can examine a broader range of factors and options. For example, a traditional risk-based approach might narrowly examine the risks of a particular agricultural pesticide, while an options-based approach might examine the availability of safer pesticides, alternatives to pesticides altogether (organic agriculture), or alternative structures such as smaller farms that might reduce dependence on pesticides. In a specific firm, an alternatives assessment might examine technology options that

would benefit both worker and environmental health or ways to reduce toxic substance, energy, and water use simultaneously.

Greater Public Participation and Burden Shifting

Examination of alternatives can fundamentally change burdens on decision makers and the public. The public will see risks as unnecessary when there are safer alternatives, and decision makers will be more willing to take action (O'Brien, 2000). Rather than being paralyzed, as U.S. government agencies often are, by having to defend each decision in detailed quantitative estimates, decision makers could use alternatives assessment both to defend themselves against challenges and to garner public support for sensible solutions.

Alternatives assessment also allows decision makers to make proponents of potentially harmful activities more responsible to examine and implement safer options, in order to prevent risks before a technology is introduced and to continuously improve safety. For example, through the New Chemicals Program of the Toxics Substances Control Act, the U.S. Environmental Protection Agency (EPA) sends signals on the types of chemicals that should be avoided and provides guidance and support so that firms examine and develop safer chemicals and syntheses (Tickner, 2000). This shifts the burden onto manufacturers to develop alternatives even when there is only limited evidence that a particular chemical might pose a risk. Such a search for alternatives reduces the uncertainty faced by both decision makers and proponents of activities in that one can expect greater certainty about the merits (availability, viability, and potential effects) of an environmentally superior alternative than about the risks of a single option (Ashford and Caldart, 1997).

Nonetheless, assessing alternatives will not eliminate the need to assess and compare hazards and risks (since we will always need to compare options and sometimes define permissible exposures)—but that can be done by incorporating a broader set of tools as described below. Further, feasibility of alternatives, both technical and economic, will always be an issue that must be considered. An alternative that is not economically or technically viable is not a reasonable alternative, although these can change with time.

Developing Rapid Screening and Assessment Tools

Given the number of hazards and risks that must be characterized by decision makers in government, communities, and industry, a more precautionary approach requires the development of useful rapid screening tools to prioritize risks,

identify safer alternatives, and make decisions. In the areas of chemicals management, more and more such tools are being developed. These focus on several areas:

- *Identifying intrinsic hazards of chemicals.* Hazard assessment focuses on the intrinsic hazards of chemicals regardless of their exposure. For example, a highly reactive or persistent or bioaccumulative chemical has greater potential to cause problems. By identifying intrinsic hazards of chemicals, it becomes easier to prioritize actions. While exposure controls can reduce risks, they cannot eliminate them (e.g., accidents), whereas eliminating the intrinsic hazard can eliminate the risk. For example, perchloroethyele used in dry cleaning will always be a carcinogen and will always require strong controls to prevent exposure, whereas water as a cleaning solvent is intrinsically safer.
- *Identifying use categories and other surrogates for exposure.* All exposures are not the same, yet understanding exposure is often one of the greatest challenges in risk assessment. One way to address this is to identify surrogates for exposure, those that can be used to qualitatively understand risks. For example, open consumer use can lead to high exposure for a wide population (in a cleaner), whereas closed-loop workplace use will likely result in low exposures to a small population. Alternatively, *use cluster*s, identification of particular uses of substances, for example, solvents in degreasing, can help identify exposures and opportunities for prevention.
- *Identifying classes of chemicals with similar characteristics or risk profiles.* Many chemicals with similar structures tend to present a qualitatively similar set of risks. Other sets present a similar set of risk issues, for example, persistent and bioaccumulative toxics. Rather than calculate the risks of each one of a group of chemicals, we could identify a hazard or risk profile for that class or group of chemicals and undertake prevention activities on the basis of that knowledge. For example, organohalogens have the potential to be persistent in the environment. Lists of such chemical categories or chemicals of concern could provide an incentive to identify alternative chemicals that present less of a risk.
- *Identifying design criteria for safer chemicals and products.* Scientists often focus on what makes a particular chemical or activity dangerous rather than on what would make it safer. Principles, such as the principles of green chemistry and green engineering, provide a benchmark for designing and assessing safer alternatives.
- *Assessing risk rapidly with flexibility to quickly modify assumptions.* Perfect risk assessments are not always feasible or needed. In many cases, more rapid assessments that allow us to identify the sensitivity of a risk distribution to changing assumptions and uncertainties about exposures, hazards, and the like can be used. Such rapid assessments are being developed by certain government agencies and industrial groups.

New Tools for Assessing Safer Chemicals and Products

Stakeholders increasingly need tools to determine the relative safety of a particular chemical or product. Without such knowledge, it is difficult to know whether a particular alternative is indeed safer, a lack of knowledge that may potentially lead to unintended impacts of substitution. While more work is needed in this area, during the past several years government agencies, academic institutions, and businesses in the United States and Europe have actively developed new tools to rapidly characterize chemical risks and assess and compare alternatives. These include:

- *The Column Model.* Developed by the Institute for Occupational Safety (BIA) of the German Federation of Institutions for Statutory Accident Insurance and Prevention, the Column Model presents data on chemical hazards in a tabular format using European Union Risk (R) phrases for criteria. The criteria for each cell in the table are determined primarily by risk phrases (R-phrase). The column model creates a framework for presenting data by hazard category and potential risk level. The columns are six hazard end points: acute health risk, chronic health risk, environmental risk, fire and explosion, liberation properties, and risks by technology.
- *Quick Scan.* Developed by the Dutch Ministry of Housing, Spatial Planning and the Environment, the Quick Scan method is a voluntary tool for companies to rapidly assess chemicals in the absence of data to prioritize for further study and action. The steps in the Quick Scan method are: gather available hazard data on chemicals, use criteria to assign chemicals to hazard levels (low, medium, high), use decision-making rules to determine concern categories, and revise concern categories based upon use data. Similar to the Column Model, Quick Scan specifies criteria for determining hazard levels of a chemical for specific hazard end points. The Quick Scan goes a step further by developing qualitative risk characterizations based on the use type of the substance (e.g., open professional use, closed system, and consumer use).
- *Pollution Prevention Options Analysis System (P2OASys).* Developed by the Massachusetts Toxics Use Reduction Institute, P2OASys is a tool to assist companies in comparing options for toxic-use reduction on the basis of their acute and chronic human toxicity, physiological impacts, ecological effects, life-cycle impacts, and physical characteristics. It converts data for each hazard category into a numeric scale of 2, 4, 6, 8, or 10, allowing comparison of hazard tradeoffs across options. P2OASys works on the basis of a maxi-min principle, meaning that the highest (most problematical) hazard value dominates any category of analysis.
- *The EPA's Pollution Prevention Framework.* An unexpected and important outcome of the EPA's New Chemicals Program has been the development of tools and processes to rapidly evaluate chemical life-cycle risks in a multidisciplinary manner and in the face of uncertain or missing data. Because required notification of new-substance manufacture occurs at the premanufacture stage, companies are only

(Continued)

required to submit available data (and in some instances some testing). As such, only a small percentage of premanufacture notifications come into the agency with toxicity or even physiochemical data. EPA must then rapidly characterize potential risks using a rapid review approach involving longstanding agency scientists with extensive knowledge about chemical structures and hazards. Due to missing data on new chemicals, over the past 20 years the EPA has developed a number of methods and tools including quantitative structure activity relationship (QSAR), as well as exposure assessment and hazard assessment tools (e.g., EcoSAR, Oncologic, CHEMSTEER, EPISUITE) (Waugh, 2004). These tools are then updated as data come in on particular chemicals. Tools such as EPA's Pollution Prevention Framework (including the PBT—Persistence, Bioaccumulation, and Toxicity—Profiler) are widely distributed to government agencies and industry (Environmental Protection Agency, 2005) to provide support to government and industry in identifying problem substances and designing safer chemicals.

Source: Lowell Center for Sustainable Production (2005).

Precautionary Assessment: A Decision-Making Tool for Preventive Decisions Under Uncertainty

An important critique of the precautionary principle is that it does not provide any guidance as to how decisions should be made. Building on decision-making tools developed for prevention activities and traditional business decision-making processes (and consistent with the Presidential/Congressional Framework for Risk Assessment and Risk Management), a process flow, called *precautionary assessment*, is outlined below to embed the precautionary principle in preventive decision-making processes (Tickner, 2000). This provides an outline of the decision-making steps that should take place under a framework to improve decision making under uncertainty. The heuristic is not a static, formulaic approach but rather a series of considerations that should form all sound decision making under uncertainty. This approach allows for learning based on accumulated knowledge, experience, and understanding, as well as flexibility to adapt decisions to the specific nature of the problem (affected communities and nature and type of evidence).

The extent to which this heuristic is carried out depends on the nature of the risk; for highly uncertain risks more effort might be placed on assessment rather than on alternatives at an early stage. For risks with potentially irreversible or generational effects emphasis might be placed on alternatives from the onset.

The steps of precautionary assessment are covered in the following sections.

Broad Problem Framing

The scope of the problem defines the types of solutions that are sought. Problems should be framed in as broad a manner as possible to identify root causes of the risks and various points of intervention. What constitutes a threat to health, for example, the disruption of social networks, should be broadly interpreted. At this stage issues of participation and burdens and responsibilities of different actors should be considered.

Environment and Health Impact Analysis (EHIA)

In the Environment and Health Impact Analysis (EHIA), evidence of risks and uncertainties are examined to determine the possibility (and plausibility) of a significant health threat and the need for precautionary action. As many environmental risks are complex and highly uncertain, such an analysis must involve both the totality and individual pieces of the evidence for plausible indications of effects. The goal is to build a coherent picture of potential impacts: a "story." In precautionary assessment this analysis is completed using a *research synthesis* (Stoto, 2000) or weight-of-evidence approach (U.S.-Canada International Joint Commission, 1994).

The Environment and Health Impact Analysis should include consideration of the wide range of sources of information and plausible harm and impacts identified during problem scoping. Evidence of potential impacts and uncertainties should be gathered from as diverse an array of disciplines and constituencies as possible, including observational studies, worker case histories and case reports, toxicological studies, wildlife and domestic animal studies, cellular studies, ecological assessments, epidemiologic studies, community health studies, structure activity analyses, modeling, and monitoring. The impacts examined in the analysis should include human and ecosystem health impacts; acute and chronic effects; interactive and cumulative effects; direct and indirect impacts; and socioeconomic, historical, and aesthetic impacts. Since the list of plausible impacts might be very large, it is useful to prioritize by impacts of greatest concern from a scientific and political point of view.

The four steps of Environmental and Health Impact Analysis include the following:

1. *Hazard analysis.* The purpose of this step is to understand the strength and quality of the evidence that there is or could be a detrimental effect. We examine studies and potential impacts individually and as a whole and consider inherent properties in the activity or substance that could lead to adverse impacts.

2. *Exposure analysis.* In this step, evidence of actual or potential exposure is gathered from various sources. We analyze the nature (direct, dispersive, controlled, closed-system) and intensity of exposure as well as when and to whom exposure occurs, including the potential for cumulative and interactive exposures.
3. *Magnitude analysis.* In this step we examine the evidence on the seriousness of potential impacts, including spatial and temporal scales of effects, potential catastrophic impacts, susceptible subpopulations, reversibility of adverse effects, and degree of connectivity of effects. When the potential magnitude of effects is large, weaker evidence provides a cause for concern.
4. *Uncertainty analysis.* This step includes both a qualitative and quantitative assessment of gaps in knowledge. Uncertainty should be analyzed broadly in terms of type (parameter, model, systemic), sensitivity to changing assumptions, and feasibility of reducing uncertainty.

The reason for having four separate analyses rather than a single risk number is that it opens opportunities for prevention and intervention. Unpacking information on hazard, exposure, magnitude, and uncertainty provides greater flexibility, understanding of the nature of potential impacts, and opportunities for preventive interventions in decision making. The results of these subanalyses are combined into a final Environment and Health Impact Analysis. Here, the weight of the evidence of potential or actual harm for a particular hazard or group of hazards is presented as one of five defined categories (based on analyses of hazard, exposure, and magnitude): (1) very significant, (2) moderately significant, (3) slightly significant, (4) relatively insignificant, and (5) cannot be ruled out. There needs to be a detailed narrative outlining the rationale for the categories, the evidence on which the determination was based, and other quantitative and qualitative considerations. A categorical, or graded classification, approach to characterizing risk has an important benefit over traditional "continuous" risk variable approaches. It provides greater accountability by providing clarity about the nature of the available evidence and choices in the analysis instead of a single number that can hide nuances and details of the information as well as the multiple hidden assumptions on which the risk number is based.

The Environmental and Health Impact Analysis narrative should be clear about what is known, is not known, and can be known about the (suspected) threat, limitations of scientific studies to understand the threat, and gaps in information, including research needs. It should also indicate the extent to which uncertainty, and particularly ignorance, can be reduced through additional research. Quantitative evidence such as uncertainty analyses and quantitative assessments of risk should be included in this narrative and final categorical determination. The plausibility and probability of various outcomes should also be considered (i.e., the

sensitivity of the results). *The analysis provides a determination, based on the weight of evidence, as to whether an activity is associated with or may cause harm, and the potential severity of that harm.*

Alternatives Assessment

As outlined previously, the other centerpiece of precautionary assessment is thorough evaluation of alternatives to prevent or minimize harm. The steps of an alternatives assessment should include:

Examination and understanding of the impacts and purpose of the activity. The purpose of this step is to better understand the function or service that the activity provides (for example, a chlorinated solvent provides degreasing, a pesticide provides pest control) and whether that service can be provided in a less damaging way; how hazardous materials are used (materials accounting); and potential impacts and benefits of the activity.

Identification of a wide range of options. Alternatives identification should be a brainstorming exercise involving a diverse range of stakeholders to identify a broad range of existing and on-the-horizon possibilities, including stopping the activity altogether. A broad problem scoping helps ensure that identification of alternatives is comprehensive and addresses the impacts of multiple risks. For example, in the case of a pesticide, options should not be narrowed to other pesticide choices but should include integrated pest management and nonchemical methods.

Comparative analysis of alternatives. The goal of comparative options analysis is to thoroughly examine and compare technical feasibility and economic, environmental, and health and safety impacts and benefits from the existing or proposed activity and identified alternatives. Where options are limited and relatively similar to the existing/proposed activity this analysis might be complex and uncertain, requiring comparative estimates of risk. In other cases, where clear environmental health benefits reside in an alternative (e.g., water as a replacement for a chlorinated solvent), the analysis will be more easily completed.

Alternatives selection. This step should include a narrative of the identified options, results of the analysis, and criteria on which the alternative was chosen. The *alternatives plan* should contain a comprehensive description of how the alternative will be implemented, including cost limitations; how technical barriers will be addressed; how specific hazards associated with the chosen alternatives will be minimized; and how any tradeoff impacts (e.g., changes in

workplace design) will be addressed. It should also contain a summary of how progress in reducing impacts will be measured and what type of monitoring will be put in place for early detection and action on potential impacts. It may be possible to institute interim alternatives while long-term alternatives with greater environmental health benefits are being developed.

Precautionary Action Analysis

The last part of precautionary assessment is to determine the appropriate courses of action. This could be considered the risk management phase of the decision process, yet it is fully integrated into all of the previous steps. *Precautionary action analysis* involves weighing the information gathered earlier to determine how much and what type of precaution should be taken. Policy tools for implementing precautionary action and preventing harm, ranging from further study to banning the activity, are chosen based on the severity of the risk, uncertainty involved, and availability of feasible alternatives. Finally, a feedback and monitoring scheme is developed to measure benefits and provide early warning of potential problems. The determination of actions is not based on a specific threshold for action but rather considers all of the available evidence in determining the most health-protective, yet reasonable, course of action. Precautionary assessment may also result in a decision that an activity is unlikely to cause harm or that its impacts would be minimal—in which case institution of a monitoring scheme may be the most appropriate action step. Decisions made under a precautionary assessment should not be considered permanent but part of a continuous process of increasing understanding and reducing overall impacts. Once precautionary actions have been chosen, follow-up and monitoring schemes for the activity should be developed (e.g., using health and environmental indicators and surveillance). This type of feedback is critical to understanding the impacts of precautionary actions, as well as providing early warnings of harm, thus helping to avoid unintended consequences. It also stimulates continuous improvement in environmental performance and technological innovation.

This heuristic is not a static, formulaic approach but rather presents a series of considerations that should form all sound decision making under uncertainty. A first step in the process is for authorities, and when appropriate for stakeholders, to identify whether the threat is of sufficient concern (either scientifically or in terms of public perception and concern) to warrant expenditure of public health resources for further examination and analysis of alternatives. In cases where sufficient concern has not been achieved, a "wait-and-see" approach could be instituted, revisiting the decision as further information accumulates. For threats that are well-established

FIGURE 15.2. THE STEPS OF PRECAUTIONARY ASSESSMENT.

I. Problem Scoping

- Broadly frame and define problem
- Outline the range and types of plausible impacts (including direct and indirect ones)
- Identify who/what are the affected populations and those that might be disproportionately affected
- Identify research and information needs about health impacts and alternatives
- Identify who is responsible for studying the risk, providing information, or taking appropriate preventive actions
- Identify who should be involved in the decision-making process and at what points during the process

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II. Environment and Health Impact Analysis

- Hazard analysis: weigh strength of evidence of plausible impacts; broadly examine evidence of hazards from multiple sources and disciplines and prioritize concerns; consider quality of studies
- Exposure analysis: examine potential for exposure from various sources; consider nature and intensity of exposure and who is exposed (if some one group may be exposed at a particularly sensitive time); consider potential for cumulative and interactive exposures
- Magnitude analysis: examine magnitude and severity of potential impacts including spatial and temporal scale, susceptible subpopulations; reversibility, connectivity
- Uncertainty analysis: examine amount and type of uncertainty as well as feasibility of reducing uncertainty and potential impacts on outcomes
- Consider weight of evidence on association, exposure, and magnitude together to determine potential threat to health or environment; develop narrative with rationale, limitations in studies, and research needs

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III. Alternatives Assessment

- Examine and understand impacts and purpose of activity
- Identify wide range of alternatives
- Conduct detailed comparative analysis of alternatives (pros/cons, economic, technical, health and safety)
- Select "best" alternative and institute implementation and follow-up plan

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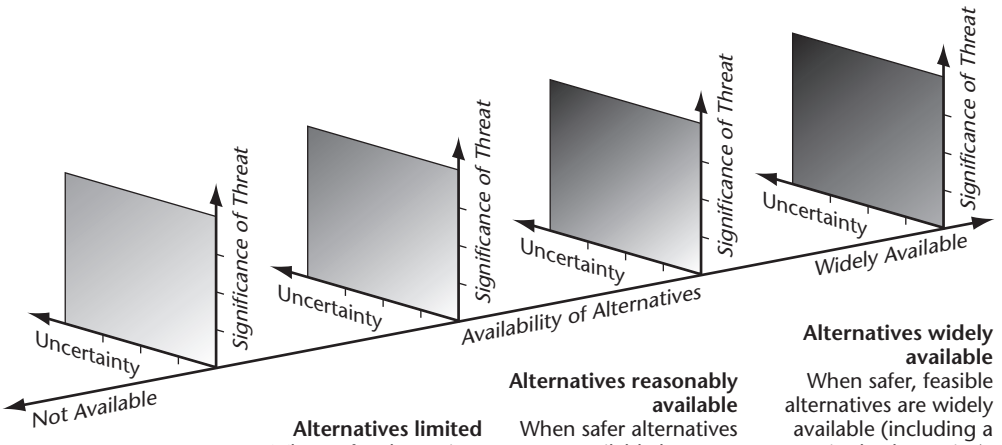
IV. Precautionary Action Analysis

- Determine appropriate level of precaution needed based on level of threat of harm, uncertainty, and availability of alternatives
- Determine what other considerations must be included in the decision—cost-effectiveness, least burdensome option, technical feasibility, political and cultural feasibility, adaptiveness?
- Determine the types of interventions needed to ensure adoption of the precautionary changes—such as technical assistance, information, technology support
- Determine "precautionary feedback" regime to minimize unintended consequences and for continuous improvement

FIGURE 15.3. GRAPHIC ILLUSTRATION OF PRECAUTIONARY ASSESSMENT.



Alternatives currently not available
When safer alternatives are not currently available or are infeasible, strict to weak precautionary measures should be taken depending on the significance of the threat and uncertainty of exposure and impacts. In the meantime, efforts should be undertaken to explore safer and feasible alternatives.

Alternatives limited
When safer alternatives are limited because of feasibility of potentially significant trade-off risks, strict to weak precautionary measures should be taken depending on the significance of the threat, uncertainty about exposure and impacts, and the potential for safer alternatives to be developed.

Alternatives reasonably available
When safer alternatives are available but may have technical or economic feasibility concerns, strict to moderate precautionary measures should be applied depending on the significance of the threat, uncertainty about exposure and impacts, and the potential of the alternatives to be refined.

Alternatives widely available
When safer, feasible alternatives are widely available (including a single alternative), strong or strict precautionary measures should generally be applied. The choice of alternative will depend on the particular characteristics of the situation.

it would be reasonable to proceed directly to an examination of alternatives and preventive interventions.

Under this framework the appropriate measures are a function of the significance of the threat, uncertainty, and the availability of safer alternatives. Significance of threat is a function of hazard, exposure, and magnitude of potential impacts. The darker color indicates the extent to which precautionary measures should be taken—from strict (restrictions) to weak (additional targeted study).

Applying Alternatives Assessment in Practice: Cleaner Production and Goal Setting

Alternatives assessment is at the heart of the concepts of pollution prevention and cleaner production. Cleaner production and pollution prevention involve changes to production systems and products to reduce pollution at the source (in the production process or product development stage). This includes reducing the raw material, energy, and natural resource inputs (dematerialization) as well as decreasing the quantity and harmful characteristics of toxic substances used (detoxification) in production systems and products. These concepts do not focus on identifying safe levels of exposure but rather on using science and technology to understand inefficiencies and impacts from chemicals and material use and options for reducing those impacts (Jackson, 1993; Geiser, 2001). Risk assessment and similar tools are used to compare options rather than determine whether to act in the first place.

A success story in this approach is the Toxics Use Reduction Program in Massachusetts, where manufacturing firms are required to undertake a materials accounting (to understand how chemicals are used and their inefficiencies) every year, as well as to undertake a detailed alternatives assessment (planning exercise) every two years. Technical support to firms in undertaking these plans and in identifying and implementing new technologies is provided. As a result of this approach, which focuses on solutions rather than acceptable risks, toxic chemical emissions in Massachusetts have been reduced more than 80 percent, chemical waste more than 60 percent, and chemical use more than 40 percent, while saving industry more than $15 million (http://www.turi.org). This pollution prevention approach can also be applied to the use of pesticides in agriculture and general pest control—integrated pest management. They can also be applied to the choice of building materials, city, design, and other risks.

Alternatives assessment activities often begin with ambitious goals. This is consistent with the forward-looking vision of the precautionary principle. Foresight involves outlining the type of world we wish to live in and the establishment of long-term goals for protection of health. Goal setting, coupled with development of short- and medium-term objectives, public policies (to address barriers to their implementation and to minimize social disruptions), and metrics and indicators, focuses attention not on what futures are likely to happen but rather on how desirable futures can be obtained, a concept called *back-casting*. For example, while we may never fully know the risks to the developing fetus from exposure to toxic chemicals in cord blood, we do know that less exposure is better and can begin to identify ways to reduce the buildup of chemicals in our bodies.

Goal setting is a practice that is fairly common in public health. Examples are the smallpox eradication campaign, smoking cessation goals, goals for reduction in certain types of disease, such as cancer, and the U.S. Public Health Service Healthy People 2010 goals (U.S. Public Health Service, 2000). The northern European countries have been leaders in developing goal-setting processes for environmental health. These processes provide an excellent example of how prevention and precaution can serve as a compass directing society toward practices that are more ecologically sound, health promoting, and sustainable. In 1997 the Swedish Parliament passed a set of Environmental Quality Objectives for the millennium (http://www.miljomal.nu/english/english.php). The overarching goal of these objectives it "to hand over to the next generation a society in which the main environmental problems have been solved." The goals that have been developed are issues-based (e.g., water quality and forests). They include implementation steps and measures to track progress. Assessment is used to weigh alternatives to achieve particular goals. Such goals are common sense and use science in a more proactive manner to solve problems rather than simply to characterize them.

Swedish Environmental Quality Goals

- Reduced climate impact
- Clean air
- Natural acidification
- A nontoxic environment
- A protective ozone layer
- A safe radiation environment
- Zero eutrophication
- Thriving wetlands
- Good-quality groundwater
- A balanced marine environment
- A good build environment
- Sustainable forests

Critiques of Precaution

There have been numerous critiques of the precautionary principle and its application in public policy. Clearly no decision tool will solve every problem, and precaution is no exception. Precaution is not about zero risk (an unachievable goal) but rather about how to expand the types of science, constituents, and considerations to make more health-protective decisions under uncertainty and com-

plexity. We must distinguish between bad application of the precautionary principle and simply bad judgment and decision making. Precaution is no guarantor against mistakes, but neither is risk assessment. Two important critiques of precaution are as follows (Tickner, Kriebel, and Wright, 2003):

1. *It leads to risk tradeoffs.* Seeking to avoid creating new problems while solving existing ones is an important aspect of the precautionary principle. Well-intended, precautionary public health interventions can result in serious adverse consequences (Goldstein, 2001). Further, a potentially hazardous activity may benefit public health, as in the case of pesticide spraying to reduce transmission of a mosquito-borne virus. In recent years there have been vigorous debates on the role of the precautionary principle in pesticide spraying for malaria and West Nile Virus control. Often these debates revolve around tradeoffs between short-term well-recognized viral risks and uncertain, less-understood chronic pesticide risks. Unintended consequences are a serious concern in all precautionary public health interventions and should be thoroughly considered. However, concern about these tradeoffs should not keep public health practitioners from taking preventive actions in the face of uncertainty. Not taking action on accumulating knowledge has consequences of its own, as demonstrated in the European Environment Agency report "Late Lessons from Early Warnings: The Precautionary Principle 1898–1998" (European Environment Agency, 2002; http://www.eea.eu.int). Rather, tradeoffs should be considered in their broadest possible sense. By exploring and implementing a wide range of preventive options (the choice is not just between the use of DDT and people dying from malaria), including a broad range of perspectives in decision-making processes, using a multidisciplinary scientific lens and systems perspective to examine risks, and developing methods to monitor public health interventions for signals of problems, such tradeoffs can be minimized or avoided.
2. *It creates false positives.* One concern often raised against precaution is that it may lead to acting against false-positive risks, overregulation that diverts important resources from "real" risks. It has been argued that precaution amounts to increasing the sensitivity of the screening tests for environmental hazards. Using an analogy to medical screening tests, it therefore follows that the number of false-positive tests must increase. A decision to act on limited knowledge about a hazard may ultimately turn out to have been due to a false positive, but if it spurs innovations, stimulates new economic forces, and raises awareness of ecologic cycles and other lessons of sustainability, then it may still be judged to have been a worthwhile decision. Yet, precaution does not mean only more-sensitive tests; it also means linking risk evaluation to alternatives assessments

and more democratic discussions of social needs and goals. The concern for false positives should also be weighed against the very substantial evidence of numerous false negatives that have resulted from past practices.

Conclusions

While a useful tool in environmental decision making, particularly around well-established risks, risk assessment and its application in risk-based policy have several important limitations. As outlined in this chapter, the uncritical use of risk assessment as the only sound science approach to decision making can not only limit information and considerations in decision-making processes but create a false sense of certainty when addressing highly complex and uncertain health and ecosystem threats. The problems of risk assessment not only relate to its use (attempts to quantify what are often unquantifiable problems) but its application in risk-based policy (where decisions are not made until some threshold of acceptable risk and certainty are crossed). A sole reliance on quantitative risk assessment—without equal consideration of options to prevent impacts—can lead to unnecessary and unethical delays in preventive actions to protect health.

The precautionary principle provides a framework—a guide or compass—for characterizing uncertain threats in a broader manner and weighing information on alternatives and prevention options. It is not an alternative to or replacement for risk assessment. Rather, it is an overarching guide to decision making under conditions of uncertainty and complexity. Risk assessment is one tool in a more precautionary toolbox for preventive public health. Yet precaution forces us to question the inevitability of risks and focus our attention on ways to prevent them in the first place. For example, in the case of mercury-contaminated fish we could advise women regarding how much of certain fish to eat based on a risk-benefit quantification balancing the nutritional benefits of fish against the potential neurological impacts to the developing fetus. We could also ask why women should be forced to worry about harming their children when they eat fish, how that mercury is getting into the fish, how to get it out of the fish, and what are their other alternative means of gaining the nutrient value they get from eating fish during pregnancy (fish or supplements)?

Precaution is more than simply additional safety factors in risk assessment processes, as some analysts have argued. Safety factors are only useful to the extent that the critical hazardous effects can be accurately observed, sensitive populations identified, and risk probability quantified. Recent research indicates that current safety factors may not be precautionary at all. EPA researchers have found that many of the *reference doses* (regulatory safety levels of exposure) may in fact corre-

spond to disease risks of greater than one in one thousand (meaning a probability of one in one thousand people exposed over a lifetime becoming ill from exposure), clearly not safe levels given uncertainties about many chemicals and their effects and the preventability of many exposures (Castorina and Woodruff, 2003).

The use of risk assessment under a more precautionary framework should be defined by the nature of the problem, available evidence, and availability of alternatives. Instead of being used to establish "safe" or "acceptable" levels of exposure (which are political judgments), it can best be used to better understand the hazards of activities, including how they can adversely affect human health and the environment; increase knowledge about the complexity and uncertainties of environmental risks; compare options for prevention; and prioritize cleanup activities.

The value information risk assessment provides for precautionary approaches can be augmented by the development of more qualitative risk assessment methods and uses, greater acknowledgement of subjective framing of assumptions, a greater incorporation of multidisciplinary methods, and increasing use of additional quantitative tools such as decision trees, multicriteria analysis, and scenario analysis. Because precaution demands a broad examination of available evidence, it is critical to harness the skills and tools that risk assessors provide and that can support precautionary, preventive decision making.

Thought Questions

1. What are some of the key strengths and weaknesses of the use of quantitative risk assessment in public health decision making?
2. How could the practice of risk assessment and its application in policy be modified/improved to better address complex and uncertain risks? How could risk assessment be more effectively used in a decision-making framework guided by the precautionary principle?
3. What are some of the benefits and drawbacks of applying the precautionary principle in decision making?

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CHAPTER SIXTEEN

RISK COMMUNICATION

Susan L. Santos

Learning Objectives

Students who complete this chapter will be able to

1. Understand what risk communication is and how it fits in the risk assessment and risk management decision-making process
2. Understand the regulatory context for risk communication
3. Identify the key principles of effective risk communication
4. Recognize how risk perception affects a lay person's assessment of a risk
5. Understand how to explain/present risk information

The Relationship Between Risk Communication, Risk Assessment, and Risk Management Decision Making

As our society has become more and more technology-based, public awareness and concern over the effects of technology on human health and the environment has heightened. Risk assessment has been used as a tool to estimate the risks to human health and the environment posed by various products, technologies, and activities. Legislation in the early 1970s and creation of several regulatory agencies, such as the Environmental Protection Agency (EPA), elevated the role of risk

assessment in the regulatory process. The procedures for assessing risk soon became a focus of criticism by scientists, industry, and public interest groups (National Research Council, 1983). Initial attempts to address these questions focused on separating the analytic functions of assessing risk from the regulatory or policy function of decision making. The process of evaluating risk was formally described in 1983 by the National Academy of Science's National Research Council (NAS-NRC) report entitled "Risk Assessment in the Federal Government: Managing the Process" (National Research Council, 1983). That study formally recommended the separation of risk assessment from risk management. *Risk assessment* was defined as an objective scientific process for assessing risks. *Risk managemen*t was defined as "The process of weighing policy alternatives and selecting the most appropriate regulatory option, integrating the results of risk assessment with engineering data and with social, economic, and political concerns to reach a decision" (National Research Council, 1983). In spite of this framework, questions remained about whether the risk assessment process could be kept free from the values, biases, and political factors associated with risk management. For example, scientific judgment is exercised throughout the risk assessment process and different choices may lead to substantially different results and corresponding policy recommendations (Jasanoff, 1986).

Over the last 20 years the practice of risk assessment has in part evolved as public worries over possible health risks, regulatory actions, and corporate concerns about liability brought risk assessment and risk management to the forefront in the public and private sectors (Krimsky and Golding, 1992). Discovery of abandoned hazardous waste sites such as Love Canal prompted Congress to pass the landmark Superfund legislation in 1980. Concerns over the potential for a major chemical accident such as what occurred in Bhopal, India, in 1984 resulted in passage of the Emergency Planning and Community Right-to-Know (RTK) Act (SARA Title III) in late 1986. With these new pieces of legislation also came the call by local citizens and citizen groups for both access to information and more involvement in decision making. In 1986 former EPA administrator William Ruckelshaus noted that the question facing government agencies and industry was not whether to involve the public in decisions about risk, but how (Davies, Covello, and Allen, 1987). For the first time, an agency head noted that the responsibility for communicating with stakeholders, including the public, rested upon those making the decisions.

While risk assessment is intended to be an objective process, social scientists, among others, point out that the definition and assessment of risk is in fact a social process that goes far beyond the empirical process of risk envisioned by the 1983 NRC committee. Slovic and Johnson, 1995, have shown that professional affiliation as opposed to scientific training and expertise affects toxicologists' views as

to whether the risk assessment process is overly conservative or needs more conservatism to account for uncertainties. The recognition that scientific and other forms of expert knowledge are socially constructed has set the stage for acceptance among scientists of a broader analytic-deliberative process as necessary to fully define and characterize risks (National Research Council, 1996). Analysis involves the use of rigorous and replicable scientific methods to address factual questions, and deliberation involves processes such as discussion, reflection, and often persuasion to raise issues, increase understanding, and ultimately collectively arrive at decisions (National Research Council, 1996). Similarly, the Presidential/Congressional Commission on Risk Assessment and Risk Management (Omenn and others, 1997) stated: "Results of a risk assessment are not scientific estimates of risk; they are conditional estimates of the risk that could exist under specified sets of assumptions and—with political, engineering, social, and economic information—are useful for guiding decisions about risk reduction."

As the boundaries and context of risk assessment have changed, so has the importance of the third part of the original NAS paradigm: risk communication. As we will explore in this chapter, the practice and theoretical underpinnings to this field have greatly changed over the last 20 years, and risk communication has become a formal recognized part of the risk assessment and risk management decision-making process.

Legal and Regulatory Considerations

As public awareness and concern about environmental issues has increased, federal legislation aimed at protecting public health and the environment has included more extensive communication and public participation requirements. For example, under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), commonly referred to as *Superfund*, public involvement provisions have become a central and also controversial part of the site investigation and cleanup process, and the use of risk assessment as a tool for making site cleanup decisions has corresponding communication challenges. The Superfund Amendments and Reauthorization Act of 1986 (SARA) broadened the public's role in the decision-making process and refer to the importance of stakeholder involvement. The Community RTK Act of 1986 (SARA TITLE III) requires companies to annually provide state and local communities and the EPA with information about the chemicals they release to the land, air, and water. Companies must also provide information on spills and accidental releases. EPA maintains all of this information in a variety of formats and makes it available to the public. SARA Title III was grounded in the belief that industrial disclosure

of risk-related information, and its potential effects on public attitudes, would serve as a powerful tool for motivating company behavior. The implementation of TITLE III has resulted in a significant reduction in facility emissions and releases; also, companies report that they pay more attention to their pollution-prevention activities and have increased their communication with the public (Santos, Covello, and McCallum, 1995). Subsequent expansion of the RTK provisions in the late 1990s requiring utilities to report their emissions has resulted in similar pressure for industry actions to restrict emissions. Section 112(r) of the Clean Air Act Amendments of 1990 requires companies meeting certain criteria to prepare facility risk management plans (RMPs) for the unintentional or catastrophic accidents that could occur for specific hazardous substances, and it requires companies to anticipate worst-case scenarios. Communicating the results of these complex risk analyses and their inherent uncertainties and assumptions has resulted in risk-communication efforts by industry and activist groups alike. The events of 9/11 have called into question, at least on the part of some industry and agency officials, how much of this potentially sensitive information should be made public.

Amendments to the Safe Drinking Water Act of 1996 [42 U.S.C. 3009-3 (c)(4)] require water suppliers to provide annual "consumer confidence reports" on the quality and source of their drinking water. The Food Quality Protection Act of 1996 provides for a comprehensive set of pesticide food safety initiatives covered by the EPA, FDA, and USDA. That landmark legislation also included a series of RTK provisions on the health effects of pesticides, including recommendations for how to avoid risks by reducing exposure to pesticides and maintaining an adequate diet, and noting which foods have tolerances for pesticide residues based on benefits considerations. The law requires that EPA publish this information annually in pamphlets to large retail grocers for public display. The law also allows states to require provisions for labeling or requiring warnings. In addition, for the first time, industry petitions for tolerances must include informative summaries that can be made publicly available. Similarly, agencies such as the USDA and FDA have begun to conduct quantitative microbiological risk assessments for purposes of making food safety decisions and also recognizing that communication of such assessments must be a structured part of the process (Federal Drug Administration, 2002).

The requirements for risk communication have also been extended to the private sector. Passage of laws such as the Occupational Safety and Health Administration's (OSHA) Hazard Communication or worker right-to-know standards requires firms producing or using certain substances to provide workers with risk information on workplace hazards so that they might understand the hazards, determine personal risks, and take appropriate action to reduce their risks. The law

requires chemical manufacturers and importers to assess the hazards of chemicals that they produce or import. Employers must provide training and education on hazardous substances including their effects, emergency procedures, and proper handling.

These examples illustrate the tremendous shift over the last 20 years in the focus and scope of communication and public participation/involvement provisions contained in various agency regulations. Access to information by the public, activist groups, and the media has become a regulatory and policy tool for a wide variety of environmental and health-related issues. The majority of environmental law and regulations have focused on performance-based standards or provided technology-based specifications. In contrast to these traditional command-and-control approaches, requirements that focus on the provision of information often provide indirect pressure through market dynamics, private litigation, and moral pressure by nongovernmental entities. Risk communication is thus a major thrust of such legislation. Further, movement on the part of some toward a *precautionary principle* in which safety must be established prior to allowing for the introduction of new products, technologies, and certain facilities will also likely require a focus on risk communication.

What Is Risk Communication?

In its simplest form, *risk communication* is the communication about some risk. In this book, it is used to refer to communicating about a health, safety, or environmental risk. Covello, von Winterfeldt, and Slovic (1987) have defined risk communication as "any purposeful exchange of information about health or environmental risks between interested parties." This simplistic definition assumes that communication is essentially unilateral, where communication flows from the transmitter or source, the "experts," via some transmission channel to a receiver or target audience (Fisher, 1991). In a *one-way model of communication,* scientists and health officials have historically assumed that rejection of the message was due to a lack of understanding on the part of the recipient rather than to the public's disagreement with either risk messages or, more often, risk management decisions. The term *two-way communication* is used to describe a communication process whereby an exchange of information occurs between source and receiver in a process of reciprocal disclosure. Both of these descriptions of risk communication fail, however, to account for the social and cultural context in which the communication exchange takes place. In reality, risk communication takes place in a multilayered and complicated environment involving a variety of stakeholders, communicators, and a spectrum of risk definitions and messages. Participants in

the communication process play very different roles. Source and receiver are continually interchanged, requiring an appreciation for the multidirectional nature of communication and the need for feedback mechanisms (McCallum and Santos, 1997).

Efforts to broaden the understanding of risk communication as a socially constructed process have come from the work of a number of social scientists (see, for example, Douglas and Wildavsky, 1982; Krimsky and Plough, 1988; Renn, 1992) who have shown that communication occurs and is interpreted within a cultural frame and sociopolitical context. This *social constructionist model* suggests that policy or risk management decisions "should not be made in private by some arhetorical means and then, through rhetoric, attempt to impose that policy on our fellows" (Waddell, 1995, p. 201). Such an approach would have technical experts providing the technical knowledge to conduct a risk assessment while allowing for the input of the stakeholders' values, beliefs, and perceptions in the risk management process. But it is also possible to have nonexperts provide input into the technical decisions to be made in a risk assessment, for example, determining what exposure pathways are of most importance or adjusting the parameters used for exposure as opposed to relying on default assumptions. In 1989, the NRC conducted an extensive study of the communication of risk information and defined risk communication as:

> [an] interactive process of exchange of information and opinions among individuals, groups, and institutions, concerning a risk or potential risk to human health or the environment. It involves multiple messages about the nature of risk and other messages not strictly about risk, that express concerns, opinions or reactions to risk messages or to legal and institutional arrangements for risk management [National Research Council, 1989].

This definition of risk communication goes beyond that one-way unilateral model and allows for the social construction of risk. It is offered here as a more useful means of integrating risk communication within the context of the risk assessment and risk management process.

The Purpose(s) of Risk Communication

Historically, many scientists and health officials in government agencies viewed communication as a way to guide recipients on how to take appropriate measures to reduce risks (Administrative Conference of the United States, 1990). Whether or not it was explicitly stated, communication was viewed as a way of getting peo-

ple to calm down or to somehow simplify risk-related information so that results would be accepted. For public health professionals and those who conduct risk assessments and then must explain their results, a more useful focus is to view risk communication as a reciprocal process whereby health officials and risk assessors may obtain valuable information that can be used in conducting the risk assessment. Ideally, effective risk communication can be used as a means of empowering the public in decision making. Covello, von Winterfeldt, and Slovic (1987) described four broad classes of risk communication based on their primary objective or intended effect: (1) information and education, (2) encouraging behavior change and protective action, (3) disaster warnings and emergency information, and (4) joint problem solving and conflict resolution. In all but the last category, communication tends to be one-way where the goal ranges from telling people what has been done or what decision has been made to telling them what specific actions to take. Renn (1992) offers a different perspective as to the purposes of risk communication: (1) to make sure that all receivers of the message are able and capable of understanding and decoding the meaning of the messages sent to them, (2) to persuade the receivers of the message to change their attitude or their behavior with respect to a specific cause or class of risk, and (3) to provide the conditions necessary "for a rational discourse on risk issues so that all affected parties can take part in an effective and democratic conflict-resolution process" (p. 492). This categorization broadens the notion that risk communication should simply be message-driven and focuses on the processes to obtain understanding and reach consensus on risk management decisions. Lundgren (1994, 2004) describes a topology of risk communication along functional and subject-related lines that embraces the three goals outlined by Renn; it is useful for the purposes of identifying the various and often conflicting goals and purposes of risk communication from a practitioner's perspective.

Lundgren differentiates *care communication* from *consensus* or *crisis* communication. *Care communication* is risk communication about health and safety risks "for which the danger and the way to manage it have already been well determined by scientific research that is accepted by most of the audience" (Lundgren, 1994, 2004). Included in this category are health care or medical communications seeking to inform or advise the audience about health risks such as smoking and AIDS and industrial health and safety risk communications to impart workplace health and safety information or the safe application of pesticides.

Crisis communication is described as communication in the face of an extreme or sudden danger (or perceived danger). Situations for which crisis communications are appropriate range from an accident at a nuclear power plant or industrial complex to the outbreak of a disease (E-coli virus, Mad Cow disease, or pandemic flu) to a natural disaster to more recently concerns about a terrorist

event such as bioterrorism or a dirty bomb. In crisis communication, getting the attention of the target audience(s) is extremely important.

The third form of communications as described by Lundgren is *consensus communication,* which is most appropriate for informing and encouraging groups to work together to reach a decision about how risks should be managed, that is, prevented or mitigated. Included in this form of communication are public participation related communications and *stakeholder involvement processes.* Examples include reaching decisions on the cleanup of a hazardous waste site, siting of a facility, or establishing regulations such as the appropriate drinking water standard. Consensus communication implies that the decision about how to manage the risks results from all those with an interest in how the risk is to be managed participating in the decision-making process (Lundgren, 2004). The concept of consensus communication thus broadens the definition of risk communication beyond that of information disclosure or even exchange. For purposes of this text, consensus communication would include the full range of public participation and stakeholder involvement activities whereby the goal is to enable a mutual discourse and empower all parties to participate in democratic decision making.

Arnstein's "Ladder of Citizen Participation" (1969) provides a framework for critically examining citizen participation and communication activities to uncover both explicit and implicit goals on the part of agencies and those making risk management decisions. This ladder has been adapted by Hance, Chess, and Sandman (1987) to illustrate the distinctions among various forms of citizen participation. One's position on the ladder can be viewed as a function of the goals of the communication and further used to examine the degree of control or power citizens are given in decision making and the corresponding form of communication.

Arnstein's ladder consists of eight rungs, each corresponding to the extent of citizen power in determining the end product. The bottom rungs of the ladder are forms of non-participation. The objective is not participation but to enable power holders to educate or "cure" the participants. Hance and colleagues refer to this as government power. In both of these schemes, communication is one-way. The next several rungs represent degrees of tokenism ranging from informing to consultation to placation (Arnstein, 1969; Hance, Chess, and Sandman, 1987). Here too communication is one-way. Many public meetings and opportunities for public comment fall into this range. One problem with activities falling into this range is that they may simply be an attempt to make the information more palatable to the recipient and thus obscure issues surrounding the transfer of knowledge or power. Further, simplistic representations can misinform as many people as they inform. It is unlikely that a one-way model would ever be appropriate or useful for consensus-type communications. Even in care and consensus communications reciprocal disclosure and feedback from the recipients may be needed to ensure that the goals of increased attention, comprehension, and/or behavioral change can be achieved.

At the top of Arnstein's ladder are forms of participation that allow for varying degrees of citizen power, where communication is used as a means of empowering people. Here communication must be multidirectional, allowing for the full expression and inclusion of multiple sources and receivers who may have conflicting messages and information needs. In this model risk communication would be used to enable people to make their own decisions about risks under their control. In the context of risk assessment and risk management, communication that is higher up the ladder would be structured to enable stakeholders to have input in the selection and framing of the problems to be studied as well as the processes used for assessing risks (e.g., data and assumptions used) and decision making.

It is also important to recognize that risk communication does not occur in a vacuum. In order to both fully understand the risk communication process and evaluate its effect, the impact of multiple communicators with their varying perspectives and goals must be considered.

Risk Communication and Stakeholder Involvement

Historically the process of risk communication has been embedded in the democratic process. Landy, Roberts, and Thomas (1990) argue that agency officials and policy makers are responsible for more than the programs they administer; they have a responsibility to go beyond outcomes to preserve and promote the constitutional democracy of which they are the agents. A similar challenge might be posed to scientists and those conducting risk and health assessments: Is there an obligation in communicating risk-related information to go beyond mere informing or transferring information to the public? In this context, the purpose of risk communication is not to tell citizens what to think. Rather, experts, officials, and decision makers use their stature and expertise to frame questions so that the debate can be made understandable.

A 1994 symposium on the role of public involvement in environmental decision making, entitled "Addressing Agencies Risk Communication Needs," helped illuminate the evolution of risk communication in government deliberation and decision making. Baruch Fischoff, in his keynote address, suggested that risk communication has evolved in seven stages. While each stage is characterized by a focal communication strategy (Fischoff, 1995, Table I, p. 138), the evolutionary process is not linear. Different organizations have been at different stages at the same time, and even within the same organization it is possible for different stages to be present. The stage of evolution may depend on a number of internal and external organizational factors.

According to Fischoff, the earliest stage of risk communication involve experts perfecting their profession or "getting the numbers right." These experts see no need to communicate because they view the risks as reasonably small or controlled.

By relying solely on the results of risk analysis or assessment, these professionals often ignore the fact that the public wants to be part of the discussion about risk and, in particular, how the problem gets defined and which questions are to be answered. By institutionalizing the methods used to assess risk, experts may become too comfortable with their discipline and assume it represents some objective truth. Further, their status as experts corresponds to a judgment that they hold valued knowledge that is expressed in a language that is usually scientific and statistical.

In the second stage, risk assessors and managers discover that they are not trusted to do their work in private, so they "hand over the numbers" to the public. Often, such communications only serve to reflect the distance between the technical analysts and the recipients. For example, attempts to clarify the uncertainty surrounding risk estimates may only serve to admit the subjectivity that exists, which extends beyond issues of technical merit and also reflects ethical values.

The third stage of risk communication focuses on the goal of trying to explain risk information more clearly by "explaining the numbers." To be meaningful, this requires understanding people's decision processes so that communications can fill in their knowledge gaps, reinforce correct beliefs, and correct misunderstandings. The danger at this stage is that professionals may rely solely on their limited technical framework to determine what information is relevant. The results at this stage of communication are evident in the growing number of public debates over government and industry decision making. Because public values are not a legitimate part of the process, the public enters into a debate about the merits of the science or methods used to determine risk. It is only by challenging the technical basis of decisions that the public can influence the decision-making process. Government agencies' tendency to "decide, announce and defend" has led to citizen challenges and the recognition that scientific explanations alone do not lead to improved risk communication or decision making.

The fourth developmental stage, and the one that is frequently used by technical professionals including risk assessors, focuses on providing some reference risk or comparisons among risks to convince the public about which risks to take seriously. Experts use comparisons to downplay or highlight the magnitude or probability of a risk. Fischoff refers to this stage as "all we have to do is show them that they've accepted similar risks in the past." This form of communication is fraught with peril and subject to manipulations by those who claim expert status and have access to information.

The fifth stage of risk communication involves giving people information on both the risks and benefits of a particular action or activity. Providing information on benefits, especially if done as a means of suggesting compensation for the risk, raises a number of ethical issues: "Analyses can be specified in different ways, with alternative specifications representing different ethical positions—belying

their ostensible objectivity" (Fischoff, 1995, p. 141). Research regarding the communication of both benefits and tradeoffs suggests that framing effects may occur whereby equivalent representations of the same tradeoffs evoke inconsistent evaluations. The presence of framing effects suggests that how we balance risks and benefits may depend on how the information is presented. The result may lead to instability in preferences over time and distrust in how information is framed (McCallum and Santos, 1997). The sixth stage, "all we have to do is treat them nice," focuses on the communicators, their demeanor and perceived trustworthiness. The focus of this stage is to train the communicator and allow for more one-on-one exchanges. Unfortunately, the focus often becomes one of packaging versus substance.

The last and the most highly evolved stage of risk communication involves building partnerships with the public. Partnering is needed to reduce the social amplification of technically small risks as well as generate concern when it is warranted. The public has demonstrated their ability to understand complex scientific information when sufficiently motivated. In this context, risk communication ensures that all sides have relevant information to learn and to share. According to Fischoff, effective risk communication can fulfill part of the social contract between those who create risks (as a byproduct of other activities) and those who bear them (perhaps along with the benefits of those activities). "Ideally, risk management should be guided by the facts. Those facts concern not just the sizes of the risks and benefits involved, but also the changes in political and social status that arise from the risk-management process" (Fischoff, 1995, p. 144).

In spite of the growing recognition that risk communication must be linked with meaningful public involvement and partnering, much of the practice of risk communication remains focused at the third and fourth evolutionary stages of explaining and putting risks into perspective for the public. Such attempts at risk communication focus on getting the public to accept risks that officials or experts believe are necessary for our technological society to function. In this context, risk communication becomes vulnerable to the criticism that it is used by experts and government and industry to legitimate the status quo and serve as a way of justifying government action or inaction.

National Research Council's Committee on Risk Characterization

In 1996 the NRC published a report by a group of experts on how the process of risk assessment, risk management, and risk communication could be improved (National Research Council, 1996). This group advocated a strong stakeholder participation process. They stated that risk assessments should be directed toward informing decisions, and that this process should start at the very beginning of the

risk assessment process and continue throughout the course of risk management and communication. "Many decisions can be better informed and their information base can be more credible if the interested and affected parties are appropriately and effectively involved" (National Research Council, 1996, p. 78). The committee offers a rich view of the interconnectedness of risk assessment to risk communication and risk management:

> A risk characterization must address what the interested and affected parties *believe to be the risk* in the particular situation, and it must incorporate their perspectives and specialized knowledge. It may need to consider alternative sets of assumptions that may lead to divergent estimates of risk and to address social, economic, ecological, and ethical outcomes as well as consequences to human health and safety. . . . Adequate risk analysis and characterization thus depends on incorporating the perspectives and knowledge of the interested and affected parties from the earliest phases of the efforts to understand the risks [National Research Council, 1996, p. 3, emphasis added].

The committee spent a great deal of effort criticizing the current process of risk characterization. The problem, according to the committee, is that the current process of risk characterization fails to pay adequate attention to questions of central concern to affected stakeholders. The failure is not with the scientific analysis, but with the integration of the analysis with a broad-based process of deliberation. The committee called for risk characterization to be an analytic-deliberative process. A series of criteria are identified for judging the success of any such process; they must have sufficiently broad participation, and the information, viewpoints, and concerns of those involved must be adequately reflected, including the fact that "their participation has been able to affect the way risk problems are defined and understood" (National Research Council, 1996, p. 7).

Principles of Effective Risk Communication

Risk communication is a process rather than a set of specific gimmicks or techniques. It requires awareness of the factors that affect the communication process and how individuals perceive risk and risk information. Focusing on the communication process rather than just the risk may be one of the most important considerations for successful risk communication.

Effective risk communication recognizes that the public has a right to receive information and to be actively involved in both the dialogue regarding the nature of the risk and the decisions about ways to minimize or control identified risks. This dialogue often blurs the distinctions between risk assessment—Is there a risk?

What is it? How bad is it?—and risk management—What should we do about the risk? Another important principle of risk communication is that those communicating risk information be perceived as credible. If not, the message will not be believed, especially if it involves risk information. Peters, Covello, and McCallum (1997) have suggested that several factors influence source credibility including the degree of empathy and caring conveyed, the degree of openness and honesty, the extent to which the source is considered competent, and, finally, the extent to which a communicator shows commitment and dedication to health and safety and resolving the risk.

No one approach or method to communicating risk or risk assessment information can be universally applied to all purposes or audiences, but certain steps can be followed to foster more effective communication. Developing an effective risk-communication program involves the following:

1. Determining communication goals and objectives
2. Identifying the audience and its concerns
3. Understanding issues of risk perception that will influence the audience
4. Designing risk-communication messages and testing those messages
5. Selecting the proper communication channels
6. Implementing the plan
7. Evaluating the risk-communication program

Some of these steps are discussed briefly below.

Goals and Objectives

Risk communication can have several goals and objectives. Sometimes the goal is to alert people to a particular risk and move them to action. At other times, the goal is to tell them not to worry, to calm down. In the latter instances the communicator wants to inform individuals that a particular situation does not pose a health risk. Because people's concerns and information needs are different when they are being alerted and when they are being calmed down, strategies for communicating also need to vary. As discussed earlier in this chapter, purposes of risk communication include:

- Education and information
- Improving public understanding
- Behavior change and protective action
- Organizationally mandated goals
- Legally mandated or process goals
- Joint problem solving and conflict resolution

Questions to Consider

A federal agency conducts a so-called baseline risk assessment of a hazardous waste site and determines that the risk from drinking water contaminated with volatile organic compounds and perchlorate exceeds EPA's "acceptable risk levels of 1×10^{-5}" and also exceeds safe drinking water standards for two compounds. No federal or state drinking water standard exists for perchlorate but levels are shown to exceed the state's "action limit" and public water supply wells have been closed. The risk assessment shows that in the absence of consuming water from potable wells there is no exposure but clearly cleanup is required. How do you communicate the risk to area residents who also wonder about their personal risks given possible historic consumption of water for a short period of time prior to perchlorate being detected? What would your goal be for holding a meeting to discuss resident health concerns?

Each event prompting the need for risk communication will have its own objectives. In designing a risk-communication program, the particular risk-communication needs and corresponding objectives lay the framework for the design of specific messages and activities. This framework establishes what needs to be communicated and why.

Audiences and Concerns

Often those responsible for communicating risk-related information and risk assessment results inadvertently place too much emphasis on designing a particular message or ways of simplifying the technical information. To ensure that communication is two-way, more attention should be focused on the receivers of the information. This means first identifying the various audiences or stakeholders.

Although it may not be possible to reach everybody, it is important to try to identify individuals and groups who have an interest or stake in the issue and to provide an opportunity for these people to be involved. Within a particular geographical area, several tiers of stakeholders will exist that may include individuals or groups with a particular interest in the issue. Your audience, however, should not be limited to just geographical neighbors. Other audiences may exist based on common demographic, educational, or other interests (see the next box).

Identifying stakeholders goes beyond just determining who needs to be informed; it includes understanding the concerns and information needs of the var-

Checklist to Aid in Audience Identification

Local government agencies
Education groups
Academic institutions
Local, state, and federal officials
Chambers of commerce
Unions
Professional organizations
Local, regional, and national environmental groups
Local businesses
Civic associations
Property owners
Religious organizations
Senior-citizen associations
Public interest groups
Sporting and recreational clubs
Media
Other interest groups

ious interested parties. Characterizing target audiences is similar to a data collection effort for conducting a risk assessment: without knowing what chemicals are present at what quantities and in what forms, it is impossible to characterize risk. Characterizing target audiences involves looking at such areas as demographics, psychographics, and information and source-utilization characteristics. For effective communication to occur public concerns must be known prior to conducting the risk assessment or relaying of risk information. Only then can the message be presented and disseminated in a manner that acknowledges and addresses the apprehensions and needs of the receivers.

Although audience concerns vary from situation to situation, it is possible to categorize them. Hance, Chess, and Sandman (1987) developed four general categories of concerns: (1) health and lifestyle concerns, (2) data and information concerns, (3) process concerns, and (4) risk-management concerns. Health and lifestyle concerns are often the most important because in any risk situation people inevitably want to know what the implications are for themselves and their

families. These what-does-it-mean-to-me series of questions are often the most difficult for risk assessors to respond to; instead they often rely on default assumptions used to characterize risk. However such questions may also be thought of as a sensitivity analysis of sorts to better bound the risk estimates provided.

Data and information concerns are usually associated with the technical basis for—and uncertainties involved in—any estimation of risk. For example, your target audience may ask, Are your studies correct? Did you sample for the right parameters? Have you considered the interaction of exposures to multiple toxicants? Process concerns relate to how decisions are made by the entity responding to a risk and to how communication occurs. They may ask, Who decides? How are we informed? Obviously, trust and credibility are important in these issues, as is the control the public feels it has in the decision-making process. Finally, risk management concerns relate to how and when the risk will be handled: Will it be effectively mitigated, avoided, or reduced?

A variety of techniques are available for documenting audience information needs and concerns, including interviews, written or telephone surveys, the use of existing public poll information, review of news coverage and letters to the editor, small informal community group meetings, and focus groups that are structured group interviews with participants from specific target groups or from the general population.

Understanding Risk Perception and the Importance of Establishing Trust and Credibility

Those who conduct health risk assessments and other technical experts often discuss frustration in that the public often makes erroneous judgments as to the nature or magnitude of a particular risk. Another principle of effective risk communication is to recognize that the public's often differing perception of risk is not misperception and that perception = reality. The field of risk communication has a rich literature examining this gap between "expert" and "lay" perception of risk. For example, studies have illustrated the effect that gender, professional affiliation, and race have on perception of risk (Flynn, Slovic, and Mertz, 1994; Slovic, Fischoff, and Lichtenstein, 1981). Researchers have identified and classified a number of dimensions or attributes of a risk that affect perception of riskiness. Risk is seen as multidimensional and represents the confluence of a variety of public values and attitudes (Slovic, 1987). This difference in definition affects the likelihood that risk messages will be "received" (Santos and McCallum, 1997). For example, a risk assessor might define risks narrowly in terms of the likelihood of developing cancer, whereas some concerned citizens might include a wider range

of harms such as that the risk is involuntary, outside their control, or artificial. Sandman (1987) popularized the risk perception work of Baruch Fischhoff and Paul Slovic among others by stating that the public's perception of risk is a function of the hazard plus outrage, whereby *outrage* is everything about a risk except its actual magnitude, or how likely it is to actually produce harm. A quantitative risk assessment may arrive at estimates of excess incremental cancer risks that experts or regulatory agencies deem insignificant. However, the public may respond as if severe harm was evident and be angered at the lack of concern on the part of experts. Several of the major characteristics affecting perception of risk are described in the next box.

Voluntary or involuntary. Risks that are voluntary are usually perceived by the public as less serious or dangerous than those that seem to be involuntary, regardless of the actual hazard. A voluntary risk (such as smoking or sunbathing) should never be compared with a perceived involuntary risk (such as exposure to contaminated air or water).

Controlled by the system or by the individual. People tend to view risks that they cannot control as more threatening than those that they can control, regardless of the actual hazard. Pesticide residues on food products (whether regulations deem them allowable or not) or emissions from a facility that are permitted are perceived to be beyond the control of the individual.

Trustworthy or untrustworthy sources. How individuals view a risk is often a function of how much they trust the organization that seems to be imposing or

Primary risk perception factors include whether the risk is perceived as:

- Voluntary or involuntary
- Controlled by the system or controlled by the individual
- Fair or unfair
- Having trustworthy or untrustworthy sources
- Morally relevant or morally neutral
- Natural or artificial
- Exotic or familiar
- Memorable or not memorable
- Certain or uncertain
- Detectable or undetectable
- Dreaded or not dreaded

Based on Slovic, Fischhoff, and Lichtenstein (1981).

allowing the risk and of how credible they believe the source of risk information to be. Trustworthiness and credibility can be increased by the source's collaboration with credible sources outside the organization who can help to communicate the message to the public.

Exotic or familiar. Exotic risks appear more risky than familiar risks. Toxic pollutants, with their long names, can certainly seem exotic. Further, the use of units of measurements that are also unfamiliar such as parts per billion or ug/l add to the exotic nature of the risk.

Dreaded or not dreaded. Risks that are dreaded seem more serious than those that carry less dread. For example, nuclear radiation or chemicals that are carcinogens may seem more risky and less acceptable than common household cleaners or a common illness such as influenza. It is important that communication efforts recognize and acknowledge this dread.

Certainty or uncertainty. Risks that are thought to be more certain or known are often perceived by the public to be less serious (and more acceptable) than those that are not. Conversely, risks that scientists are uncertain about are considered far more serious. In these cases, the public tends to want to err on the side of caution. Risk-communication efforts must acknowledge points of uncertainty, but it is important to be careful not to overwhelm people by pointing out all the uncertainty associated with risk estimates.

In summary, risk-perception considerations cannot be ignored or minimized as emotional, unfactual, or irrelevant. Emotions, feeling, values, and attitudes carry as much—if not more—importance for the public than the technical magnitude of the risk situation.

Issues in Explaining Risk and Designing Messages

The potential for distorted communication is not solely based on the public's lack of a technical background or the relevance of the information provided. Those assessing risk need to be aware that the varying and often conflicting interpretations of risk results that get communicated are a function of several factors. In part, the problems may stem from the lack of a clear message as to what the results are or the limitations of scientists and risk assessors to place results in context for various stakeholders. Messages about risk are further obscured by technical jargon. For example, simply listing tables of carcinogenic risk estimates or hazard indexes for noncarcinogens will not answer people's concerns about safety and possible health consequences. In addition, results are interpreted not only by the

scientists themselves but by other parties and institutions, including government agencies, activist or interest groups, and the media.

The two-way nature of risk communication requires that messages contain the information the audience wants, as well as the information the communicator wishes to convey. Effective messages should also clarify points that might be difficult to understand. For example: Are the risks to children, to fetuses, or to adults? Was exposure assumed over a lifetime or of a shorter duration? As stated earlier in this chapter, the goal of risk communication should be to make the differences in language (and rationalities) between experts and others more transparent. Strong differences between the two languages serve as barriers to dialogue and deliberation, and impede the possibility of developing a shared understanding. For example, experts may not be aware of or value information that the various stakeholders have including pertinent value issues and beliefs that influence their decisions of perceived riskiness. In general, the public receivers of this information have limited access to the information used in decision making. Even when the information is available, it may not be fully understood or accepted due to a lack of trust.

Written messages and oral presentations must transmit the information to the public in an understandable form. Many risk analysts tend to use overly technical or bureaucratic language, which may be appropriate for the risk assessment document and for discussions with other experts but not for communicating with the general public. Similarly, experts in seeking to simplify risk messages may leave out important content that provides context. The challenge is to provide sufficient detail and content—while taking time to explain concepts that are key to understanding. Take care in using words such as *insignificant* or *significant* risk. At a minimum, explain what you mean by the term. Is it based on a regulation? Expert judgment? And risk to whom? Health effects associated with acute exposure must be differentiated from those associated with chronic exposure, and carcinogenic effects must be differentiated from noncarcinogenic effects. Risk messages need to place health effects information into the proper perspective so that people can comprehend the difference between significant and less significant risks. Messages should explain, as simply and directly as possible, such things as risk estimates, exposure considerations, and what uncertainties drive the risk estimate.

Because different audiences have different concerns and levels of understanding, one risk message may not be appropriate for all interested parties. It may be necessary to develop a series of messages on the same topic. Finally, a critical part of successful message design is testing or trying out the message. This can be done formally, for example, by the use of focus groups or citizen advisory committees, or informally, for example, by testing the material on uninformed third parties.

Dealing with Uncertainty

Scientists are by nature precise and, as such, tend to describe all the uncertainties and limitations associated with a risk assessment. This may be overwhelming for the public, who is trying to figure out what the risk means and wants certainty, not caveats. It is important to discuss the major sources of uncertainty. When interpreting the results of health risk assessments for the public, explaining how health standards were developed and their applicability to the population at risk may be very important. In other instances, limited sampling data may be the most important uncertainty to explain. While the public may press for assurances of whether it is safe or unsafe, experts need to take care to be neither overly reassuring nor overwhelming with uncertainties. Explaining what you will do to reduce uncertainty may be especially important to communicate.

Risk Comparisons

In an attempt to make risk information understandable to the public, experts often focus on providing comparison as a means of placing risks in context. Care must be taken in attempting to make such comparisons. Research on risk comparisons is limited and contradictory (Lundgren, 2004). Comparisons can be useful, but only when they are part of an overall communication strategy that requires that the communicator to

> understand the nature of the risk—both the hazard that it presents and the qualitative attributes that influence perception by the target audience; understand the audiences that are being addressed and their relationship to the hazard; understand how the risk comparison interacts with other components of the message; and have a way to evaluate the audience's response (Santos and McCallum, 1997).

Covello, Sandman, and Slovic (1988) have offered a hierarchy for risk comparisons (see box on next page). Comparisons based on quantity are considered the most intelligible and accessible. Comparisons of the probability of an event, such as the probably of being struck by lightning versus the probability of getting cancer from exposure to a particular substance, are considered much less useful. It is also important that risk comparisons take into account the variables that determine risk acceptability, which includes issues of fairness, benefits, alternatives, control, and voluntariness (Slovic, 1987).

The complex nature of risk communication calls into question the value of requiring simple comparisons of risk end points with either common risks of daily

Acceptability of Risk Comparisons

Most Acceptable

- Same risk at different times
- Risk vs. standard
- Different estimates of the same risk

Less Desirable

- Doing something vs. not doing it
- Alternative ways of lessening risk
- Risk in one place vs. risks in another place

Even Less Desirable

- Average risk vs. peak risk at a particular time or location
- Risk from one source of harm vs. risk from all sources of that harm
- Occupational risk vs. environmental risk

Rarely Acceptable

- Risk vs. cost
- Risk vs. benefit
- Risk vs. other specific causes of same harm

Adapted from Covello, Sandman, and Slovic (1988).

life or other risks posed by chemical or physical agents or bright line risk values. Without a context, this information might provide inaccurate or confusing messages for the public. For most individuals these types of comparisons ask the primary question: What does the information mean to me? And, more specifically, What does the risk mean to me? To address such broad issues, risk communication efforts should seek to inform and enhance a recipient's understanding by providing information within a context. To be complete, risk messages should also provide information that can help facilitate individual decision making.

Experience in risk communication suggests that risk comparisons should be presented in ways that provide cues to action and respect the values of participants in the process. Failure to consider social and political issues and values will increase the likelihood that a comparison will not be meaningful (Santos and McCallum, 1997).

Thought Questions

1. How would you develop a risk communication plan for addressing environmental health concerns in an urban community? What message considerations are important given the variety of audiences, for example, government workers, local politicians, community residents with multiple racial and ethnic backgrounds? What tools would you use to determine these different audience concerns and information needs?
2. How do you explain the concept of a one in one million cancer risk to a nontechnical audience?
3. How would you explain exposure to a nontechnical audience concerned about their possible health risk to contamination in air and water from a hazardous waste site?
4. How would you describe the risk for several chemicals of concern to a nontechnical audience where the hazard indexes (HI) are all less then one? How would you address their concern about possible cumulative risk or the possible interactions?
5. Describe how a maximum contaminant level is set for a drinking water contaminant. Consider how to explain building in uncertainty factors and accounting for the most sensitive receptor from a risk communication perspective.
6. Cite an example of an effective risk message, either from a government agency or a corporation.
7. Describe how you would address people's concerns about health effects from historical exposures in a risk assessment.
8. How would you go about evaluating the effectiveness of your risk communication program?

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CASE STUDIES IN RISK ASSESSMENT

CHAPTER SEVENTEEN

IMPROVEMENT OF RISK ASSESSMENTS FOR MULTICONTAMINANT SITES IN THE FACE OF CRITICAL DATA GAPS

Yoram Cohen
Adrienne Katner

Learning Objectives

Students who complete this chapter will be able to

1. Assess the adequacy of monitoring data for quantitative risk assessments (QRAs)
2. Identify chemicals of potential concern (COPCs) and chemicals of concern (COCs) via ranking of chemicals using a scoring methodology based on physicochemical and toxicological properties, and site-specific monitoring data
3. Identify potential exposure scenarios and receptor locations on the basis of site visits, regulatory and private information requests, public surveys, and informational meetings
4. Estimate air concentrations using the risk screening environmental indicators model
5. Perform tiered screening of potential exposure scenarios via risk assessment information system (RAIS) tools, default exposure assumptions, and dose ratios (DRs) to prioritize exposure pathways and exposure hot spots

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The gold standard in scientific risk assessments is *quantitative risk assessment* (QRA), which relies on the sufficiency of data that will enable quantification of variability and uncertainty in the estimated risk outcome. However, it is not always possible to conduct QRAs when the monitoring data are inadequate due to lack of resources or when retrospective analysis is sought for sites for which historical monitoring data are unavailable. If QRA techniques such as Monte Carlo probability analyses are performed on limited or inadequate data, uncertainties in the input parameters may result in large uncertainties in the resulting risk estimates. While more monitoring would resolve this issue, most public health risk assessments are constrained by limited funding. Notwithstanding, regulatory decisions must be made, and this can produce a situation ripe for biased risk management and public distrust (Johnson and Slovic, 1998). Therefore, it is critical that a systematic, comprehensive, and transparent assessment of public health impact be conducted, not only for decision-making purposes but also for public credibility and support; for without public support control measures can languish.

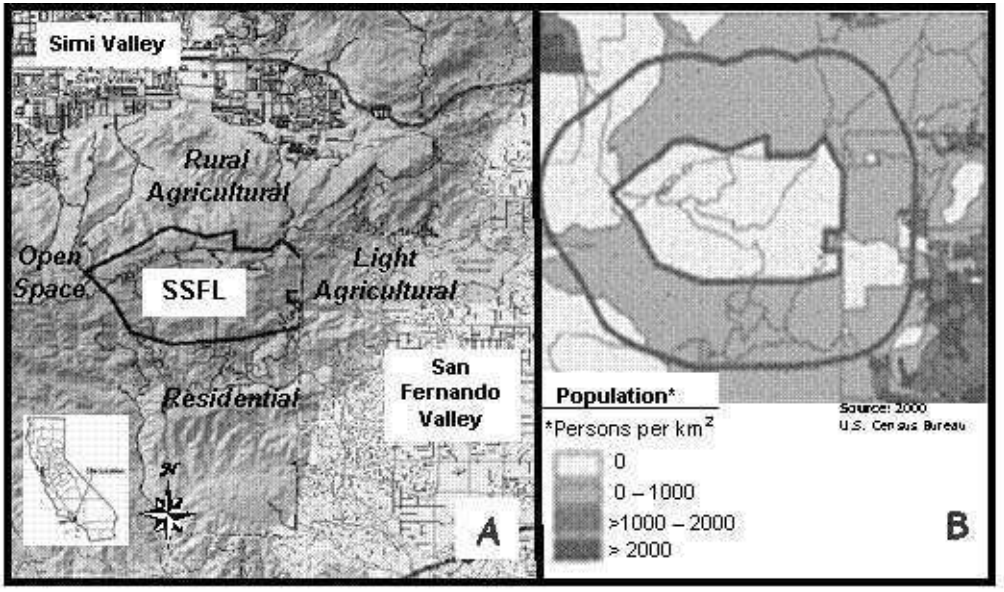
Santa Susana Field Laboratory

The Santa Susana Field Laboratory (SSFL) facility is a complex of multiuse industrial and government research and testing facilities. Since 1948 the site has been used primarily for testing liquid fuel-propelled rocket engines, many of which were for the early Apollo space missions. SSFL occupies roughly 2,600 acres in the Santa Susana Mountain range of Ventura County, California, at an elevation of 1,500 to 2,200 feet (Figure 17.1). It is located approximately 30 miles northwest of downtown Los Angeles between Simi and San Fernando Valleys. Main sources of contaminants were from rocket engine testing (RET), air stripping of contaminated groundwater, and the collection, open air burning and/or release of wastewater via several surface impoundments and storm drains. Operations at SSFL have involved the use of various chemicals including chlorinated organic solvents, hydrazine fuels, kerosene-based fuels, oxidizers, liquid metals, asbestos, and PCBs. Given the limited monitoring (Table 17.1), a reliable and comprehensive quantitative risk assessment is impractical. The subsequent section outlines the approach for evaluating and screening the chemicals and chemical degradation/oxidation products of potential concern.

Methods

The assessment procedure presented here is outlined in Figure 17.2 and consists of (1) assessment of data adequacy and sufficiency for quantitative risk assessment, (2) records review for identification of chemicals of potential concern (COPCs),

FIGURE 17.1. SANTA SUSANA FIELD LABORATORY (SSFL).



(A) Land use permits (B) Population

Source: Agency for Toxic Substances and Disease Registry. "Draft Preliminary Site Evaluation: Santa Susana Field Laboratory (SSFL), Ventura, CA, CERCLIS No. CAD074103771," Dec. 3, 1999. (A) Available at http://www.atsdr.cdc.gov/HAC/PHA/santa/images/figure4.gif. (B) Available at http://www.atsdr.cdc.gov/hac/pha/santa/san_p1.html#_1_16.

(3) application of chemical scoring and ranking methodologies for identification of chemicals of concern (COCs), (4) identification of potential exposure scenarios and receptors, (5) compilation of monitored environmental concentrations and modeling and estimation of chemicals not monitored for, (6) tiered screening of hypothetical conservative exposure scenarios, and (7) tiered screening of probable site-specific scenarios.

Identification of Data Gaps and Assessment of Data Adequacy for QRA

Quality and reliability of available monitoring data were assessed on the basis of the following indicators of data quality: (1) measurement sensitivity in relation to present health-based standard, (2) randomness of sampling, (3) sufficiency and representativeness of data points (spatially and temporally), (4) appropriateness of methodology for reported objectives, (5) QA/QC, (6) reproducibility/comparability

TABLE 17.1. QUANTITATIVE ASSESSMENT OF RISK.

Monitoring	• Lack of long-term historical air monitoring data
	• Insufficient offsite monitoring
	• Inadequate sampling methods
	  • No systematic stratified sampling to assess spatial and temporal variability
	  • Limited groundwater sampling at pertinent depths for compounds denser than water
	• Inappropriate background sample locations

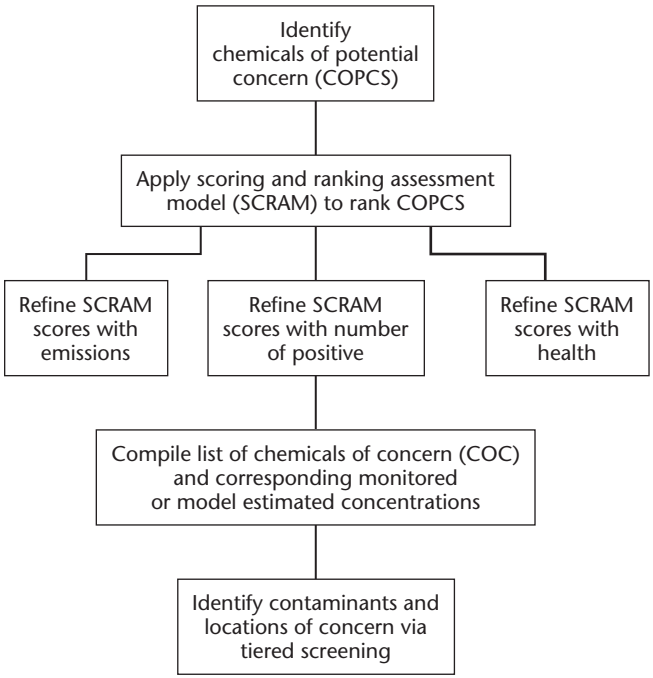
Analytical Methods	• Inadequate QA/QC measures • Use of inappropriate analytical methods that lead to under-detection • Use of filtered water samples to assess the concentration levels of hydrophobic chemicals • Incomplete analytical evaluation with respect to monitoring for all potential chemicals of concern
Well Use Data	• Lack of current well use surveys • Lack of cooperation from private water supply companies (with respect to obtaining monitoring and well use data) that do not have to comply with the Freedom of Information Act

in related datasets, (7) comprehensiveness of chemical assessment with consideration given to site activities and accident history, (8) objectivity of reporting laboratories (i.e., absence of conflict of interest in the outcome of the analysis), and (9) reported uncertainty values.

Identification of Chemicals of Potential Concern

Chemicals used throughout the history of the facility were identified from archived chemical usage and activity reports, permitting, and waste reports as well as from the existing monitoring reports. In order for a chemical to be included as a *chemical of potential concern* (COPC), it had to meet one of the following criteria: (1) its detection method sensitivity was above the existing health-based standard; (2) the chemical was detected above levels in associated blanks, above reliable background samples, or above health-based standards; (3) the chemical was historically associated with the site but not monitored or was inadequately monitored (e.g., lack of temporal and spatial resolution of field monitoring or inadequate monitoring methodology); or (4) the chemical was identified as a transformation product in soil, groundwater, surface water and/or air.

FIGURE 17.2. ASSESSMENT METHODOLOGY.



Identification of Chemicals of Concern (COC)

Chemicals were scored using the scoring chemicals and ranking assessment model (SCRAM) based on chemical-specific factors such as toxicity, environmental persistence, mobility, bioaccumulation potential, and uncertainty[1] (Mitchell and others, 2000, 2002; Table 17.2). A refined site-specific ranking was obtained by weighting SCRAM scores with (1) release rate estimates[2]; (2) the maximum detected or modeled contaminant concentration in various media[3] relative to specific health-based standard[4]; and (3) the number of offsite and onsite detections relative to the number of times the chemical was monitored. SCRAM ranking (R_{SCRAM}) for air contaminants was refined (R_{Air}) as follows:

$$R_{AIR} = R_{SCRAM} E/(I_{AIR} RfC) \tag{17.1}$$

in which E is the estimated or reported chemical emission rate (mg chemical/day), I_{air} is the inhalation rate (m^3 air/day), and RfC (mg pollutant/m^3 air) is the reference

TABLE 17.2. CHEMICAL-SPECIFIC FACTORS USED TO RANK CHEMICALS OF POTENTIAL CONCERN.

SCRAM Ranking Factors	Specific Ranking Variables
Acute Terrestrial and Aquatic Effects	LD_{50} or ED_{50}
Sub-chronic/Chronic Terrestrial Effects	LOAEL or ≥ 90 day NOAEL
Sub-chronic/Chronic Aquatic Effects	MATC, NOEC, or LOEC
Sub-chronic/ Chronic Human Effects	LOAEL or ≥ 90 day NOAEL
Carcinogenicity	$(1/ED_{10})$ × (Weight of Evidence)
Reproductive Toxicity	RfD
Mutagenic Effects	Potency/severity
Behavioral Effects	Severity
Immune System Effects	Severity
Endocrine Effects	Potential
Persistence in Biota, Air, Water and Soil	(Half-life or $t_{1/2}$)
Bioconcentration, Bioaccumulation	BAF, BCF, or water solubility log K_{ow}

Note: SCRAM = scoring chemicals and ranking assessment model.

inhalation concentration. With the above ranking, chemicals with significantly low emissions or those for which the threshold concentration of concern (RfC) is high would be ranked low, while chemicals with high emissions and low RfC would be assigned a higher rank.

Two different refined SCRAM rankings of groundwater or surface water contaminants were developed. In the first approach the score was refined as:

$$R_W = R_{SCRAM} N_{MCL} \tag{17.2}$$

in which R_w is the weighted score for either surface or groundwater and N_{MCL} is the number of detections at concentration levels above the MCL standard. In the second approach the $SCRAM$ score was refined as follows:

$$R_w = R_{SCRAM} \left(\frac{C_w^{\max}}{MCL} \right) \tag{17.3}$$

where MCL is the maximum contaminant level (mg/L) health standard and

$$C_w^{\max}$$

is the maximum detected concentration (*mg/L*) for the chemical under consideration. The above rankings were limited by lack of monitoring data and *MCL* standards for some of the chemicals associated with SSFL. Refinement of *SCRAM* ranking for soil contaminants was as given below.

$$R_{soil} = R_{SCRAM}\, I_{soil} \left(\frac{C_{soil}^{\max}}{RfD} \right) \tag{17.4}$$

in which I_{soil} is the rate of soil intake (kg soil/kg body mass),

$$C_{soil}^{\max}$$

is the maximum detected concentration of the specific chemical in soil (mg chemical/kg soil) and *RfD* is the Reference Dose. COPCs were ranked according to their numerical weighted scores and chemicals identified in the top 10 to 20 of the various weighted rankings were pooled and listed as COCs. COPCs without emission estimates or monitoring data were retained on a list of COPCs requiring further investigation.

Identification of Potential Exposure Scenarios and Receptors

Potential exposure scenarios and receptors were identified from site visits, public surveys and informational meetings, and regulatory and private information requests. Information obtained included the following:

- Proximity of surrounding communities
- Pathways of waste and storm drainage channels
- Locations of neighborhood gardens and agricultural/livestock facilities
- Locations of areas where sensitive populations may congregate, for example, playgrounds, schools, camps, retirement communities, and hospitals
- Locations of potential soil resuspension, for example, horse and biking trails, gardens, construction sites, and hiking paths
- Locations with potential for unauthorized access onto facility grounds via security gaps
- Groundwater well usage and monitoring reports (from water resource and quality agencies as well as private water supply facilities)
- Permit violation and site inspection reports (from air, water, and resource control agencies)
- Land use permits and development plans (from development and environmental resource agencies)
- Community population estimates (from the U.S. Census Bureau)[5].

Examples of selected potential receptor areas of concern that were identified from site visits are depicted in Figure 17.3.

Estimation of Air Receptor Concentrations

Due to lack of historical air monitoring data, air concentrations were derived from air emissions inventories and facility operational records. Emission sources for SSFL include air-stripping towers (for treatment of the groundwater TCE plume), rocket engine testing stands, and an outdoor waste incineration facility. Emission rates were assumed to occur uniformly throughout each day or were approximated based on reported site activities. Air dispersion modeling (CalPUFF model, Earth Tech, Inc.[6]) was conducted using local meteorological and topographical data to derive conservative offsite chemical-specific receptor concentrations (Environmental Protection Agency, 1998). Model output was in the form of ambient concentrations for short (one-hour) periods, and post-processing was performed to obtain long-term (annual or multi-annual) averages.

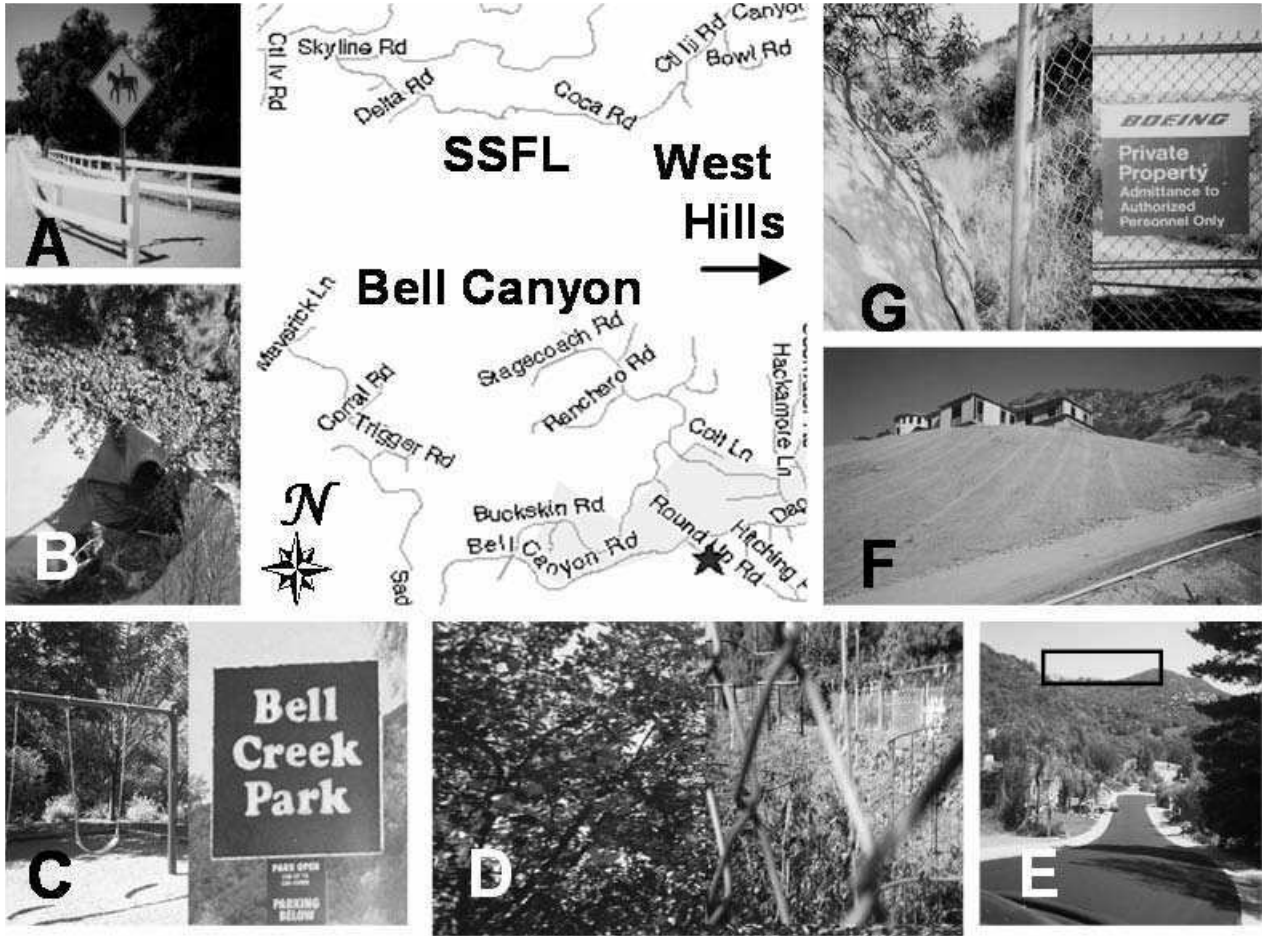
Tiered Screening of Exposure Scenarios

Tier I: Hypothetical conservative scenario screening. Highly conservative assumptions were used in these scenarios to bracket the upper exposure range and rank potential doses for various receptor locations of concern. Available monitoring and modeling data were reviewed and maximum contaminant concentrations at potential receptor points were compiled. Receptor concentrations were input into Oak Ridge Institute's Human Health Risk Exposure (HHRE) model which estimates a lifetime average daily dose (LADD) (or chronic daily intake [CDI]) from various exposure pathways (ingestion, inhalation, and dermal) for the exposure scenarios (residential, occupational and recreational) using EPA-based default exposure values (Table 17.3). Exposure doses of chemical-specific contaminants were estimated for the duration of the emission or activity periods and these exposure doses were averaged over an estimated standard exposure period of 30 years for noncarcinogens and 70 years for carcinogens.

Only contaminants resulting in hazard indices (HI) that exceed unity or cancer risks greater than $1x10^{-6}$ (derived from the HHRE model or from standard 1996 EPA risk assessment methodology) were included in further analyses.[7] LADDs were derived using EPA-recommended exposure dose equations and default assumptions for the lifetime residential inhalation scenario. The LADD was calculated as follows:

$$LADD\ (mg/kg\text{-}day) = \frac{C \times I \times F \times D}{W \times T} \tag{17.5}$$

FIGURE 17.3 LOCATIONS OF POTENTIAL EXPOSURE AND POSSIBLE RECEPTORS IDENTIFIED IN SITE VISITS.



A) Horse trails kick up dry soil around Bell Creek (90 percent of SSFL NPDES waste discharged into Bell Creek). (B) Surface water runoff channels accessible to children. (C) Recreational activities center on Bell Creek. (D) Orcutt Ranch is one receptor for surface runoff, a community orchard in West Hills. (E) Rocket engine testing areas are one to two miles from homes. (F) Area is under heavy construction and soil is not covered here. (G) Unsecured gate makes SSFL accessible to children.

TABLE 17.3. DATA SHEET FOR SCORING CHEMICALS AND RANKING ASSESSMENT MODEL (SCRAM) RESULTS.

	Scenario		
Pathways Assessed	**Recreational**	**Occupational**	**Residential**
Soil ingestion	Exposure Frequency= 75 day/yr Exposure Time = 1 hr/day Ingestion Rate = 0.0001 kg/day	Exposure Frequency= 225 day/yr Exposure Time = 1 hr/day Ingestion Rate = 0.0001 kg/day	Exposure Frequency= 75 day/yr Exposure Time = 1 hr/day Ingestion Rate = 0.2 kg/day
Vegetable ingestion	na[a]	na	Exposure Frequency= 350 day/yr Ingestion Rate = 0.2 kg/day
Groundwater ingestion from private wells	Exposure Frequency= 45 day/yr Exposure Time = 1 hr/day Ingestion Rate = 0.05 L/day	Exposure Frequency= 225 day/yr Ingestion Rate = 0.8 L/day	Exposure Frequency= 350 day/yr Ingestion Rate = 2 L/day
Groundwater dermal contact (showering)	na	na	Exposure Frequency= 350 day/yr Exposure Time = 0.24 hr/day
Groundwater inhalation during household use	na	na	Exposure Frequency= 350 day/yr Inhalation Rate = 20 m^3/day
Surface water dermal contact	Exposure Frequency= 45 day/yr Exposure Time = 1 hr/day	na	Exposure Frequency= 45 day/yr Exposure Time = 1 hr/day
Air inhalation	Exposure Frequency= 96 day/yr Exposure Time = 8 hr/day Inhalation Rate = 20 m^3/day	Exposure Frequency= 240 day/yr Exposure Time = 8 hr/day Inhalation Rate = 20 m^3/day	Exposure Frequency= 365 day/yr Exposure Time = 24 hr/day Inhalation Rate = 20 m^3/day

[a]na = not applicable

in which C is the contaminant concentration (mg/kg, mg/L, or mg/m^3), I is intake rate (mg/day, L/day, or m^3/day), F is exposure frequency (e.g., days/yr), D is exposure duration (yr), W is body weight (kg) and T is average exposure time. Calculated doses were converted to dose ratios (DRs) defined as the ratio of pathway-specific lifetime average daily dose (LADD) to the pathway-specific acceptable lifetime average daily dose (ALADD).

$$DR = \frac{LADD}{ALADD} \tag{17.6}$$

where ALADD is calculated as

$$ALADD = \frac{1 \times 10^{-6}(Acceptable\ Risk)}{CPF} \text{ for carcinogens} \tag{17.7}$$

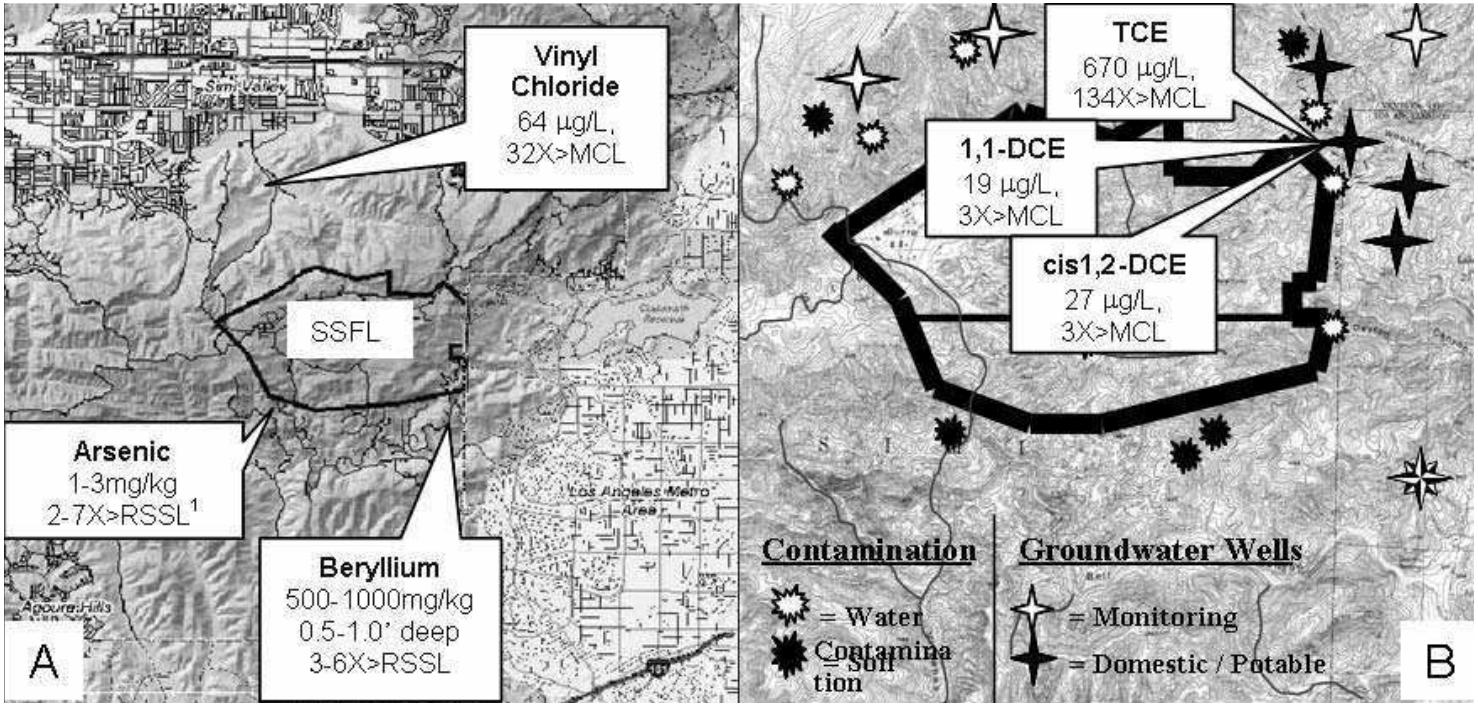
$$ALADD = RfD \text{ for non-carcinogens} \tag{17.8}$$

Tier II: Screening of probable site-specific scenarios. The hypothetical conservative scenarios resulting in DR > 1 were re-evaluated with more realistic site-specific information. Offsite contamination may be at levels of concern but were not considered unless they were near areas of potential exposure (Figure 17.4A). For example, in Tier II, only water contaminants near potable or domestic wells were considered in ingestion scenarios (Figure 17.4B), while assessment of exposure to air contaminants considered the change in concentrations over the years of changing emissions from SSFL. In order to construct likely exposure scenarios, information was obtained from the following sources: (1) population statistics; (2) local population time-activity surveys; (3) public comments and surveys; (4) well usage reports; (5) site visit information; (6) land use information; and (7) proximity of receptor to the contamination location of concern. Refined DR scores were ranked numerically and exposure scenarios with DR scores > 1 were marked as deserving further risk management analysis.

Results and Discussion

Specific contaminants of concern for which the dose ratios (DRs) were estimated to be above unity are summarized in Tables 17.4 and 17.5; associated exposure locations are presented in Figures 17.5 and 17.6. Scenarios with exposure levels that results in DR > 1 suggest the potential for past or continuing community exposure and thus potential adverse health impacts. DR ratios above unity were estimated for inhalation exposure to TCE, hydrazine, and hydrazine derivatives in multiple

FIGURE 17.4. EXAMPLES OF OFFSITE CONTAMINANT DISTRIBUTION IN RELATION TO POTENTIAL RECEPTORS.



(A) Contaminants in relation to surrounding communities. (B) RSSL is the residential soil screening level health-based standard.

receptor locations around the SSFL facility (Table 17.5 and Figure 17.6). It is important to recognize that high DR values of up to about 100 and 60 for TCE and hydrazine, respectively, are for long term exposure of residents (>50 years). Ranking of receptor areas identified potable wells north and northeast of the facility as potential hotspot locations. Previous SSFL studies (Groundwater Resource Consultants, 1988; Agency of Toxic Substances and Disease Registry, 2000) assumed there were no functioning wells in these areas; however, recent well surveys are lacking.

While the above results do not provide quantitative measures of risk, the tired approach is effective in minimizing the overwhelming assignment of environmental impact assessment into discrete attainable tasks so as to facilitate ranking of chemicals of concern, potential exposure levels, and exposure areas of concern. It is acknowledged that bias in the refined relative rankings could be introduced when emission data and field monitoring data are inadequate, health-based standards are unavailable, and information is lacking regarding toxic transformation products. Nonetheless, the tiered screening approach with multiple weighting methods and reported range of DR values should provide confidence in the assessment of site-specific COCs and exposure levels of concern and enable the identification of contaminants in need of further review.

It is emphasized that the methodology described in the present case study emphasizes a risk-informed rather than risk-based decision-making process. In other words, information and analysis of potential exposure is used in a deliberative process that considers public concern. This is a critical step toward identifying exposure issues requiring further attention and for engendering public trust and support. An approach that clearly defines deficiencies in the analysis, clarifies need for assumptions and the impact of such assumptions, and adheres to scientific rigor while adhering to a transparent analysis process is essential, especially in the face of significant monitoring data gaps. It is anticipated that the study will serve as an important resource for the concerned communities and decision makers in their evaluation of future needs for site mitigation and land use options.

Thought Questions

1. Use the SCRAM methodology to score and rank the following chemicals of potential concern (COPCs): arsenic, benzene, beryllium, carbon tetrachloride, hexachlorobenzene, hydrazine, lead, manganese, PCBs, perchlorate, trichloroethylene, and vinyl chloride. Compare your scores with a classmate. Is this method reproducible between different users? Is there variability in the scores obtained by different users? List some of the reasons for variability of scores. Does variability in scores affect the rankings? If so, how could this affect a study designed to prioritize potential risks due to exposure chemicals from a facility in which the listed chemicals are found?

TABLE 17.4. DOSE RATIOS[a] OF CONCERN FROM OFFSITE MONITORED SOIL AND GROUNDWATER.

				Scenario					
				Recreational		*Occupational*		*Residential*	
Chemical and Concentration	**Locale**	**Media[b]/ Year of Detection**	**Pathway[c]**	**Dose (mg/kg-d)**	**Dose Ratio**	**Dose (mg/kg-d)**	**Dose Ratio**	**Dose (mg/kg-d)**	**Dose Ratio**
Arsenic (8–24 mg/kg)	South (3)[d]	S 1998	Ingestion	5.0×10^{-9} to 7.0×10^{-8}	0.007 to 0.1	3.8×10^{-7} to 5.3×10^{-6}	1 to 8	5.9×10^{-7} to 8.2×10^{-6}	1 to 12
			Veg. Ing.	—	—	—	—	4.7×10^{-6} to 6.6×10^{-5}	7 to 99
	North (1)	S 1992	Ingestion	4.1×10^{-8} to 1.2×10^{-7}	0.1 to 0.2	1.0×10^{-6} to 3.0×10^{-6}	2 to 5	4.8×10^{-6} to 1.4×10^{-5}	7 to 21
			Veg. Ing.	—	—	—	—	$3.9 \times 10^{-45}$to 1.1×10^{-4}	58 to 170
TCE (10–900 µg/L)	Northeast (2)	GW 1994	Ingestion	3.8×10^{-7} to 3.4×10^{-5}	0.2 to 14	3.0×10^{-5} to 2.7×10^{-3}	12 to 1087	1.2×10^{-4} to 1.1×10^{-2}	48 to 4227
			Inhalation	—	—	—	—	5.9×10^{-4} to 5.3×10^{-2}	235 to 21135
			Dermal	—	—	—	—	4.5×10^{-6} to 4.0×10^{-4}	12 to 1073
			Veg. Ing.	—	—	—	—	1×10^{-4} to 1×10^{-2}	44 to 4000

Vinyl Chloride (64 µg/L)	Northeast (2)	GW 1994	Ingestion	2.4×10^{-6}	3	2.0×10^{-4}	271	7.5×10^{-4}	1052
			Inhalation	—	—	—	—	3.8×10^{-3}	117
			Dermal	—	—	—	—	2.1×10^{-5}	29
1,1-DCE (19 µg/L)	Northeast (2)	GW 1996	Ingestion	7.2×10^{-7}	0.3	5.7×10^{-5}	23	2.2×10^{-4}	89
			Inhalation	—	—	—	—	1.1×10^{-3}	196
			Dermal	—	—	—	—	8.6×10^{-6}	5
			Veg. Ing.	—	—	—	—	3.4×10^{-4}	20

[a] Dose Ratio (DR) = ratio of LADD to ALADD for 1×10^{-6} cancer risk (as determined by EPA's Cancer Potency Factor [CPF]); ALADD = 1×10^{-6} risk/CPF

[b] Media: GW = groundwater; S = soil.

[c] Pathway: Veg. Ing. = Vegetable Ingestion; ingestion for soil was assumed to be incidental, and comparable to drinking water levels for groundwater.

[d] Numbers identify detection locations from Figure 17.5.

Note: DR values above unity were obtained for exposure to arsenic; however, available monitoring data and record of site activities did not suggest site-specific sources of arsenic releases. It is important to note that arsenic is naturally occurring due to releases from erosion of mineral deposits, though human activities can also lead to substantial contamination (Agency of Toxic Substances and Disease Registry, 1990). Background arsenic concentrations of 2.3–11 mg/kg were reported in a 1986 survey of CA soil samples (surface to ~2.5 ft sub-surface) (Agency of Toxic Substances and Disease Registry, 1990).

TABLE 17.5. INHALATION DOSE RATIOS OF CONCERN FROM MODELED AIR CONCENTRATIONS AND AIR EMISSIONS[a].

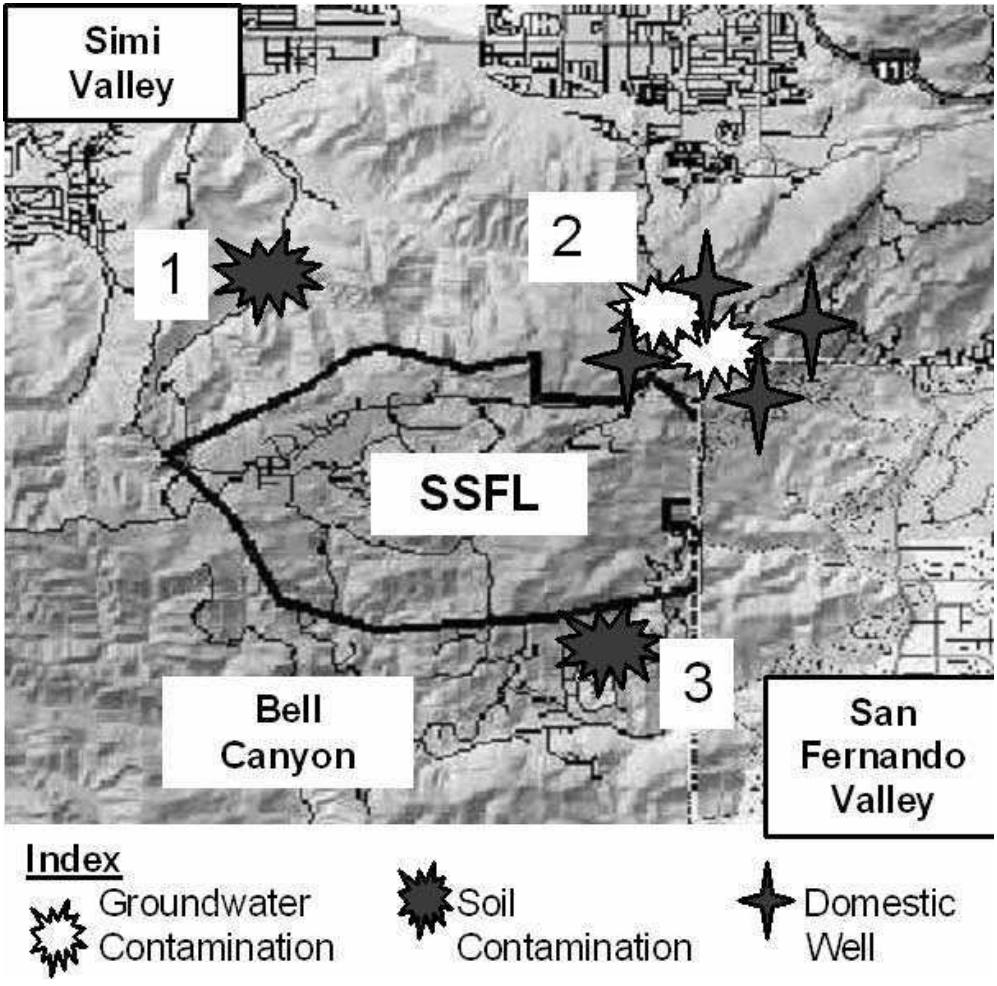
Location	TCE	Location	Hydrazine Derivatives[b]
West Hills	29–104	Bell Canyon	2–60
Bell Canyon	21–85	Dayton Canyon	2–25
Dayton Canyon	25–83	West Hills	1–25
Simi Valley	22–70	Woodland Hills	1–18
Canoga Park	7–22	Canoga Park	0–14
Santa Susana Knolls	7–22	Simi Valley	0–9
Chatsworth	7–19	Hidden Hills	0–7
Woodland Hills	4–16	Chatsworth	0–4
Hidden Hills	3–12	Santa Susana Knolls	0–3

[a] DRs were calculated for 1953–2004 from estimated maximum concentrations and emission estimates.

[b] Hydrazine derivatives include hydrazine, UDMH (asymmetrical dimethyl hydrazine), and MMH (monomethyl hydrazine). The reported DR range is from the minimum DR (obtained for a single source) to the maximum DR obtained by combining the dose due to exposure associated with multiple sources.

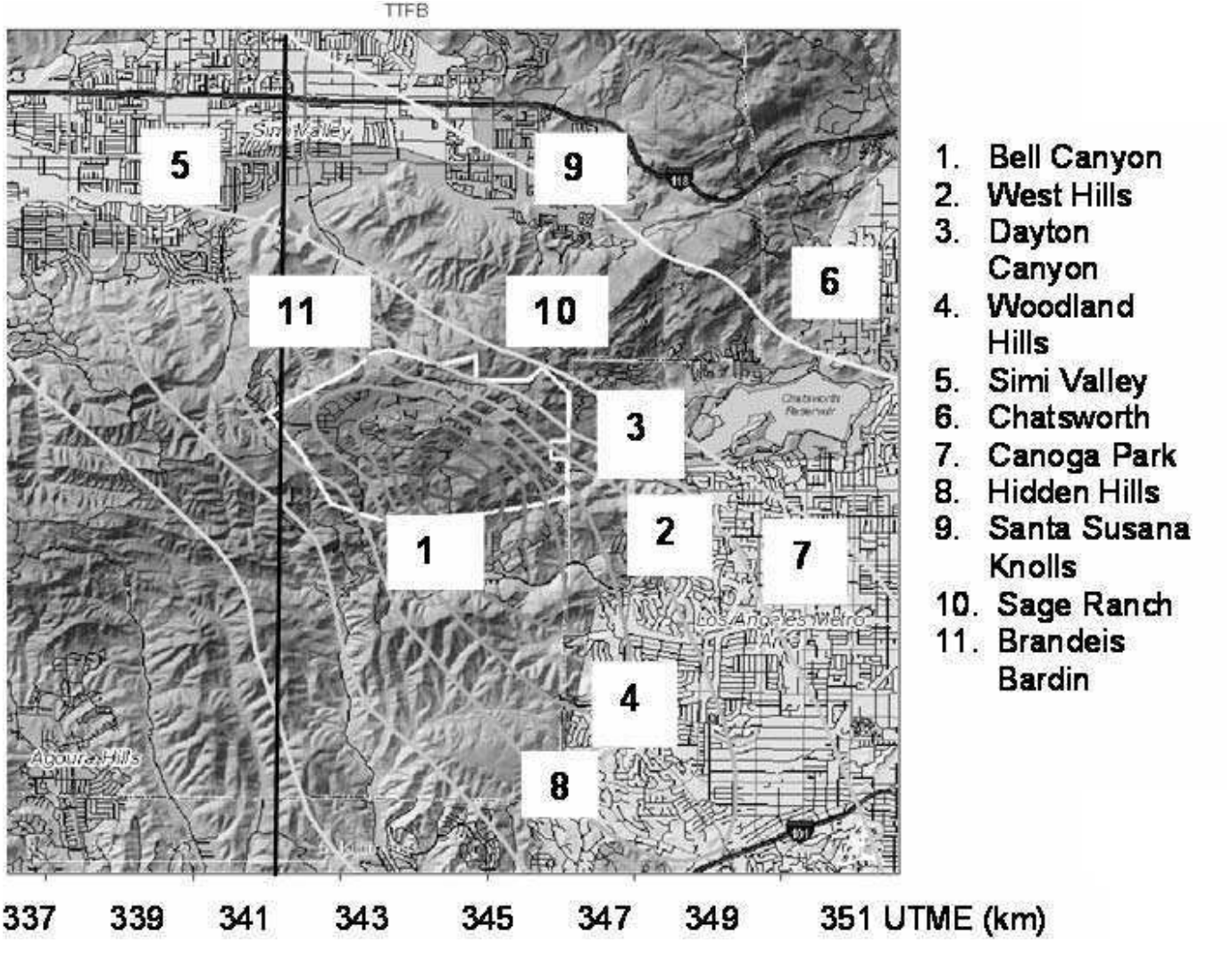
Chemical Name	*Chemical Score*	*Uncertainty Score*	*Composite Score*	*Ranking*
Hexachlorobenzene				
PCBs				
Hydrazine				
Trichloroethylene (TCE)				
Benzene				
Beryllium				
Perchlorate				
Carbon tetrachloride				
Arsenic				
Manganese				
Vinyl Chloride				
Lead				

FIGURE 17.5. POTENTIAL RECEPTOR EXPOSURE LOCATIONS.



2. EPA's Risk Screening Environmental Indicators model (RSEI) can be used to acquire rough estimates of receptor contaminant air concentrations from the TRI (Toxic Release Inventory) emissions database. TRI-releases are reported by facilities to the Toxics Release Inventory as mandated by the Emergency Planning and Community Right-to-Know Act (EPCRA). RSEI uses the reported quantities of stack and fugitive air releases to model air emissions from TRI facilities via the Industrial Source Complex Long Term (ISCLT)

FIGURE 17.6. POTENTIAL AIR RECEPTOR EXPOSURE LOCATIONS.



model. ISCLT is a steady-state Gaussian plume model used to estimate pollutant concentrations downwind of a stack or area source. The model estimates concentrations up to 50 km in the four cardinal directions from the facility. The contaminant concentration is a function of facility-specific parameters, meteorology, and physicochemical and degradation rate parameters for the contaminant of concern. Information on the RSEI model is available at http://www.epa.gov/opptintr/rsei/. To obtain a copy of the model contact TSCA Assistance Information Service, (202) 554-1404, Tsca-hotline@epa.gov.

Find all TRI-industries that reported air releases of methyl tert butyl ether (MTBE) for the 1998 submission year in Los Angeles County, CA. (*Hint:* Select release media code ≤2 to exclude releases to all media except stack and fugitive air emissions.) How many facilities reported air releases of MTBE to TRI in the Los Angeles County area in 1998? Identify the facility which contributes the greatest relative risk to the county. Using the selecting facilities location button (the binoculars button), identify this facility on the map and model MTBE stack air release concentrations for these reported TRI-emissions. What is the facility's contribution to MTBE air concentrations within the 50-mile perimeter (what is the range of MTBE air concentrations resulting from these emissions)? Derive the 1998 aggregate MTBE concentration range (or the resulting MTBE air concentration range from all TRI facilities emitting MTBE in Los Angeles County). What is the aggregate MTBE air concentration range? (*Hint:* You can divide the toxicity-weighted concentration ranges by the RSEI Inhalation Toxicity-Weighting factor [ITW] to derive the aggregate MTBE air concentration.) Use the default number of classes and class break types. (*Extra Credit:* What would the resulting cancer risk be from a lifetime inhalation exposure for a person located in the center of this aggregate source plume [or exposed to the highest aggregate concentration]? Assume that there are no changes in the air releases over the resident's lifetime.)

3. The Human Health Risk Exposure (HHRE) model can be used to estimate the lifetime average daily doses (LADDs) from various exposure pathways (ingestion, inhalation, and dermal) for several common exposure scenarios (residential, occupational, and recreational) using EPA-based default exposure values. This model is part of the Oak Ridge Institute's Risk Assessment Information System (RAIS) (http://risk.lsd.ornl.gov/homepage/rap_tool.shtml). Rank the contaminants found in well water which supplies the potable water for a community with high incidence of a systemic disease (non-cancer). Assume that there were lifetime contaminant intake due to ingestion, inhalation, and dermal uptake. Use RAIS to evaluate lifetime well water exposures for local residents using default EPA assumptions. Calculate the lifetime average daily doses

(LADDs)(or chronic daily intake [CDI]), the acceptable lifetime average daily doses (ALADDs), and the dose ratios (DRs) for all potential exposure pathways. The monitored well water contaminant concentrations are 0.001mg/L of perchlorate, and 0.01mg/L of TCE. Which contaminant poses the greatest threat? What exposure pathway poses the greatest threat? What would you advise the local residents?

Notes

1. See National Library of Medicine, 2004, and Environmental Protection Agency, 2005. Pertinent chemical-specific factors were compiled from relevant articles, books, and databases.
2. Air emissions, and water and land release estimates can be derived from facility records or Toxic Release Inventory (TRI) databases.
3. Monitoring data can be obtained from facility records, National Pollutant Discharge Elimination System (NPDES) databases, regional water quality departments, or individual private water supply facilities.
4. Examples of health-based standards include: (1) Maximum Contaminant Level (MCL—the drinking water concentration above which chronic exposure could pose a health risk; (2) Reference Dose (RfD—the exposure dose above which chronic exposure could cause disease; Reference Concentration (RfC)—the air exposure concentration above which chronic exposure could cause disease. Values for the above standards are available from EPA's Risk Assessment Information System (RAIS) website: http://risk.lsd.ornl.gov.
5. It is noted that if necessary the Freedom of Information Act (FOI) can be used to pressure agencies into complying with formal requests. However, it is important to keep in mind that only U.S. government agencies are subject to FOI. The Freedom of Information Act is available online at http://www.usdoj.gov/oip/foia_updates/Vol_XVII_4/page2.htm.
6. CalPUFF is a multilayer, multispecies nonsteady-state puff dispersion model that can simulate the effects of time- and space-varying meteorological conditions on pollutant transport, transformation, and removal. CalPUFF is used by the Environmental Protection Agency in its Guideline on Air Quality Models as the preferred model for assessing long range pollutant transport.
7. See Environmental Protection Agency (1999). Contaminants that did not have the relevant Cancer Potency Factor (CPF) or Reference Dose (RfD) for cancer risk and hazard index derivation, respectively, were included on the list of COCs requiring further review.

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CHAPTER EIGHTEEN

INTRASPECIES DIFFERENCES IN ACUTE ACRYLONITRILE TOXICITY

Gwendolyn Ball
Clif McLellan
Lori Bestervelt

Learning Objectives

Students who complete this chapter will be able to

1. Appreciate that there can be individual differences in response to a chemical exposure
2. Understand that genetics can play a role in these differences
3. Understand the importance and limitations of case reports
4. Describe the emerging field of toxicogenomics
5. Predict what individual differences other than genetics could affect response to a chemical exposure

Acrylonitrile or vinyl cyanide is a small, polar molecule. Its structure is shown in Figure 18.1. Although its boiling point of 77.3°C is well above room temperature, a vapor pressure of 109 mm Hg at 25°C favors its existence in the vapor state. Acrylonitrile is a high production volume chemical, meaning that greater than one million pounds per year are produced or imported by the United States or the European Union. Major uses are as a monomer in the manufacture of acrylic and modacrylic fibers used in textiles, as a monomer in the manufacture of acrylonitrile-butadiene-styrene (ABS), styrene acrylonitrile (SAN), and other plastics, and as a chemical intermediate. Although generally produced and handled in closed

FIGURE 18.1. STRUCTURE OF ACRYLONITRILE AND ITS 2-CYANOETHYLENE OXIDE METABOLITE.

Acrylonitrile

2-Cyanoethylene oxide (reactive metabolite)

systems, occupational exposure to acrylonitrile by inhalation or dermal absorption may occur during transfer, transport, or other handling of the chemical, or during industrial accidents. The current occupational exposure limit, or Threshold Limit Value, for an eight-hour shift is 2 ppm or 4.3 mg/m^3. The public may be exposed to very low levels of acrylonitrile through handling and use of clothing or plastics having small amounts of residual monomer (Hazardous Substances Data Bank, 2005).

Multiple pathways have been identified for the metabolism of acrylonitrile (Environmental Protection Agency, 1983; Agency for Toxic Substances and Disease Registry, 1990):

- A major pathway involves conjugation with glutathione catalyzed by the enzyme glutathione-S-transferase (GST), followed by enzymatic conversion to cyanoethylated mercpturic acid, a water-soluble metabolite eliminated in the urine. This pathway does not involve the production of cyanide as a metabolite.
- Another significant pathway involves cytochrome P450 CYP2E1 enzymatic oxidation of acrylonitrile to 2-cyanoethylene oxide, which can also be conjugated with glutathione through a reaction catalyzed by glutathione-S-transferase. Further metabolism of this conjugate leads to several water-soluble organic acids plus cyanide.
- Two other pathways, not involving glutathione conjugation, also lead to formation of cyanide as a metabolite.
- Both acrylonitrile and its 2-cyanoethylene oxide metabolite are able to covalently bind to protein, DNA, and other biological macromolecules, removing them from the cyanide-forming pathways.

Many plants (e.g., almonds, spinach, lima beans, and cassava root in the tropics) used as food sources include low levels of cyanide-containing chemicals that the body can readily handle (Agency for Toxic Substances and Disease Registry,

1990). Acute (high level of exposure) acrylonitrile toxicity in humans resembles acute cyanide toxicity. The level of cyanide produced following an acute acrylonitrile exposure is dependent on the degree to which each of the above pathways is followed. A European research group has monitored adduct formation as well as glutathione-S-transferase and cytochrome P450 CYP2E1 polymorphisms in 59 workers industrially exposed to variable low levels of acrylonitrile, and in a few workers overexposed to acrylonitrile in industrial accidents, in an attempt to identify factors influencing the observed variability in human response to acrylonitrile exposure.

Thier and others (1999; Thier, Lewalter, Selinski, and Bolt, 2002) studied the effect of genetic polymorphisms of glutathione-S-transferase on the degree of formation of the N-terminal N-cyanoethylvaline adduct of acrylonitrile with hemoglobin. Blood collected from the 59 workers at different locations with varying levels of exposure to acrylonitrile was analyzed for N-(2-cyanoethyl) valine and for the glutathione-S-transferase polymorphisms GSTM1 and GSTT1. Smoking status of the workers was considered. N-2-cyanoethylvaline levels ranged from 3.7–232 μg/L blood during the first test and from 2–231 μg/L blood in a second test of the same workers one year later, with a disproportionate number of the high values in smokers. There was no apparent correlation between glutathione-S-transferase genotype and N-2-cyanoethylvaline adduct level. The authors concluded that neither GSTM1 nor GSTT1 was a major metabolizing isoenzyme for acrylonitrile.

Failure of the initial study to explain the different N-cyanoethylvaline adduct levels prompted additional study of two variants of the GSTM3 and multiple variants of the GSTP1 genotypes of glutathione-S-transferase (Thier and others, 2001). There was no apparent correlation between the glutathione-S-transferase GSTM3 genotype and the N-2-cyanoethylvaline adduct level. However, a single amino acid substitution on GSTP1, which occurred in approximately 34 percent of the workers studied, resulted in significantly higher N-2-cyanoethylvaline adduct levels. The authors therefore concluded that glutathione-S-transferase polymorphisms could affect the toxicity of acrylonitrile on an individual basis.

Thier and others (2001) also studied the influence of polymorphic variations of cytochrome P450 CYP2E1, which mediates the first step in the oxidative pathway, on the N-2-cyanoethylvaline adduct level. No effect was observed. Additional study of CYP2E1 variants produced no statistically significant effect, although there was a trend to higher adduct levels in individuals with one specific CYP2E1 mutation. The overall conclusion of Thier and colleagues' studies (1999, 2001) was that there may be multiple genetic variations influencing individual metabolism of acrylonitrile.

Thier, Lewalter, and Bolt (2000) investigated eight cases of industrial overexposure to acrylonitrile, all previously reported in the literature. In two of these

cases, subjects were overexposed by dermal absorption and inhalation in the same incident. One subject developed headache, nausea, and fatigue, with respective peak acrylonitrile and cyanide levels of 824 and 4,300 μg/L blood, and required treatment. This subject was described as a nonconjugator deficient in GSTM1 and GSTT1. The nonconjugator was a heavy smoker with a baseline blood cyanide level of 250 μg/L, and no significant urinary excretion of cyanomercapturic acid was detected during monitoring of the overexposure. The other subject, in spite of a 1,250 μg/L blood acrylonitrile level, had a blood cyanide level of < 500 μg/L and exhibited no clinical symptoms. This subject was described as a conjugator and was positive for GSTM1 and GSTT1. The study was conducted in Germany, where Leng and Lewalter (2002) report that 38–62 percent of the population is deficient in GSTM1 and 10–30 percent is deficient in GSTT1. The conjugator had N-cyanoethyl valine, N-cyanoethyl asparaginic acid, and N-cyanoethyl mercapturic acid levels in blood that were, respectively, > 3, > 4, and > 20 times the blood levels of the nonconjugator, indicating the conjugator had far greater ability to metabolize and eliminate acrylonitrile than the nonconjugator.

Response of the deficient conjugator was so extreme that Leng and Lewalter (2002) studied the baseline blood cyanide and N-cyanoethylvaline levels, as well as urinary acrylonitrile levels, of 360 nonsmokers who were not exposed to acrylonitrile. Urinary acrylonitrile levels were < 10 μg/L for all groups. Blood cyanide levels were 50 μg/L or less in 39 percent of the subjects, who had N-cyanoethylvaline blood levels averaging 1.7 μg/L. Blood cyanide levels were > 50–150 μg/L in 56 percent of the subjects, who had N-cyanoethylvaline blood levels averaging 2.1 μg/L. Blood cyanide levels were > 200 μg/L in 5 percent of the subjects, having N-cyanoethylvaline blood levels averaging 7.3 μg/L. The authors concluded that individuals in the latter group should avoid acrylonitrile exposure.

In these reports, GSTM1, GSTT1, and cytochrome P450 CYP2E1 polymorphisms had little or no effect on subjects occupationally exposed to low levels of acrylonitrile. Deficiency of the GSTM1 and GSTT1 genes had a dramatic effect in the case of occupational overexposure. Leng and Lewalter (2002) did not recommend use of glutathione-S-transferase polymorphisms as a measure of occupational risk evaluation at this time, however, because of limited data.

Understanding the influence of genetic variations in toxic response to chemical exposures is emerging as an important area of environmental, toxicological, and pharmaceutical research. Recognizing this importance, the National Institutes of Health, under the National Institute of Environmental Health Sciences, has established a National Center for Toxicogenomics (National Center for Toxicogenomics, 2000). Goals of this center include understanding the relationship between environmental exposures and human disease susceptibility and identifying useful biomarkers of disease and exposure to toxic substances.

Thought Questions

1. Are there other genetic variations you would expect to cause differences in response to chemical exposure?
2. Might individuals with asthma or chronic obstructive pulmonary disease be more sensitive to chemical exposure? What types of chemicals would you expect to cause problems for these individuals?
3. How could age affect the response to a chemical exposure?
4. How could toxicogenomics be applied in the pharmaceutical industry?
5. What ethical issues might arise as a result of applying toxicogenomics?

Discussion Aids

1. Polymorphisms of alcohol dehydrogenase and aldehyde dehydrogenase affect the reaction to alcohol and the susceptibility to alcoholism. Search on PubMed.
2. Inhalation of particulate matter < 10 microns in diameter (PM_{10}), acids, and other air pollutants has much more serious consequences for individuals with respiratory or circulatory diseases than it does for individuals with normal respiratory and cardiac function. See reports of the 1952 London smog event on the Internet at http://www.portfolio.mvm.ed.ac.uk/studentwebs/session4/27/greatsmog52.htm.
3. Children have immature metabolizing enzyme systems the first few years of life. The elderly may have circulatory or kidney diseases that affect distribution or elimination of a chemical, and may be taking pharmaceuticals that also affect how a chemical is handled.
4. Drugs could be developed for individuals with certain genetic polymorphisms, or the dose could be adjusted based on knowledge of individual genetics.
5. See the National Center for Toxicogenomics web site.

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CHAPTER NINETEEN

DRINKING WATER CONTAMINATION BY PERCHLORATES FROM DEPARTMENT OF DEFENSE ROCKET FUEL FACILITIES

Terry Gratton
Norman Trieff

Learning Objectives

Students who complete this chapter will be able to

1. Perform a risk assessment with limited environmental, human, and animal data
2. Recognize that the dose-response for a contaminant is not always linear
3. Recognize that the effect of a contaminant may be influenced by many factors
4. Understand that setting reference doses might include diet and other factors
5. Distinguish the need for different doses for different populations or answer the question "Does one size fit all?"

During the six decades since World War II, rocket fuel has been manufactured at various facilities in the United States. Some of the components, including the strong oxidant perchlorate (ClO_4^-) as either Na^+, K^+ salts or NH_4^+ due to improper disposal, have been increasingly discovered in soil and in both surface and groundwater in various parts of the country. This has resulted in the contamination of drinking water supplies in several states. Perchlorate contamination is found more frequently in groundwater than in surface water. Conventional water treatment processing does not remove perchlorate contamination. Since water consumption is essential for human health, the amount of any contaminant in drinking water must be limited so that no adverse effect can be attributed to a substance. Perchlorate can affect thyroid function by competitively inhibiting the

transport of iodine into the thyroid gland. This competitive property of perchlorate (potassium perchlorate) gave physicians a means for the treatment of hyperthyroidism in the 1950s and 1960s. The medical literature of that era speaks of successful treatment of more than one thousand hyperthyroid patients given doses of 400–1,200 mg/day with no significant side effects.

There is some concern that long-term exposure to perchlorate at doses below therapeutic levels may pose potential health effects on humans. Greer, Goodman, Pleus, and Greer (2002) performed two cross-sectional occupational studies of perchlorate. Plant workers exposed to relatively high doses of perchlorate revealed no evidence of adverse health effects. In both studies serum thyroid function tests revealed no adverse effects from perchlorate exposure. One study looked at 35 males and 2 females in which approximately 15 were exposed for more than 5 years; and the other study looked at 39 males and 9 females exposed for 1–27 years (Greer, Goodman, Pleus, and Greer, 2002). The exposures in these studies were at levels far above the currently recommended reference dose for perchlorate. On the basis of the variability in these studies it may be concluded that the probability of inhibiting thyroid iodine uptake is insignificant in persons already with sufficient iodine intake. They concluded that this would most likely be due to a long-term physiological compensation of the thyroid hormones: triiodothyronine (T_3), thyroxine (T_4), and thyroid-stimulating hormone (TSH).

However, certain susceptible populations can be affected by perchlorate uptake, for example, persons with reduced iodine intake, women who develop hypothyroidism during early pregnancy, and their fetuses. Fetal risk may include impaired physical and mental development as a consequence of altered thyroid hormone fractions. Hypothyroidism during infancy is also a major factor in mental retardation and neurological development.

To ensure that perchlorate in drinking water is well below levels that produce even mild hypothyroidism it is important to determine a dose response for perchlorate inhibition of iodine uptake and the relationship between inhibition and thyroid hormone levels.

In 1999 the EPA and the Department of Defense designed eight animal studies to determine subchronic, reproductive, and developmental effect of perchlorate. The subjects consisted of adult males, pregnant and nursing females, and, to a limited extent, fetal rat pups.

EPA contracted with the National Academy of Sciences to study the effects of perchlorate on the public. The National Research Council produced the document titled "Health Implications of Perchlorate Ingestion." This document suggested a reference dose of 0.0007 mg/kg/day (National Research Council, 2005).

In general, a reference dose (RfD) is an estimate of a daily oral exposure to the human population, including sensitive populations that are likely to be without an appreciable risk of health effects during a lifetime. This dose assumes that a

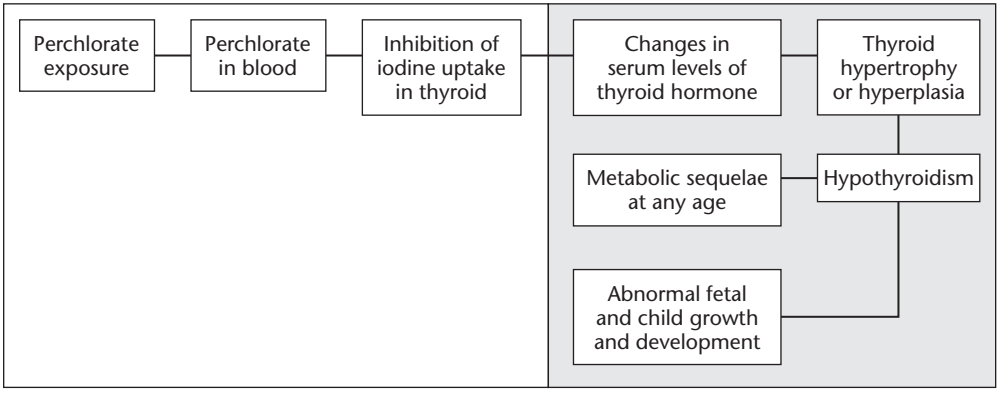
threshold exists for certain toxic effects such as cellular necrosis and is expressed in units of mg/kg/day.

EPA used a safety factor or uncertainty factor (UF) of 10 to adjust for errors in extrapolating both human and animal data to a no-observed-effect level (NOEL) for humans and to make allowances for uncertainty and safety. Therefore the RfD was set at 0.0007 mg/kg/day.

Inhibition of iodide uptake is a key biochemical event that precedes all potential thyroid-mediated effects of perchlorate exposure. Because iodide uptake inhibition is not an adverse effect per se but a biochemical change, this is a NOEL. The use of a NOEL differs from the traditional approach to deriving an RfD, which bases the critical effect on an adverse outcome. Using a nonadverse effect that is upstream of the adverse effect is a more conservative and health-protective approach to perchlorate hazard assessment. The point of departure is based on a nonstatistically significant mean 1.8 percent (standard error of the mean 8.3 percent) decline in radioactive iodine uptake in healthy adults following two weeks' exposure to a daily perchlorate dose of 0.007 mg/kg/day. The intraspecies uncertainty factor of 10 is applied to protect the most sensitive subgroups of the population.

The major risk factor for perchlorate toxicity is inadequate iodine intake (see Figure 19.1). Perchlorate has been found in groundwater in California, Arizona, and parts of New Mexico. In addition, perchlorate has been detected in commercial fertilizers and presumably vegetables grown in soils or irrigation water where perchlorate has been detected.

FIGURE 19.1. HYPOTHETICAL MODEL OF PERCHLORATE TOXICITY IN HUMANS.



Source: Adapted from National Research Council (2005).

Thought Exercise

For this exercise the exposed population is the population living near a solid rocket fuel plant somewhere in the western United States. Two cities, whose water supply is from groundwater, will be studied for excess hypothyroidism. These cities are demographically very similar. Assume there are an equal number of people in the normal and high-risk categories.

City A: The "average" person drinks two liters of water a day and has a daily intake of iodine that meets the FDA's recommended daily allowance for vitamins and minerals. However, perchlorate at 250 ppb was detected in the water supply.

City B: The average person drinks two liters of water a day, and has a daily intake of iodine that meets the FDA's recommended daily allowance for vitamins and minerals. The water supply in this city has a perchlorate contamination of <25 ppb.

Discussion Questions

1. What disease pathology would you expect to see when comparing Cities A and B?
2. What is the expected disease rate for hypothyroidism in an unexposed population? Where would you get these data?
3. Would you expect to see a difference in hypothyroidism between the two cities?
4. What two things could be done to reduce the incidence of hypothyroidism in the affected city?
5. From a public health viewpoint, what is the simplest/most cost-effective approach to reduce the risk of hypothyroidism in a population exposed to perchlorate?

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Further Readings

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CHAPTER TWENTY

MULTI-PATHWAY RISK ASSESSMENT FOR CHILDREN LIVING NEAR A HAZARDOUS WASTE SITE

Serap Erdal

Learning Objectives

Students who complete this chapter will be able to

1. Estimate dose received via each exposure pathway
2. Integrate exposure and toxicity information to characterize risks
3. Quantitatively estimate cumulative cancer and noncancer risks and interpret the significance for public health protection
4. Identify/evaluate uncertainties in risk assessment
5. Understand cancer risk assessment guidelines

Problem: A hazardous waste site near a park in a residential area is contaminated with the specific chemicals of concern (COCs) shown in Table 20.1. You, as a public health scientist, are tasked with determining whether excess cancer and noncancer risks posed by these COCs at the site to resident children are within acceptable regulatory criteria. You will need to quantitatively estimate the cumulative reasonable maximum exposure (RME) carcinogenic and noncarcinogenic

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TABLE 20.1. INFORMATION RELATED TO COCS IN SOIL AT A HAZARDOUS WASTE SITE.

Chemical of Concern (COC)	Conc. in Soil (mg/kg)	Cancer Slope Factor (CSF) $(mg/kg\text{-}day)^{-1}$	Reference Dose (RfD) (mg/kg-day)	Target Organ
Benzo(a) pyrene (BaP)	56.7	7.3—oral 7.3—inh 12.6—dermal	na	na
Dibenz (a,h) anthracene (DbA)	43.2	7.3—oral 7.3—inh 12.6—dermal	na	na
Beryllium (Be)	123.8	8.4—inh	2×10^{-3}—oral 5.7×10^{-6}—inh 1.4×10^{-5}—dermal	Immune and Respiratory System (inh) Alimentary System (oral)
Cadmium (Cd)	59.4	6.3—inh	5×10^{-4}—oral 1.2×10^{-5}—dermal	Kidney (oral)
Barium (Ba)	65.9	NC	7×10^{-2}—oral 4.9×10^{-3}—dermal	Kidney (oral)

na = not available; inh = inhalation

health risks associated with children's exposure to contaminated soil at the site via incidental ingestion, dermal contact, and inhalation of particulates pathways using the deterministic approach. Chemical-specific toxicity information for risk characterization is also included in the table.

Solution: Risk is a function of exposure and toxicity, consisting of a four-step paradigm as described in detail in NAS (1983) and EPA (1989). A number of exposure parameters are integrated into an estimate of dose received by an exposed individual via each exposure route (ingestion, dermal contact or skin absorption, and inhalation). In the estimation of health risks posed by hazardous waste sites, the magnitude of human exposures, in general, is dependent on COC concentration in soil, exposure parameters describing human physiology (e.g., soil ingestion rate or body weight), and population-specific parameters describing exposure behavior (exposure frequency, duration). When evaluating subchronic or chronic exposures to noncarcinogenic chemicals, dose is averaged over the period of exposure, thus referred to as *average daily dose* (ADD). However, for carcinogens, dose is averaged over an entire lifetime (i.e., 70 years), thus referred to as *lifetime average*

daily dose (LADD). The ADD for noncarcinogenic COCs and LADD for carcinogenic COCs are calculated for each exposure pathway as shown below:

$$\text{Soil Ingestion: } L(ADD)_o = \frac{C_s \times IR_o \times EF \times ED \times CF}{BW \times AT} \tag{20.1}$$

$$\text{Dermal Contact: } L(ADD)_d = \frac{C_s \times SA \times AF \times ABS \times EV \times EF \times ED \times CF}{BW \times AT} \tag{20.2}$$

$$\text{Inhalation of Particulates: } L(ADD)_i = \frac{C_s \times IR_i \times EF \times ED \times \left(\frac{1}{PEF}\right)}{BW \times AT} \tag{20.3}$$

where:

C_s:	Exposure concentration (i.e., 95th Upper Confidence Limit on the Mean) of COC in soil (mg/kg)–(chemical-specific; estimated using Environmental Protection Agency 2004a)
IR_o:	Ingestion rate of soil (mg/d)–200 mg/d
IR_i:	Inhalation rate (m^3/d)–10 m^3/d
SA:	Skin surface area (cm^2)–2800 cm^2
AF:	Soil-to-skin adherence factor (mg/cm^2)–0.2 mg/cm^2-event
ABS:	Dermal absorption fraction (unitless)–(chemical-specific; 0.13 for PAHs and 0.001 for inorganics)
EV:	Event frequency (events/d)–1 event/d
EF:	Exposure frequency (d/y)–350 d/y
ED:	Exposure duration (y)–6 y
PEF:	Particulate emission factor (m^3/kg)–1.36 x 10^9 m^3/kg per EPA (2002a)
BW:	Body weight (kg)–16.3 kg
AT:	Averaging time (days)–(ED*365 d/y for noncarcinogens; 70 y*365 d/y for carcinogens)
CF:	Conversion factor–10^{-6} kg/mg

The values of the exposure parameters shown above (representing the RME scenario for children) were obtained from EPA's *Exposure Factors Handbook* documents (Environmental Protection Agency, 1997, 2002b). Since all COCs have low volatilization potential, dose received via inhalation of volatiles pathway is

assumed to be negligible at this site. In compiling toxicity values, that is, chronic oral and inhalation *reference doses* (RfDs) and *cancer slope factors* (CSFs), the hierarchy used was EPA's *integrated risk information system* (IRIS) (Environmental Protection Agency, 2005a) and provisional peer reviewed toxicity values developed by EPA's National Center for Environmental Assessment (NCEA) following the most recent EPA guidance (Environmental Protection Agency, 2003). The CSFs for PAHs (BaP and DbA) were based on EPA's *toxic equivalency factor* (TEF) methodology using potency of each compound relative to that of BaP (Environmental Protection Agency, 1993). The dermal RfDs and CSFs for the COCs at the site were derived from oral RfDs and CSFs, adjusted for chemical-specific gastrointestinal absorption efficiency, based on the recommended methodology in EPA's guidance for dermal risk assessment (Environmental Protection Agency, 2004b).

In risk characterization, a *hazard quotient* (HQ) as an indicator of risks associated with health effects other than cancer and an *excess cancer risk* (ECR) as the incremental probability of an exposed person developing cancer over a lifetime are calculated by integrating exposure and toxicity information. If HQ > 1, there may be concern for potential adverse systemic health effects in the exposed individuals. If HQ ≤ 1, there may be no concern. It should be noted that HQs are scaling factors and they are not statistically based. The EPA's acceptable criterion for carcinogenic risks is based on public policy as described in the National Contingency Plan (NCP) and is the exposure concentration that represents an ECR in the range of 10^{-4}–10^{-6}, that is, 1 in 10,000 to 1 in 1,000, 000 excess cancer cases (Environmental Protection Agency, 1990).

$$\text{Noncancer Risk: } \textit{Hazard Quotient}\,(HQ) = \frac{ADD}{RfD} \tag{20.4}$$

$$\text{Excess Cancer Risk (ECR): } ECR = L(ADD) \times CSF \tag{20.5}$$

To account for exposures to multiple COCs via multiple pathways, individual HQs are summed to provide an overall Hazard Index (HI). If HI > 1, COCs are segregated based on their critical health end point, and separate target organ-specific HIs are calculated. Only if target organ-specific HI > 1 is there concern for potential health effects for that end point.

$$\text{Cumulative Cancer Risk: } \textit{Hazard Index} = HI = \sum_{COC_{NC}=1}^{n} (HQ_o + HQ_d + HQ_i) \tag{20.6}$$

$$\text{Cumulative Excess Cancer Risk: } \sum_{COC_C=1}^{n} ECR = \sum_{COC_C=1}^{n} (ECR_o + ECR_d + ECR_i) \tag{20.7}$$

Table 20.2 summarizes the results of COC- and exposure-pathway-specific and cumulative RME cancer and noncancer risk estimations for children who are exposed to COCs in site soil, which were obtained following the algorithms outlined in Equations 20.1–20.7.

EPA's reliance on the concept of RME for estimating risks is based on a conservative but plausible exposure scenario (which is defined to be the 90th to 95th percentile exposure, signifying that less than 5 percent to 10 percent of the population would be expected to experience a higher risk level), and has been scientifically challenged over the years. For example, Burmaster and Harris (1993) showed that the use of EPA-recommended default exposure parameter values resulted in exposure and risk estimates well in excess of the 99th percentile due to multiplication of three upper-bound values (i.e., 95th percentile) for IR, EF, and ED. The authors argued that this leads to hazardous waste site cleanup decisions based on health risks that virtually no one in the surrounding population would be expected to experience. They advised that the EPA endorse and promote the use of probabilistic methods (e.g., Monte-Carlo simulations) as a way to supplement or replace current risk assessment methods, to overcome the problem of "compounded conservatism" and enable calculation of risks using a more statistically defensible estimate of the RME. Although EPA published the probabilistic risk assessment guidelines in 2001 (Environmental Protection Agency, 2001), its application has so far been limited.

TABLE 20.2. SUMMARY OF RISK CHARACTERIZATION FOR RESIDENT CHILDREN.

	ECR			*HQ*		
COC	**Ingestion**	**Dermal**	**Inhalation**	**Ingestion**	**Dermal**	**Inhalation**
BaP	4.2×10^{-4}	2.6×10^{-4}	1.5×10^{-8}			
DbA	3.2×10^{-4}	2.0×10^{-4}	1.2×10^{-8}			
Be			3.9×10^{-8}	7.3×10^{-1}	2.9×10^{-1}	9.4×10^{-3}
Cd			1.4×10^{-8}	1.4×10^{0}	1.6×10^{-1}	
Ba				1.1×10^{-2}	4.4×10^{-4}	
EP total[1]	7.4×10^{-4}	4.6×10^{-4}	8.0×10^{-8}	2.1×10^{0}	4.6×10^{-1}	9.4×10^{-3}
Cumulative	1×10^{-3}			HI = 2.6		

Note: The numbers in this table may not add up to the total estimates due to rounding.

[1]EP total: Exposure pathway-specific estimates

Therefore, proper evaluation of uncertainties, which are associated not only with compounded conservatism but with potential underestimation of quantitative risk estimates (e.g., due to the presence of COCs without established toxicity values), is intrinsic to any risk-based scientific assessment. In general, uncertainties and limitations are associated with sampling and analysis, chemical fate and transport, exposure parameters, exposure modeling, and human dose-response or toxicity assessment (derivation of CSFs/RfDs, extrapolation from high animal doses to low human doses), and site-specific uncertainties.

Since the recommendations by the National Research Council (National Academy of Sciences, 1983) to promote consistency and increase technical quality in risk assessments by U.S. federal agencies were published, numerous guidance documents have been published by EPA. Among the more recent initiatives, the new cancer risk assessment guidelines (Environmental Protection Agency, 2005b) and supplemental guidance for assessing susceptibility from early-life exposures to carcinogens (Environmental Protection Agency, 2005c) are likely to have the most impact on the ways that ECRs are estimated for both adults and children. Major changes in the new cancer risk assessment guidelines include (1) the use of chemical-specific mode of action (MOA) information, if available (i.e., data on the sequence of physiological, biochemical, and/or genetic changes induced by chemical exposure that lead to the development of specific tumors) and (2) use of either linear (threshold) and/or nonlinear statistical models to estimate human cancer dose-response or potency (via low-dose extrapolation from the range of high experimental animal doses to the much lower doses typical of actual human exposures), based on MOA data. (In the past, only low-dose linear extrapolation was considered acceptable.) These changes are due to significant advances in our understanding of cancer biology and to the development of new statistical methods for dose-response analysis. Moreover, the guidelines view childhood as a series of sensitive life stages, rather than considering children's susceptibility to chemical exposures to be the same as adults (Environmental Protection Agency, 2005b). In the supplemental guidance, EPA recommends that default age-dependent adjustment factors (ADAF) be applied to CSFs (which do not address the impacts of early-life exposures) for carcinogens with a genotoxic or mutagenic MOA to reflect the possibility that early-life exposures make a greater contribution to the development of cancer appearing later in life than do adult exposures only.

The rationale for this approach is that the developing young are likely to be more susceptible to chemically-induced adverse effects because their less well-developed toxic defense systems and rapid growth and development during this period lead to increased sensitivity to chemical mutagens and genotoxins. Applications of ADAFs to CSF ought to be combined with age-specific exposure estimates to estimate cumulative lifetime ECRs for these compounds. Default ADAFs

are a multiplicative factor of 10 for < 2 years of age, 3 for 2–< 16 years, and none for ≥ 16 years. For COCs for which a MOA has not been established or a nonmutagenic, nongenotoxic MOA has been established, no adjustments are currently recommended (Environmental Protection Agency, 2005c). These proposed changes are likely to impart significant changes to the traditional ECR estimates when applied to real-world problems, including excess cancer risks posed by hazardous waste sites.

The improvement in the scientific quality and validity of health risk estimates depends on advancements in our understanding of human exposure to, and toxic effects associated with, chemicals present in environmental and occupational settings. Therefore, it is important to continue to develop research data to refine future risk assessments for informed regulatory decision-making and to ensure that costs associated with site cleanup are scientifically justified and public health-protective.

Thought Questions

1. What would the target-organ specific estimates be for the COCs at this site?
2. Which chemicals and exposure pathways are driving the cancer and noncancer risks of children at this site?
3. What would be your conclusions and recommendations to risk managers concerning acceptability of estimated cancer and noncancer risks posed by COCs to resident children at this site? Why?
4. What are the major uncertainties associated with the exposure and toxicity information utilized in the risk characterization?
5. If you were performing this analysis for resident adults instead of resident children, what would your excess cancer risk estimates be for the same exposure scenario and what is your response to Question #3 for adult receptors?
6. If you were performing a probabilistic risk assessment instead of a deterministic one, how would you approach this problem? Please lay out conceptually the steps you would take and information you would need for each step.

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CHAPTER TWENTY-ONE

CHILD WITH ASTHMA LIVING IN A MOISTURE-DAMAGED HOME

Myrtis Sullivan

Learning Objectives

Students who complete this chapter will be able to

1. Describe the known and suspected effects of fungi on the health of children and adolescents
2. Explain the current understanding of the relationship between mold exposure and illness and describe an approach to environmental assessment, risk communication, and management
3. Take a history of a child who has a suspected exposure to indoor fungi and an adolescent who has been exposed to indoor mold
4. Describe multidisciplinary intervention strategies including remediation, control, and prevention of indoor mold contamination
5. Recognize the clinical importance of exposure to microbial (fungi/mold) and other contaminants/toxins as important trigger(s) and possible causes of allergic and toxic health reactions in susceptible individuals

RJ is an eleven-year-old diagnosed with mold-sensitive asthma. Since age 3 he has made five visits to the ER and has been hospitalized once over the past 12 months. The child's pediatrician is concerned because his asthma symptoms have become increasingly more frequent and severe. He was initially diagnosed with

mild intermittent asthma over the previous five years. However, over the past year it became severe persistent asthma. RJ reports taking more asthma medications and using them more frequently than usual. The physician also learns the following: RJ's father lost his job, RJ is staying with his grandparents, and he sleeps in the basement.

What Would You Do at This Point?

1. Take a more extensive health history; list known allergies and asthma triggers; record details of medication use
2. Take an environmental history; conduct a home inventory of environmental health hazards (American Academy of Pediatrics, 2003)

A helpful mnemonic to use when taking an environmental history is CH2OP: Ask about attributes of the *C*ommunity, *H*ome, *H*obbies, *O*ccupation, *P*ersonal history and habits (American Academy of Pediatrics, 2003).

Key questions to ask are:

1. Where does the child live or spend time?
2. Does anyone in the home smoke?
3. What do the parents or teenagers do for a living?

Case Progression

Upon taking an environmental history the primary care physician learns that there is a water leak in the home. The primary care physician decides to refer RJ to the pediatric environmental specialty unit (PEHSU) at the local hospital where he is seen by a team of specialists, including a pediatric allergist and EOHS specialists. Following are the historical findings and results of physical examination and laboratory tests conducted at the hospital.

Historical Data

- Known triggers: ETS; molds, dust mites, cats and dogs
- Medication use: asthma medications: Albuterol inhaler 2 puffs three times daily; Advair 2 puffs twice daily.
- Days missed from school over past 12 months: 23
- ER visits in past 12 months: 5
- Night cough: daily
- Home inventory: no pets, no smokers, water damage throughout the basement

Laboratory Tests

- IgE-specific allergens: high and very high positive for alternaria, aspergillus, and fusarium moniforum (class 4); penicillium. Phoma betae, rhizopus nigricans, mouse protein urine
- IgE-specific allergens (moderate positive class 2) for dpteronyssinus, mucor racemossus, trichoderma v., chaetomiun g., rat urine
- Elevated stacchybotrys chartarum specific IgE: 0.99 (nl = < 0.35 KU/L)
- Elevated total serum Ige and elevated number of eosinophils suggestive of signs of allergic disorder
- Environmental tobacco smoke (ets): serum cotinine levels < 10 (nl = < 10 Ng/mL)
- Pulmonary (lung) functions tests (78 percent pred.) signs of obstruction found in asthma and other chronic obstructive lung diseases

Physical Examination (Significant Findings)

- Epistaxis; boggy nasal mucosa, minimal wheezing (both lungs)

These findings show that RJ has poorly controlled asthma and hypersensitivity to a number of allergies, including various species of mold. The serum cotinine levels confirm the verbal report that there are probably no smokers in the home.

What Would You Do at This Point?

Because RJ has mold-sensitive asthma and there is evidence of water damage in his home, he is eligible for a local HUD-funded program. RJ's family is enrolled in the in-home mold remediation demonstration project funded by HUD in collaboration with the PEHSU and the local and state health departments.

Case Discussion

Health Effects Associated with Molds

Description and routes of exposure. Molds are composed of linear chains of cells (hyphae) that branch and intertwine to form the fungus body (mycelium), and they produce spores that are dispersed by air currents. At least 60 species of mold have spores thought to be allergenic (Etzel, 2003; Burge, 1989). Exposure to molds occurs via inhalation of contaminated air and through skin contact with surfaces where they are deposited (Burge, 1989).

Systems affected and health effects. Molds may affect the mucous membranes of the eyes, nose, throat, and respiratory tract (Wigle, 2003; American Academy of Pediatrics, 2003, Bornehag and others, 2001; Richerson, 1990). Health effects may be allergic or toxic. Between 10 and 32 percent of all asthmatics are sensitive to fungi (Horner and others, 1995; Wigle, 2003; American Academy of Pediatrics, 2003). Toxic effects of molds may be due to inhalation of mycotoxins, lipid-soluble toxins that are readily absorbed by the airways (American Academy of Pediatrics, 2003). Species of mycotoxin-producing molds include fusarium, trichoderma, and stachbotrys. Exposure to stachybotrys and other molds has been associated with acute pulmonary hemorrhage among young infants (Dearborn and others, 1999; American Academy of Pediatrics, 2003). Children are more susceptible than adults to adverse health for a number of developmental and physiological reasons. They breathe more air, drink more water, and eat more food per kilogram of body weight than adults do. An infant's respiratory rate is more than twice an adult's rate. Other factors that influence both exposure to and absorption of environmental agents include a child's home, play, or day care environment; physical stature; mobility; metabolic rate; and increased surface area to body mass ratio (in young children).

It appears that RJ's asthma-related symptoms may be exacerbated by exposure to mold overgrowth in his home due to water damage throughout the house, particularly where he spends a great deal of time—in his bedroom. Therefore, it is a very good idea to determine if indeed mold is a problem in his home because removal of the mold from the water-damaged areas could result in a tremendous reduction in RJ's asthma symptoms.

In-Home Intervention

Inspection of RJ's home reveals multiple areas of water seepage, including the remodeled basement area where his bed is located. Visible mold is seen throughout the basement. Evidence of *Stachbotrys c.* is also detected in the home. In addition to mold assessment, remediation and repair of water leakage and damage are conducted according to the U.S. Department of Housing and Urban Development (HUD) guidelines outlined below.

Mold exposure in homes primarily occurs via inhalation of airborne spores and hyphal fragments. HUD recommends the following steps in assessing mold hazards in the home:

- Visual assessment
- Sample collection: source sampling; air sampling
- Sample analysis (including counting colonies cultured for specific species; identifying and/or counting spores; chemical analysis of fungal components to

quantify total fungal loads (biomass); immunoassays (elisas) to measure allergen levels; and genetic probe technologies to identify fungal species

Following are methods recommended by HUD to mitigate mold hazards in the home (Verhoeff and Burge, 1997; Department of Housing and Urban Development, 2001):

- Location and removal of sources of moisture (control of dampness and humidity and repair of water leakage problems)
- Increasing ventilation
- Cleaning of mold-contaminated materials
- Physical removal of materials with severe mold growth
- Use of high-efficiency air filters
- Maintenance of heating, ventilation, and air-conditioning systems
- Prevention of spore infiltration from outdoors by closing doors and windows and by using air conditioning

Case Progression

By six months, after the initial clinical workup and home remediation followed by the team in conjunction with the primary care physician, RJ began to show marked signs of improvement (e.g., days missed, clinical signs, PFTs, RAST indices). All of his symptoms were alleviated between 15 months and a year. RJ was given an action plan with instructions for self-management of his asthma symptoms. His family was instructed to move his bed from the basement area, and RJ was referred back to his primary care physician for long-term follow-up.

Discussion

Risk Assessment Overview

Risk assessment is often defined as the use of a factual base to define the health effects of exposure of individuals or populations to hazardous materials and situations (National Academy of Sciences, 1983). The goal of risk assessment is to provide an evidence base for decisions on policies and programs to protect the identified health hazards.

According to Wigle (2003) the process involves the synthesis of epidemiologic, toxicologic, and related research findings and judgments on causal relationships

and exposure-risk relationships. Unfortunately, this process can be arduous and difficult, particularly with children, because of the paucity of available data. After comparing chemical risk assessment procedures, assumptions, and policies across four federal agencies, the U.S. General Accounting Office (GAO) concluded that incomplete scientific information on human health effects and exposure to hazards continues to be a major source of uncertainty (General Accounting Office, 2001). Therefore, it is often necessary to use available tools, which may include the following four steps:

Risk Assessment Parameters (National Library of Medicine)

Hazard identification. Determine whether a particular chemical is a causal factor for particular health outcome. This is usually a qualitative step that seeks to identify and review health effects data associated with exposure and to determine whether a particular substance or chemical is causally linked to a particular health effect.

Dose-response assessment. Quantify the relationship between the dose (or exposure) and the probability of adverse health outcomes. This step seeks to determine the relationship between the administered dose and the occurrence of health effects. Dose-response almost always is based on animal toxicity data.

Exposure assessment. Quantify the extent of human exposure before or after application of regulatory controls. This step is used to determine the likely human exposures to a hazard or chemical. To be useful, it must accurately characterize all important sources of a particular toxicant in the environment (e.g., point or nonpoint source, mixture, chemical form), identify sources of exposure (e.g., groundwater, surface water, air, soil, food, breast milk), and measure exposures (e.g., microgram per liter in drinking water, microgram per gram in soil). Because of the complexity of this task, exposure assessment frequently is the most incomplete portion of the risk assessment, particularly with respect to pediatric exposures that are less well-studied and poorly characterized. Increasingly in recent years biomarkers for various environmental toxicants have been developed that can be measured directly in representative exposed populations to eliminate some of the uncertainties in modeled exposures (National Library of Medicine, 2005).

Risk characterization. This is the final step of risk assessment and involves the synthesis of the dose-response and exposure assessments. The result is expressed as the maximum acceptable exposure that is protective of health in the expressed population and a description of the nature and magnitude of the human risk, including attendant uncertainty (Wigle, 2003).

Indoor Air Assessment Indoor air assessment includes self-report information on indoor air monitoring and measurement. Indoor air pollutants can be categorized as follows:

1. *Aero-allergens:* House dust mites, which are usually found in furnishings such as mattresses, sofas, carpeting; pets, furry or feathered; and mice and other rodent infestation should be considered in the inner city, as well as cockroaches.
2. *Indoor gases:* Formaldehyde and VOCs are respiratory irritants produced by many substances in modern homes, including insulation, fabrics, carpets, solvents, floor adhesives, particle board, wood stain, paint, cleaning products, polishers, and room deodorants and fresheners.
3. *Indoor particulates.* These include environmental tobacco smoke (ETS) and particulates from burning wood in a fireplace or wood stove.

Assessment of Fungi and Molds Measurement of fungal exposure is complicated by large numbers of fungi and fungal products. The most prevalent mold genera in homes are alternaria, cladosporium, and penicillium. Besides allergic effects, some toxigenic molds (e.g., *Stachybotrys chartarum/atra*) produce mycotoxins and glucans, which cause toxic effects. Fungal spores are ubiquitous in the outdoor environment and indoor dust, and can readily grow indoors under certain conditions of persistent high humidity and in homes with a dirt floor or a crawl-space type of basement. Indoor storage of wastes (for composting) for a week or longer is associated with a five-to-eightfold increase in levels of fungal extracellular polysaccharides and β-glucans on living room and kitchen floors. Other factors contributing to mold growth include carpeted floors, dampness, past flooding, indoor storage of firewood, and unvented dryers (Wigle, 2003).

Fungal exposure has often been assessed by crude indicators such as the presence of visible mold or dampness. Quantitative indices include spore counts, culturable fungi, ergosterol (a fungal cell membrane sterol), β (1–3)-glucans, extracellular polysaccharides, fungal volatile organic compounds (3-methylfuran, 1-ocetene-3-ol, geosmin), mycotoxins, specific DNA sequences, and fungal lipids (Dillon and others, 1999). Settled dust concentrations of β (1–3)-glucans are highly correlated with those of endotoxin, house dust mite and cat allergens, and mold spores (Wigle, 2003).

Assessment of Other Indoor Hazards Although mold is common in water-damaged homes, asthma can be exacerbated from other indoor triggers or pollutants. The EPA, EPS, and SAB ranked indoor air pollution among the top five risks to public health in the United States. Children in developed countries spend over 90 percent of their time indoors (e.g., home, day-care centers, schools) (Wigle, 2003, p. 270).

Sources of other air contaminants, including environmental tobacco smoke (ETS), dust mites, cockroaches and pets, consumer products, inadequately ventilated cooking and heating devices, and influx of outdoor air pollutants must also be investigated (Wigle, 2003). According to Pirkle and others, 43 percent of children in the United States live with at least one smoking parent (1996). Exposure to ETS is associated with an increase in asthma attacks, increased medication use, and a more prolonged recovery from acute attacks (Weitzman, Gortmaker, Sobol, and Perrin, 1992; Albuhosn and others, 1997).

For adverse health impacts that may be a result of environmental exposures, we must consider the known toxicity and concentration not only of a given agent to which the individual was exposed but the frequency, duration, pathways, and routes of these exposures. We should also consider the age of the individual.

Risk Management of Fungi and Endotoxin and Other Indoor Exposures: Prevention and Monitoring

In general, for atopic individuals, allergy testing by skin prick would likely be very useful in guiding the avoidance measures. For example, it is difficult for families to get rid of a cat or dog, and this solution should only be advised when there is evidence of cat or dog allergy.

Low humidity levels and prevention and avoidance of water damage are essential for mold control. According to the NAS, there is suggestive evidence that interventions can reduce fungal allergen levels indoors but inadequate evidence to determine if such interventions improve asthma symptoms or lung function in sensitized asthmatics. Nor is there adequate evidence to determine if interventions reduce endotoxin levels in the home (National Academy of Sciences, 2000). There is limited evidence that the fungus stachybotrys charturum can cause idiopathic pulmonary hemisiderosis in infants, especially those exposed to ETS (Dearborn and others, 2002). Unfortunately, it appears that no country has comprehensive programs to address indoor air health hazards and to evaluate progress in reducing children's exposures (Wigle, 2003). In the United States, there are a number of demonstration prevention/intervention programs funded by EPA, NIEHS, and HUD (Department of Housing and Urban Development, 2001; Breysse and others, 2004). However, there is no comprehensive monitoring:

- Biomonitoring
- Indoor environment surveys
- Cockroaches.

  Minimize exposure to pesticides. Proper food clean-up and storage. Fix leaks and cracks in floors, walls, and other areas where they're frequently found.

- Mold

  Reduce humidity (e.g., keep humidity levels below 30 percent; use a dehumidifier). Clean contaminated areas with chlorine bleach. Repair and remove water-damaged materials.

  Proper ventilation is important.

Thought Questions

1. How do any risk assessments complement clinical advice and data?
2. *Other risk assessment tools.* What are other indirect methods of assessment?
3. *Advocacy.* Currently there are too few environmental health-related policies that protect children:

   Describe key legislation that protects children from adverse exposures.

   What policies are needed?

   What are key tools, steps, or opportunities for pediatric (child) environmental health advocacy?

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CHAPTER TWENTY-TWO

ENDOCRINE DISRUPTION THROUGH PHTHALATES/PLASTICIZERS

Christine Ziebold

Learning Objectives

Students who complete this chapter will be able to

1. Recognize that in endocrine disruption the timing of exposure during a particular developmental period rather than the quantity of exposure is crucial
2. Be familiar with the effects of endocrine disruption: decreased fertility, embryonic and fetal programming, increased in-utero lethality, and oncogenesis, which are hard to capture in standard risk assessment
3. Acknowledge the difficulty in identifying the cause of endocrine disruption, as well as the virtual impossibility of proving the cause for a health effect via exposure measurement after damage has occurred; this is often due to the long latency and difficulty of establishing or recalling exposure intensity, duration, and frequency; the uncertainty of an exact mechanism of action of most endocrine disruptors; and the paucity of developmental toxicological data in humans versus other species
4. Recognize the complexity of a real-life scenario, the inherent uncertainty and incompleteness of historical information, and the multiplicity of contributing factors (lifestyle, parental occupation, and diet) resulting in multiple simultaneous exposures
5. Become familiar with the difficulty of treating developmental defects, the pediatrician's dilemma

This case study is structured like a medical history (subjective-objective-assessment-plan). It starts with a chief complaint, the history of this complaint, the general past medical history (which includes developmental, dietary, and immunization history), the family history, and the social history (which should include occupational/environmental exposures). It is followed by a physical examination, diagnosis, and a treatment plan. For the purpose of this text, the case ends with a discussion of the causes. While it is entirely fictional it is based on the author's decade-long pediatric experience.

A two-year-old overweight boy is brought into the pediatrician's office on a busy Friday afternoon. His mother is concerned about his undescended testicles. She says she has never discovered them in his scrotum. There is no other complaint. She has not brought the child in for a year because he was essentially well. She wonders when the undescended testes will be fixed. At the boy's last checkup a year ago she was told that this condition usually outgrows and corrects itself.

The boy's medical record is not available. His past medical history is remarkable for his preterm birth at 28 weeks by normal spontaneous vaginal delivery in Arizona. He spent "some time" in the neonatal intensive care nursery and one month in the special care nursery. The mother recalls he was intubated for two weeks, fed through tubes in his veins and later tubes through his mouth into the gut; he also required transfusions for anemia. Later he was fed soy formula and never breast-fed. The mother remembers, "they couldn't circumcise him" when he was born because "something was different with his penis." She thinks she had an "uneventful pregnancy." She admits smoking but denies any other legal or street drug use. She recalls having had "very bad morning sickness," necessitating several emergency room visits with intravenous fluid administrations during her pregnancy. According to his mother the boy has been developing "normally." He eats a "normal diet"; that is, he shares all the table food the rest of the family is having. He is not allergic to anything and his immunizations are up-to-date according to his mother. He is not taking any medications.

The family history reveals several relatives with breast cancer on the mother's side. The child's father has recently been diagnosed with leukemia. He has had diabetes mellitus and high blood pressure for some time, but none of his relatives have. The child has one older brother, who is apparently healthy. Upon further questioning there are indications of decreased fertility in the child's parents, with at least one miscarriage in the first trimester.

The child's social history is significant for in-home care. He grew up in Yuma Valley, Arizona. His father, a veteran who served in Vietnam from 1970 through 1975, is currently unemployed. His mother works as a beautician. The family has moved within the continental United States several times, but has never lived overseas. They have frequently lived next to major highways. For about a year they

have dwelled in a single-family home in northeast Arkansas at the edge of a cotton field. Over-the-counter DEET-based tick and insect repellents are usually used from May until October. Both parents smoke, although the mother denies any smoking around the children.

The physical examination reveals an obese male with normal vital signs in good spirits (body mass index = 30). His exam is remarkable for his genitalia: both scrota are empty. A small testis can be palpated with much difficulty in the left groin, where it is fixed. His penis is not circumcised and looks small, but it is straight and slightly hooded by his foreskin. His urethra opens on the underside of the tip of his penis (hypospadia).

The pertinent diagnoses for this patient are (1) bilateral undescended testicle (cryptorchidism) and (2) hypospadia of the glans penis.

There are no laboratory tests that can be ordered in support of the diagnosis, although ultrasound can help to locate a testicle that cannot be felt.

The treatment of undescended testicles after the first year of life consists of surgically fixing the testis in the scrotum, although sometimes hormonal injections are tried to stimulate movement of the testicle into the scrotum. Hypospadias of the glans penis are the mildest form of hypospadias and usually do not require treatment (unlike more severe cases like hypospadia of the penile shaft, where the shaft is bent).

Hypospadia is a relatively frequent birth defect ranging in frequency between 1–8/1,000 births, with a rising incidence in the United States and Europe.[1] From an embryologic point of view, hypospadias arise very early during the first month of pregnancy from a closure disorder of the spongy part of the urethra. The cause for this disorder is multifactorial: an altered synthesis of testosterone or an anomaly of testosterone receptors, due to genetic and environmental factors. A number of environmental chemicals are known to be antiandrogenic, including fungicides, herbicides, and insecticides, as well as plasticizers, the most common type of which are phthalates. While they are often environmental chemicals, "endocrine disruptors" are defined as anything that can cause an imbalance within the endocrine system.

The constellation of undescended testicles with hypospadia and other genital abnormalities, summarized as "incomplete virilization," has been named *testicular dysgenesis syndrome*.[2] First observed in rodents exposed to certain phthalates in utero more than 20 years ago, it was called *phthalate syndrome* and also includes early fetal death, reduced anogenital distance, malformed epididymis, reduced spermatogenesis, and testicular tumors, with birth defects known to be proxy for abnormalities occurring later in life.

The prime candidate for endocrine disruption in the child's case is the group of phthalates, in particular di (2-ethylhexyl) phthalate (DEHP), which is added to

make polyvinylchloride (PVC) flexible. PVC is not only a ubiquitous household product but also the most widely used plastic in medical products. Because DEHP is not covalently bound it readily leaches out at well-defined rates. The largest exposure in this case occurred through intravenous (IV) tubing and intravenous fluid bags. These were administered to the mother prenatally and to the child as a preterm baby in the form of transfusions and nutrition through nasogastric, urinary, and respiratory tubes. The mother's skin and respiratory tract also were likely to have been heavily exposed to phthalates at work: shampoos, hair sprays, nail varnish, perfumes, and other personal care products contain the lower molecular phthalates, which are added because of their solventlike character.

Phthalates have been measured in the majority of the U.S. general population in all three of CDC's biennial large-scale biomonitoring studies.[3] The human health effects from high-level and occupational phthalate exposure such as infertility have been known for at least a decade. However, the effects of low-level and prenatal exposure in humans were not studied until very recently,[4] even though exposure of newborns to phthalates, for example, in neonatal intensive care units, have been known to exceed average daily adult exposure by two to three orders of magnitude.[5] It is now evident that humans are more sensitive to prenatal exposure than rodents. The National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction has updated its draft toxicity assessment accordingly.[6]

The public health response and risk management has so far been limited to calls of voluntary restrictions and phase-outs in toys and teething products by the U.S. Consumer Products Safety Commission and Toy Manufacturers Association. The latter agreed upon a voluntary limit of DEHP at 3 percent in pacifiers in 1986 and called for a phaseout in 1998. The Food and Drug Administration (FDA) issued a little known safety assessment and recommendation for health care providers in 2001 and 2002, respectively. It asked to consider DEHP-free alternatives where the "tolerable intake" was exceeded, that is for high risk populations defined as newborn boys, pregnant women, peripubertal males, and for certain high risk procedures, such as exchange transfusions, cardiac bypass and artificial feeding."[7] However, the FDA did not mandate to label phthalates in products, often considered trade secrets, which has hampered the implementation of their recommendation. California has been listing DEHP as a reproductive toxicant,[8] and New York State is considering regulation. The European Union banned all four main reproductive toxicant phthalates in 2000 from child-care items, two from cosmetics, three from chewable toys, and is now considering a ban on DEHP in household products. Japan has banned all phthalates from food-handler gloves and containers.

For completeness' sake it may be worth considering other antiandrogenic compounds that the child may have been exposed to, namely pesticides via residence in an agricultural area, contaminated well water, and household use, as reviewed in footnote 2 (Fisher). Yet other classes of endocrine disruptors in this case are cadmium from cigarette smoke in the family, but also from ambient air pollution due to traffic and from food, especially grains and broadleaf vegetables (accumulation of metals due to atmospheric deposition has been documented for lead and cadmium). Vegetables grown in cadmium-contaminated soils have been found to uptake cadmium more efficiently than other heavy metals.[9] Cadmium mimics estrogens.[10] The father's illnesses are exemplary for exposure to polychlorinated biphenyls and polychlorinated dibenzodioxins in the form of the herbicide Agent Orange, for which the Veteran's Administration recognizes that there is sufficient evidence of an association.[11] Another endocrine disruptor the child may have been exposed to is perchlorate from water and dietary intake. Perchlorate is the ingredient of rocket fuel and has been contaminating drinking water, water used for irrigation of crops in Yuma Valley, as well as cow's milk. Perchlorate is exhibiting antithyroid effects and suspected of numerous other health problems.[12]

Thought Questions

1. How can risk assessment incorporate risk due to endocrine disruption?
2. What upstream interventions would effectively prevent endocrine disruption in this case?

General Resources

Books

Berkson, D. L. *Hormone Deception: How Everyday Foods and Products Are Disrupting Your Hormones—and How to Protect Yourself and Your Family.* New York: McGraw-Hill, 2001.

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Web Sites

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http://europa.eu.int/comm/environment/endocrine/index_en.htm.

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http://www.ourstolenfuture.org/NewScience/newscience.htm.

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9. Agency for Toxic Substances and Disease Registry Draft Toxicological Profile for Cadmium, CDC Atlanta, July 1999, p. 242. http://www.atsdr.cdc.gov/toxprofiles/tp5-c5.pdf. Accessed April 17, 2006.
10. Henson, M. C., and Chedrese, P. J. Endocrine Disruption by Cadmium, A Common Environmental Toxicant with Paradoxical Effects on Reproduction." *Experimental Biology and Medicine,* 2004, *229*(5), 383–392. http://www.ebmonline.org/cgi/content/full/229/5/383. Accessed April 17, 2006.
11. U.S. Department of Veterans Affairs' Agent Orange-Herbicide Exposure, Veterans Benefits and Services. http://www.vba.va.gov/bln/21/benefits/herbicide/#bm03. Accessed April 17, 2006.
12. Agency for Toxic Substances and Disease Registry Draft Toxicological Profile for Perclorates. Atlanta: CDC, September 2005, Chapters 2 and 3. http://www.atsdr.cdc.gov/toxprofiles/tp162.html. Accessed April 17, 2006.

CHAPTER TWENTY-THREE

ESTIMATION OF HEALTH AND SAFETY RISKS FROM EXPOSURE TO CHLORINE AND CHLOROFORM FOR SWIMMERS IN POOLS

Richard P. Hubner

Learning Objectives

Students who complete this chapter will be able to

1. Understand how risk assessment techniques can be applied to a real world scenario
2. Know what a "margin of exposure" is and how it is calculated
3. Understand how risk assessment can aid in the development of safe levels of exposure

Chlorination of swimming pools is an essential public health measure for protecting against exposures to dangerous pathogens. To be fully effective, chlorine (and any other) disinfectant must be present continually in sufficient concentrations to act as a barrier against the survival of newly introduced pathogens. Achieving this goal requires continuous maintenance of an optimum free available chlorine (FAC) residual of 2–5 ppm with a maximum of 10 ppm. Periodic superchlorination to about 10 ppm such as that recommended by the National Spa and Pool Institute and the National Swimming Pool Foundation is needed to ensure that the minimum chlorine level is always present.

Superchlorination is defined as the periodic addition of chlorine at 10 times the amount of combined chlorine, also called chloramines. For example, if the combined chlorine in pool water is 1 ppm, then 10 ppm (10 × 1) chlorine should be

added. In residential swimming pools, disinfection often relies solely on the periodic (e.g., weekly or biweekly) application of gaseous and other forms of chlorine, which is applied in quantities sufficient to achieve the benefits of superchlorination and to maintain an adequate measure of health protection for swimmers between applications. The application of chlorine to swimming pools is generally of two types: (1) direct addition of chlorine (including gas, liquid bleach, tablet and/or granular chlorine) to residential pools by a homeowner or pool company and (2) a combination of periodic superchlorination and continuous feed of chlorine through a fixed chlorinator, as is usually found at commercial pools.

The U.S. Environmental Protection Agency (EPA), as part of its process to reregister chlorine as a disinfectant under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), has proposed a reentry standard of 4 ppm FAC following superchlorination.

Accordingly, the study outlined in this chapter was undertaken to determine whether the reentry guideline could be justifiably raised to 10 ppm FAC with no undue health risk from chlorine and its major byproduct, chloroform. To accomplish this goal, human exposure to chlorine and chloroform was characterized to estimate safe levels for reentry into pools treated with gaseous and other forms of chlorine. Evaluating exposure required identifying the demographics of the exposed population, the magnitude and frequency of contact with the substances, the routes of exposure, and the durations of contact. The routes of exposure considered are (1) absorption through skin contact while in the pool, (2) inhalation of compounds in the breathing zone of pool users, and (3) incidental ingestion of water during swimming. Furthermore, for chloroform, the rates of absorption by body tissues were used to integrate doses systematically.

Data on the presence of chlorine and chloroform are available for commercial indoor and outdoor pools that use chlorine. These data provide an indication of the range of concentrations of chloroform expected in pool water and in the swimmer's breathing zone. They have served as a means of approximating median concentration levels for long durations as well as peak levels for brief periods.

The population of swimmers includes people of all ages and of both genders. Swimming activities are defined as mostly recreational, some therapeutic, and some competitive. The selected range of exposure scenarios is broad, from those who do not go near the water to those who swim nearly every day for most of their lives.

These exposure parameters were used to derive the margins of exposure (MoE) that served as a basis for proposing a 10 ppm health-protective rerentry level of FAC as an alternative to EPA's proposal of 4 ppm FAC.

Methods

Exposure Assessment

For this analysis, the "average" exposure for a swimmer was defined as swimming in a chlorinated pool:

- 1 hour per day
- 2 days per week
- 39 weeks per year (for outdoor pools) for 35 years, or 50 weeks per year (indoor pools) for 35 years, and an inhalation rate for swimmers of 1 m^3/hour (representing the weighted [9:1] average of recreational swimmers and competitive swimmers)

Chemical Concentration in Water and Breathing Zone

Exposure estimates were obtained by considering the populations exposed, swim conditions that influenced breathing rates, and the concentrations of chloroform in the breathing zone. Major limitations of the exposure assessment include:

- The relatively few data characterizing the concentrations of chloroform in the air above the water of swimming pools
- The relatively large variation in measured chloroform above water in swimming pools
- The measurement of chlorine in pool water

Results

The following data are the result of combining the exposure information with the hazard information. The results are presented as a matrix for each compound that takes into account routes and durations of exposure—factors that are related directly to the estimations of safety and risk for humans. The measure used to define safety is the margin of exposure or MoE between actual exposure under actual conditions of disinfection practice in the United States and the relevant adjusted human NOAELs. This method of deriving the MoE is in contrast to the approach used by USEPA which divides the experimentally derived NOAEL by the dose.

Chlorine

The safety and risk to those who swim in pools superchlorinated periodically with gaseous and other forms of chlorine is characterized by comparing the anticipated levels of exposure to aqueous chlorine considered unlikely to pose a danger to health. The results are presented in Table 23.1.

Chloroform

The decision on a re-entry guideline for chlorine in periodically treated pools is likely to consider the possible health risks, if any, that chloroform, a by-product of chlorination, may pose. The safety and risk to those who swim in pools treated periodically with gaseous or other forms of chlorine up to 10 ppm is characterized by comparing the anticipated doses to chloroform considered unlikely to pose a danger to health. The results are presented in Tables 23.2, 23.3, and 23.4.

Discussion

All MoE values are conservative inasmuch as they incorporate uncertainty factors in adjusting the observed values to human situations and rely on maximum measure of exposure. In addition, it should be noted that had the EPA approach for estimating the RfD and RfC been applied, all MoE calculations would be approximately one hundred times greater than our values.

Chlorine

Although the MoE for skin contact cannot be estimated because of limited toxicity information, sufficient indirect evidence (including the 4 ppm maximum disinfection residual level goal [MDRLG] for chlorine that is considered safe with an adequate margin of safety by EPA for bathing and/or showering) suggests that skin exposures up to 10 ppm chlorine will cause no harm. Furthermore, the volume of water ingested during swimming (i.e., 0.05 L) is considerably smaller than that on which EPA's 4 ppm MRDLG is based (i.e., 2 L); therefore, ingestion of chlorinated water during swimming is unlikely to pose any health risk. Finally, because chlorine gas once in water at the concentrations used in pools is not apt to volatilize, inhalation exposure is considered to be essentially absent and thus represents no risk of adverse health consequences.

TABLE 23.1. COMPARISON OF UPPER-BOUND EXPOSURE TO CHLORINE BY POOL USERS WITH ADJUSTED HUMAN NOAELS.

	Dermal			*Inhalation*			*Ingestion*		
Scenario	**Exposure (mg/LH_2O)**	**Adjusted Human NOAEL[1] ($mg/L\ H_2O$)**	**MoE[2]**	**Exposure ($\mu g/m^3$)**	**Adjusted Human NOAEL[1] ($\mu g/m^3$)**	**MoE[2]**	**Exposure (µg/kg-d)**	**Adjusted Human NOAEL[1] (µg/k-d)**	**MoE[2]**
Subchronic	1–10	>10	?	0 (est.)	2,433	∞	0.02	140	7,000
Chronic	1–10	>10	?	0 (est.)	2,433	∞	0.02	140	7,000
Acute	1–10	>10	?	0 (est.)	4,866	∞	0.02	9,000	450,000

[1] Uncertainty factors are incorporated in these values

[2] MoE = margin of exposure, which is obtained by dividing the adjusted human NOAEL by the corresponding exposure estimate

TABLE 23.2. COMPARISON OF UPPER-BOUND EXPOSURE TO CHLOROFORM BY OUTDOOR POOL USERS WITH ADJUSTED HUMAN NOAELS.

	Dermal			*Inhalation*			*Ingestion*		
Scenario	**Exposure (µg/p-d)**	**Adjusted Human NOAEL[1] (µg/p-d)**	**MoE[2]**	**Exposure (µg/p-d)**	**Adjusted Human NOAEL[1] (µg/p-d)**	**MoE[2]**	**Exposure (µg/p-d)**	**Adjusted Human NOAEL[1] (µg/p-d)**	**MoE[2]**
Subchronic	0.23	3,600	15,650	10	1,000	100	1.03	1,800	1,800
Chronic	0.23	1,200	52,000	10	600	100	1.03	600	600
Acute	0.23	7,000	30,400	10	3,000	100	1.03	3,500	3,500

[1] Uncertainty factors are incorporated in these values

[2] MoE = margin of exposure, which is obtained by dividing the adjusted human NOAEL by the corresponding exposure estimate

µg/p-d = micrograms of chloroform per person per day

TABLE 23.3. COMPARISON OF UPPER-BOUND EXPOSURE TO CHLOROFORM BY INDOOR POOL USERS WITH ADJUSTED HUMAN NOAELS.

	Dermal			*Inhalation*			*Ingestion*		
Scenario	**Exposure (µg/p-d)**	**Adjusted Human NOAEL[1] (µg/p-d)**	**MoE[2]**	**Exposure (µg/p-d)**	**Adjusted Human NOAEL[1] (µg/p-d)**	**MoE[2]**	**Exposure (µg/p-d)**	**Adjusted Human NOAEL[1] (µg/p-d)**	**MoE[2]**
Subchronic	0.15	3,600	24,000	40.8	1,000	24	1.44	1,800	1,250
Chronic	0.15	1,200	8,000	40.8	600	15	1.44	600	400
Acute	0.15	7,000	46,600	40.8	3,000	75	1.44	3,500	2,430

[1] Uncertainty factors are incorporated in these values

[2] MoE = margin of exposure, which is obtained by dividing the adjusted human NOAEL by the corresponding exposure estimate

µg/p-d = micrograms of chloroform per person per day

Table 23.4. COMPARISON OF UPPER-BOUND CUMULATIVE EXPOSURE TO CHLOROFORM BY POOL USERS WITH THE MOST CONSERVATIVE ADJUSTED HUMAN NOAEL.

Exposure (µg/p-d)				Adjusted Human NOAEL[3]	
Dermal[1]	Inhalation[2]	Ingestion[2]	Total	(µg/p-d)	MoE[4]
0.23	40.8	1.44	42.5	600	14

[1] Based on maximum concentration reported at outdoor pools.

[2] Based on maximum concentration reported at indoor pools.

[3] Adjusted human NOAEL for chronic ingestion of chloroform; includes uncertainty factor of 100.

[4] MoE = margin of exposure which is obtained by dividing the adjusted human NOAEL by the corresponding exposure estimate. Using USEPA's reference dose (RfD) and reference concentration (RfC) method, the MoE would be 1,400.

µg/p-d = micrograms of chloroform per person per day

Chloroform

The evaluation of risks and safety of chloroform is somewhat more complex than that for chlorine for several reasons. Unlike chlorine, chloroform is a systemic toxicant; therefore, the doses by various routes of exposure are summed to reflect full exposure. The systemic doses of chloroform were estimated by individual routes of exposure and then summed to produce cumulative systemic doses. The highest doses were compared to the most conservative NOAEL for chloroform (chronic ingestion). The resulting MoE was 14, which provides an additional margin of safety to that incorporated in the adjusted human NOAEL, a value that EPA had recently recommended as the basis for an MCLG of 300 ppb for chloroform in drinking water. Had the USEPA approach for estimating the RfD and RfC been applied, the MoE for each value would be approximately 100 times greater than our value (i.e., 1,400).

Conclusions

The investigation demonstrates that the levels of chlorine and chloroform to which swimmers are exposed in a pool having a concentration of 10 ppm chlorine, regardless of the means of chlorination, provide a reasonable certainty of no harm to the health of swimmers. These findings strongly support the reliance on 10

ppm chlorine as a guideline for reentry of swimmers into chlorine-treated pools. Adopting 10 ppm chlorine as the reentry value will ensure continued public health protection without contributing an undue health risk to swimmers.

Thought Questions

1. What is the difference between hazard and risk as it applies to this case history?
2. How was the uncertainty associated with safe exposure levels addressed in this case history?
3. How can risk assessment techniques be used to develop public health goals?

CHAPTER TWENTY-FOUR

U-SHAPED DOSE-RESPONSE CURVE FOR RISK ASSESSMENT OF ESSENTIAL TRACE ELEMENTS

Copper as a Case Study

Bonnie Ransom Stern

Learning Objectives

Students who complete this chapter will be able to

1. Understand what an essential trace element (ETE) is and how ETE risk assessment differs from risk assessment for nonessential elements and chemicals
2. Know what an *acceptable range of oral intake* (AROI) is and how to calculate one for copper
3. Understand the factors that can affect the AROI for copper (and other ETEs) and associated uncertainties

Essential trace elements (ETEs) pose unique challenges when establishing regulatory guidelines because too little as well as too much intake can lead to adverse health consequences. ETEs are inorganic micronutrients with specific biological functions that are indispensable for human health at all life stages. They differ from other chemical compounds in that (1) appropriate intakes are required to maintain health and (2) organisms have evolved nutrient-specific homeostatic mechanisms to regulate absorption, excretion, distribution, and storage in order to adapt to varying intake levels and ensure a sufficient supply for performance of essential functions. Thus, both deficiency and excess can cause adverse health effects; the dose-response curve is approximately U-shaped and its slope is likely

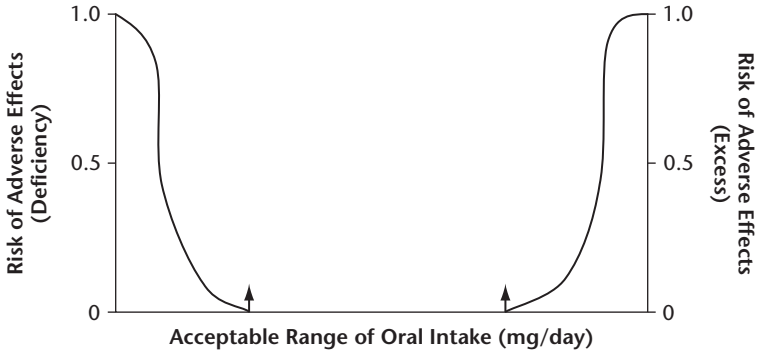
to be zero within the homeostatic boundaries. In contrast, toxic nonessential elements and chemicals are metabolized very differently from ETEs, usually by nonspecific metabolic pathways (e.g., glutathione conjugation), and decreasing the dose never induces adverse health responses.

General Approach

The major challenge of ETE risk assessment is to determine an *acceptable range of oral intake* (AROI), using available scientific data, that meets the nutritional requirements of healthy populations in order to prevent deficiency while simultaneously avoiding excessive intakes that can be toxic (International Programme on Chemical Safety, 2002). Dose-response assessment involves the identification of upper and lower dose boundaries for essentiality. The AROI is considered to be the "trough" of the U-shaped dose-response curve, a range in which indicators of toxicity or deficiency are not observed and any noted changes are assumed to be adaptive rather than adverse. The points of inflection on both sides of the U-shaped dose response are those at which deficiency and toxicity first begin to be observed. Adverse health symptoms subsequently increase with decreasing intake (deficiency) and also increase with increasing intake (excess).

To conduct an ETE risk assessment, all data on toxicity and deficiency should be critically evaluated, homeostatic mechanisms identified, bioavailability and nutrient interactions considered if known, and end points used to define the lower (deficiency) and upper (toxicity) bounds of the AROI should be similar in terms of functional significance (International Programme on Chemical Safety, 2002).

FIGURE 24.1. U-SHAPED DOSE-RESPONSE CURVE.



Subclinical changes indicating organ or enzyme impairment are typically selected as the critical effects (the earliest measurable adverse effects or its precursors in a cascade of increasingly severe effects with increasing or decreasing dose) for establishing regulatory values or reference intakes for public health protection. Therefore, it is important to identify biomarkers of effect that are sensitive and specific to nutrient deficiency or excess, demonstrate a dose-response, and are predictive of adverse clinical outcomes (Stern and others, forthcoming).

Essentiality and Toxicity of Copper

Copper (Cu) is a naturally-occurring essential metal with numerous commercial uses and is found in all environmental media. It is a critical component of many metal-containing enzymes whose biological functions involve reduction-oxidation (redox) reactions in which copper participates by cycling between Cu1+ and Cu2+ oxidation states. Copper is also a requisite structural component of many large proteins. Copper deficiency impairs enzymatic formation and activities and can lead to severe structural or functional abnormalities, especially during early growth and development (Institute of Medicine, 2000). However, Cu1+ is a free radical, seeking an electron donor; in an unbound state, it has the capacity to bind to nearby cellular constituents and disrupt cell function, resulting in oxidative damage. To prevent this from occurring, Cu transport in the body is a tightly-regulated process involving numerous Cu-binding proteins called transporters and chaperones. Under conditions of excess, protein-binding capacities may be exceeded and free Cu radicals produced; this is the mechanistic basis for Cu toxicity. Thus, the properties of copper that make it essential to life can also lead to toxicity if intake is high.

Essential copper-containing enzymes include (1) ceruloplasmin (Cp—the major blood protein involved in copper transport from the liver to other tissues, with an important role in iron metabolism and hemoglobin synthesis); (2) superoxide dismutase (SOD—an anti-oxidant enzyme also containing zinc and protecting against oxidative damage); (3) cytochrome-c-oxidase (essential for electron transport and energy production in cells); (4) lysyl oxidase (essential for forming and maintaining the structural integrity of collagen and bone); and (5) enzymes involved in synthesis and maturation of bioactive hormones including neurotransmitters (International Programme on Chemical Safety, 1998).

Hazard Characterization Deficiency

As with most ETEs, deficiency is more of a public health concern than excess. Although severe copper deficiency is rare in developed countries, it occurs in premature infants, infants and children suffering from malnutrition, and individuals

undergoing dialysis, on total intravenous nutrition lacking adequate Cu supplementation, with chronic or recurrent digestive diseases, or ingesting megadoses of zinc and iron without appropriate Cu intake (these ETEs can inhibit Cu absorption). Clinical outcomes are similar to those observed in severely Cu-deficient animals and include (1) anemia unaffected by iron levels but readily reversible with Cu supplementation; (2) bone abnormalities mimicking changes observed in scurvy, osteoporosis, bone fractures, and deformed bone growth; (3) significantly decreased white blood cell counts (neutropenia); (4) increased incidence of infections; and (5) impaired growth and hair hypopigmentation in infants and children. Severe Cu deficiency in pregnant animals significantly reduces fertility and induces teratogenicity (Danks, 1988; International Programme on Chemical Safety, 1998).

Unrecognized or marginal copper deficiency appears to be widespread in the general population. Animal studies show that chronic intake of suboptimal dietary copper is likely to contribute to a range of chronic degenerative diseases including coronary and cardiovascular disorders, altered lipid/carbohydrate metabolism, osteoporosis/arthritis, neurological disease, and disorders resulting from a chronically-depressed immune system (Strain, 1994). Marginal Cu deficiency in utero and/or during infancy and childhood appears to have long-lasting irreversible consequences, leading to increased risk of development of degenerative diseases in adulthood (Strain, 1994). These concerns also apply to other ETEs.

Hazard Characterization Excess

Few cases of Cu toxicity due to excessive intake have been reported in individuals without known genetic susceptibilities to Cu overload. The liver is the primary organ of Cu toxicity, followed by the nervous system. Hepatitis, cirrhosis, and acute liver failure may result from long-term high-dose Cu intake; neurological effects may include movement disorders and behavioral abnormalities (International Programme on Chemical Safety, 1998). Little evidence indicates that chronic human exposure results in adverse effects in other systems. Although the data are inadequate to assess the fertility or developmental effects of copper excess in humans, animal studies do not demonstrate either reproductive or developmental toxicity. Available data do not demonstrate that copper is causally associated with the development of cancer. Ingestion of elevated copper in drinking water may produce immediate gastrointestinal symptoms (nausea, vomiting, cramps) in some individuals, which resolve following cessation of drinking or with adaptation over time (International Programme on Chemical Safety, 1998).

Homeostasis, Bioavailability, and Nutrient Interactions

Numerous studies have demonstrated that absorption and biliary excretion play major roles in Cu homeostasis. Under conditions of low Cu levels, absorption is upregulated and excretion downregulated; the reverse occurs when Cu levels are high. Excess copper is stored in the liver and released upon demand or excreted mainly in the feces. Copper homeostasis and bioavailability are affected by interactions among copper, zinc, iron, and molybdenum. The type and level of dietary protein, carbohydrates, and fiber, as well as other nutrients, also influences the absorption and utilization of copper.

Subclinical Biomarkers of Deficiency and Excess

Low levels of copper in the liver and blood, accompanied by decreased Cp and low fecal copper, are indicative of deficient Cu status. Other biomarkers include decreased levels or activities of Cu-containing enzymes such as red blood cell SOD, lysyl oxidase, and reduced white blood cell counts (leukocytes, platelets) involved in immune defense. Concerns about the use of biomarkers for assessment of Cu-deficient status relate to their sensitivity and specificity. Are these biomarkers sensitive enough to identify a large proportion of copper-deficient individuals? And are they specific to copper deficiency or can they be altered by the status of other nutrients? Because of nutrient interactions and the effects of multiple nutrients on a single endpoint, individual biomarkers may not be sufficient to correctly identify most Cu-deficient individuals with a high degree of certainty and a constellation of biomarkers may be needed for this purpose. Similar considerations apply to biomarkers of Cu excess. Serum biomarkers of Cu excess include elevated levels of copper, Cp, and liver enzymes. However, these biomarkers can also increase when health is impaired due to infection, inflammation, cancer, and other disorders unrelated to Cu status; therefore, they lack specificity. Elevated liver Cu content is the most reliable marker of Cu excess.

Dose-Response Assessment

In general, human data are preferred over animal data because of uncertainties about whether animal models are suitable for this purpose. For copper, few animal toxicity studies have been published. Although numerous animal deficiency studies exist, most have tested only one deficient dose and are not amenable to dose-response evaluation. For a comprehensive dose-response assessment, combining results from many studies using complex statistical analysis (e.g., categorical

regression) of multiple endpoints of differing severity at different doses would be necessary (Stern and others, forthcoming). In the absence of this type of analysis, dose-response assessment is inferred from available data on no-effects and effects levels in human studies, taking into account what is known about homeostasis and causality (International Programme on Chemical Safety, 2002).

Deficiency

In population studies, the median intake for adults ranges from 1–2 mg Cu/day; adults typically consume a diet of 1–5 mg Cu/day without apparent adverse consequences (Institute of Medicine, 2000). At Cu intake levels of < 1 mg/day (0.4–0.9 mg/day), observed human effects include decreased plasma Cu and Cp levels, reduced SOD activity, increases in urinary biomarkers indicative of bone loss, altered plasma cholesterol profiles, impaired glucose clearance, abnormal cardiac function, and changes in white blood cells indicative of immune stress (Stern and others, forthcoming). In patients on intravenous nutrition low in copper (0.3–0.4 mg day), clinical signs of severe deficiency were observed (Higuchi, Higashi, Nakamura, and Matsuda, 1988). The weight-of-evidence from these studies suggests that 1 mg/day is likely to be sufficient for the general adult population, and is a reasonable estimate of the lower bound of the AROI.

Excess

Limited human data are available on the effects of copper at higher doses. No adverse gastrointestinal or liver effects were reported in adults consuming water containing about 8.5 mg/L of copper for over 20 years beginning in childhood (Scheinberg and Sternlieb, 1994). Pratt and others (1985) reported no evidence of liver damage or gastrointestinal effects in a well-controlled study with human volunteers given 10 mg/day of Cu gluconate for 12 weeks. In one case study, acute liver failure was reported in a young adult male with no known genetic defects in Cu homeostasis who consumed 30 mg Cu/day from supplements for 2 years, followed by 60 mg/day for an additional unspecified time period (O'Donohue and others, 1997). Other reports of Cu excess are limited to accidental or suicidal ingestion of very high doses.

The no-observable-adverse-effects level (NOAEL) for copper is 10 mg/day. An uncertainty factor of 1 is used because (1) the principal study was conducted with humans; (2) the human database is large and of good quality; (3) causality is understood; and (3) animal data support the liver as the critical organ of toxicity (Institute of Medicine, 2000). Based on weight-of-evidence, 10 mg/day is con-

sidered to be a reasonable estimate of the upper bound of the adult AROI. Thus, the AROI for adults in the general population ranges from 1–10 mg/day.

Assumptions and Uncertainties

The case study of copper demonstrates several points with regard to ETE risk assessment. A weight-of-evidence approach is generally used, which considers all available data in humans as well as human and animal data on homeostasis and mechanisms of toxicity and deficiency. Uncertainty factors are applied with caution because of concern about setting reference values so low that they will induce deficiency. Nonetheless, several uncertainties remain. For copper, the amount required for different life stages and potentially sensitive subpopulations is not well characterized. Most studies quantifying dose-response are of short-term duration and there is some concern that long-term exposure at the upper bound may result in increased liver Cu retention, eventually resulting in toxicity. A similar concern exists with the lower bound; chronic intakes at this level may lead to adverse health consequences associated with deficiency in some groups. The nature and extent of interactions between copper and other nutrients is not well known; in the absence of this information, intake levels may not be a reliable indicator of Cu sufficiency or excess. Finally, Cu biomarkers of mild-to-moderate deficiency and toxicity are not well established. Many of these concerns are common to most ETEs. Research in these areas is ongoing and poses exciting challenges to nutritionists, toxicologists, and other public health specialists.

Thought Questions

1. Why and how do ETE risk assessments differ from conventional risk assessments? What are some other ETEs of concern to environmental health scientists?
2. Why is consideration of homeostatic mechanisms of regulation important in ETE risk assessment?
3. Why would ETE requirements vary according to life-stage, health status, and metabolic and genetic susceptibilities?
4. How would you view ETE risk assessment in the context of the precautionary principle? On a population level, would you be more concerned with deficiency or excess? Why?
5. Given that low intake levels of ETEs can cause serious health effects and large population impacts, do you think that conventional risk assessment policies and regulatory frameworks should be modified for essential elements? Should ETEs be treated differently than conventional chemicals? Would a risk-benefit

analysis for individual ETEs be appropriate? *Hint:* Think about the risk-benefit of adding fluoride to drinking water and iodine to salt.

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CHAPTER TWENTY-FIVE

ECOSYSTEM RISK ASSESSMENT

The Neuse River Estuary, North Carolina

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Learning Objectives

Students who complete this chapter will be able to

1. Appreciate the role of models in ecological risk assessment
2. Recognize the high intrinsic uncertainties in making ecological forecasts
3. Understand the distinction between science and policy in environmental decision making
4. Become familiar the concept of "adaptive management"

Ecosystem risk assessment involves evaluating the current state of an ecosystem, deciding what state the system should be in, and forecasting its future state under alternative management options so that decision makers can choose the management actions that are most likely to attain the desired ecosystem state.

Decision Making Under Uncertainty

Assessing the state of an ecosystem and forecasting its future are largely scientific endeavors. They require collecting and synthesizing data to better understand and quantify the processes that govern the behavior of the system. Determining the desired state of the ecosystem is a policy decision in which the needs and values

of society must be considered. Often there are difficult tradeoffs that have to be simultaneously evaluated. Typically, the scientific assessment and forecasts will contain a high degree of uncertainty, which occurs because our knowledge of ecosystem behavior is always incomplete. By identifying the biggest sources of uncertainty we can monitor and design studies to reduce them. However, additional research takes time and no amount of additional study will completely eliminate uncertainty. Thus, it is extremely important for scientists to provide quantified estimates of the uncertainty that accompanies their assessments and forecasts.

Quantifying uncertainty serves several purposes. It helps to identify the most important sources of uncertainty so that additional research can be appropriately targeted to reduce these uncertainties. It also provides decision makers with additional information to allow them to appropriately weigh the likely consequences of their decisions.

Probability is the language in which uncertainty is communicated. Most uncertainties can be expressed as relative probabilities of alternative behaviors or outcomes. There are several interpretations of what probability means. The most widely appreciated is *long-term relative frequency of a particular event.* Coin flipping is a common example of this probability interpretation. The probability of flipping a coin and obtaining heads is approximately 50 percent—meaning that if a coin is flipped enough times, approximately 50 percent of those flips will result in the coin landing heads-side up. The other interpretation of probability is *degree of belief.* If I pull a coin from my pocket and ask the probability of heads if I flip the coin it is likely that the response will be "approximately 50 percent." In this instance there is no long-term relative frequency involved; in fact, I haven't even flipped the coin once. The response "50 percent" represents the respondent's degree of belief that the coin will land heads-side up. If the respondent were more certain of a heads result, he or she might indicate 90 or 95 percent. Thus, the degree-of-belief notion of probability is a quantification of the confidence an individual has in the occurrence of a particular result.

These two notions of probability are not mutually exclusive; in fact they can be reconciled using Bayes theorem. Bayes theorem:

$$\pi(\theta|y) = \frac{\pi(\theta) f(y|\theta)}{\int_{\theta} \pi(\theta) f(y|\theta) d\theta} \tag{25.1}$$

where $\pi(\theta|y)$ is the posterior probability of θ (the probability of an event, θ, after observing new data, y), $\pi(\theta)$ is the prior probability of θ (the probability of θ before observing y), and $f(y|\theta)$ is the likelihood function, which incorporates the statistical relationships as well as the mechanistic or process relationships between y and θ. In this representation the integral in the denominator on the right side of the

equation is just a scaling constant that makes the total probability of all events equal to one.

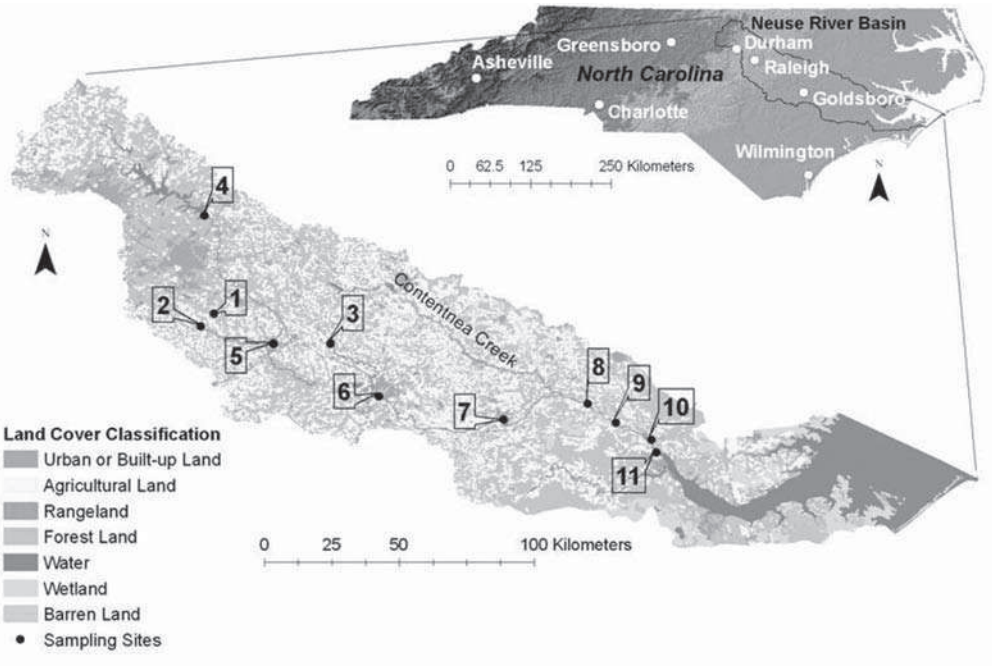
The interpretation of Bayes theorem is that our prior beliefs (those we held before the experiment), $\pi(\theta)$, for example, the probability of heads, are combined with new information, $f(y|\theta)$, such as an experiment in which a coin is flipped one hundred times, to obtain our posterior beliefs, $\pi(\theta|y)$, our beliefs once we have observed the new information provided by the experiment. If, for example, before flipping a coin we believed that the probability of heads was 50 percent, and in our experiment of one hundred flips we obtained fifty heads and fifty tails our belief would be unchanged; posterior belief would be the same as the prior belief. However, if our experiment resulted in ninety-five heads and five tails, then we would likely conclude that there was something unusual about this particular coin, and our posterior belief in the probability of heads would be closer to 95 percent than 50 percent. Our prior belief of 50 percent was probably based on previous experience and the general knowledge that when coins are flipped they produce heads approximately 50 percent of the time, whereas our posterior belief is based on an accumulation of evidence about the particular coin with which we are conducting an experiment. For more detailed information regarding the use and interpretation of Bayes theorem we suggest consulting one of the many texts available on the topic, for example, Winkler (2003).

An appreciation of Bayes theorem is very useful for ecosystem-scale risk assessment because uncertainty can be a dominant feature of our understanding of ecosystem behavior. Gaining a deep understanding of ecosystem behavior, including the processes that occur, the rates at which they proceed, and the feedbacks that may reinforce certain processes, is challenging, in part because it is difficult to do meaningful experiments at the ecosystem scale. Typically, we have to rely on information from small-scale experiments, other similar ecosystems, or observational data in which many underlying factors may be confounded, making it difficult to discern the influence of individual factors. Thus, expressing our knowledge of ecosystem behavior probabilistically is appropriate for providing assessments and forecasts. In a manner analogous to the coin-flipping example, Bayes theorem provides a formal and rigorous means for incorporating our current knowledge of the ecosystem based on existing information and its uncertainty and for updating this knowledge as new data become available.

The Neuse River Estuary

The Neuse River Estuary is located in the central portion of coastal North Carolina (see Figure 25.1). The estuary is long and narrow and relatively shallow with a depth of approximately 4 to 5 m. The Neuse River originates northwest of

FIGURE 25.1. MAP OF NEUSE RIVER ESTUARY.



North Carolina's capital, Raleigh, and flows approximately 320 km through the central piedmont to the coastal plain with a watershed area of 16,108 km^2. Land cover in the watershed includes agriculture (~35 percent) and forests (~34 percent), and the remainder is a mix of developed areas, wetlands, and open water. In 1983 the upper 35 km of the river was impounded to create Falls Lake, a multipurpose reservoir providing drinking water and recreational opportunities to residents and visitors in the Raleigh area.

In the 1980s a series of blue-green (cyanobacteria) algal blooms near the mouth of the river led to concerns about the possible impacts of nutrient inputs (nitrogen and phosphorus) to the estuary. These concerns resulted in a phosphate detergent ban that became effective in 1988. As a result of this ban there was a rapid, pronounced decrease in phosphorus concentrations throughout the watershed (Qian, Borsuk, and Stow, 2000).

However, beginning in the early 1990s the estuary experienced a series of fishkills prompting renewed public concern about the possible effects of pollutants

from the watershed. Sometimes the fishkills were quite large, with upwards of several hundred thousand dead fish appearing on the surface of the water at a time. The larger fishkills usually consisted predominantly of Atlantic menhaden (*Brevoortia tyrannus*), a species native to the east coast of the United States.

At about the same time these fishkills were occurring researchers discovered a new species of microorganism present in the estuary, which they claimed was responsible for many of the fishkills (Burkholder, Glasgow, and Hobbs, 1995). The microorganism, a dinoflagellate they named *Pfiesteria piscicida*, was reported to have a complex life history with many distinct life stages. This organism was alleged to produce a powerful toxin that was responsible for killing fish and was also capable of harming humans who might encounter it. The notoriety of *Pfiesteria* was widely reported, with the popular media labeling the organism the "cell from hell." By the late 1990s the *Pfiesteria* had been discovered in many locations along the Atlantic coast resulting in a considerable outcry from the affected public.

However, some members of the research community were not convinced that *Pfiesteria* was responsible for fishkills in the Neuse Estuary. Many researchers held a more conventional view, believing that these fishkillls were occurring primarily as a result of oxygen depletion in the bottom of the estuary; in other words, the fish were dying from suffocation (Paerl, Pinckney, Fear, and Peierls, 1998). Hypoxia (dissolved oxygen <2 mg/L) and anoxia (0 mg/L dissolved oxygen) are conditions of low dissolved oxygen that have been well-documented in freshwater lakes and coastal aquatic systems. These low-oxygen conditions occur when the oxygen depletion rate in the bottom of the water column exceeds the supply rate from the surface for an extended period of time. In coastal areas this imbalance typically arises from density-induced stratification. During stratification, lighter, more buoyant freshwater and denser, heavier ocean water form nearly distinct vertical layers, with freshwater at the surface and saltwater at the bottom. The formation of these two layers inhibits mixing from the surface to the bottom and thus cuts off the oxygen supply to the deeper water. If there are processes occurring in the deep water that consume oxygen, for example, microbial respiration, then oxygen levels can quickly become too low for many fish species to survive. Stratification is a natural process, and bottom-water hypoxia can occur naturally, although the incidence of hypoxia is believed to be increasing due to higher inputs of pollutants that can cause oxygen depletion rates in the bottom water to rise.

The disagreement over the proximal cause of fishkills in the Neuse Estuary, *Pfiesteria* versus low dissolved oxygen, became spirited and at times acrimonious (Burkholder, Mallin, and Glasgow, 1999; Paerl, Pinckney, Fear, and Peierls, 1999). The debate was not confined just to scientists and researchers; it entered the public arena as well, with regular coverage in both the local and national media. But while the immediate cause of fishkills was being contested, there was a general

consensus among scientists that the root cause of the problem was a rapid and recent increase in nutrient inputs to the estuary, particularly nitrogen.

In coastal waters nitrogen is typically regarded as the nutrient most responsible for the increased growth of algae, a process called *eutrophication*. Under high nitrogen conditions algae proliferate in the surface water where sunlight supplies energy for growth. When the algae die they sink to the bottom, where they are eaten by bacteria, a process that consumes oxygen. If the estuary is stratified, the decomposing algae on the bottom can cause the probability of hypoxia or anoxia to become very high. Alternatively, it was argued, the primary cause of fishkills was not nitrogen-induced eutrophication but rather the direct stimulation of *Pfiesteria* and other toxic microorganisms by increased nutrient inputs.

The argument for recent, large increases in nutrient inputs, particularly nitrogen, was indeed plausible. Economically, the Raleigh-Durham area in the upper watershed was doing very well, experiencing substantial population increase and rapid development, resulting in increased nutrient discharges from municipal sewage treatment plants. At the same time, concentrated animal farming was experiencing rapid growth in the watershed, and there were reports of storm water runoff and manure from these operations entering local waterways and eventually flowing into the Neuse River. Thus, although there was considerable disagreement regarding the direct cause of the fishkills, the way to fix the problem was generally agreed to be the same: reduce nitrogen inputs to the river and the problem would diminish.

Reducing nitrogen inputs, however, is expensive. Municipal sewage treatment plants need to be upgraded, requiring cities to spend more for sewage treatment. Concentrated animal feeding operations would also be required to change the way they operated, costing them additional money to produce their products. In addition, urban, suburban, and agricultural operations would all have to manage their storm water runoff in a manner that would reduce the flow of nitrogen into streams feeding into the Neuse River. Therefore, to avoid excessive, and possibly unnecessary, costs to the stakeholders in the watershed, it was necessary to predict how much the nitrogen inputs would have to be lowered to reduce the frequency of the fishkills.

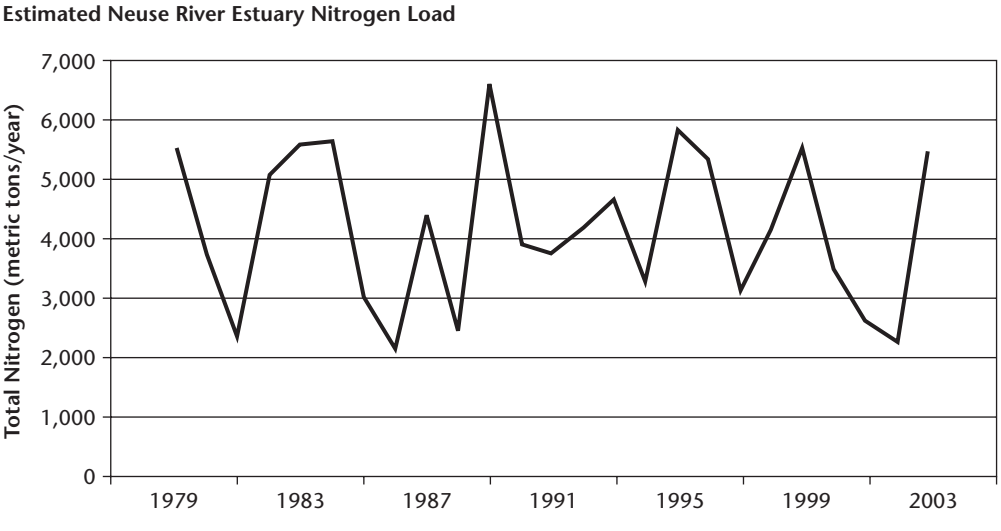
In addition to the direct costs associated with nitrogen reduction, reducing nitrogen inputs too much also carries ecological risks. Algae form the base of the food web in the estuary; lowering nitrogen too much could cause algal production to become very low, resulting in lower food availability for zooplankton, benthic invertebrates (such as shrimp), and fishes. Therefore, even if nitrogen reduction were inexpensive and costs to stakeholders were not a concern, we still would not want to lower nitrogen inputs too much for fear of lowering the overall productivity of the estuary. Lowering productivity too much could adversely

affect another stakeholder group in the watershed, those whose livelihood was dependent on the seafood industry.

Thus, there are conflicting constraints influencing the decision to manage nitrogen inputs to the river and estuary; maintaining high nitrogen levels promotes a productive fishery, while nitrogen levels that are too high may increase the risk of fishkills. Typically, when conflicting constraints exist there is an optimum, in this case a nitrogen level that maintains a productive fishery without causing the risk of fishkills to increase.

To further complicate the situation in the Neuse, researchers studying the available long-term monitoring data from the river and estuary arrived at a surprising conclusion: there was no evidence of a recent nitrogen increase either entering the estuary or within the estuary (see Figure 25.2) (Qian, Borsuk, and Stow, 2000). Many simultaneous changes were occurring in the watershed, some with the potential for increasing nitrogen inputs to the estuary, others that would likely cause nitrogen inputs to drop (Stow, Borsuk, and Stanley, 2001). In particular, the completion of the dam to form Falls Lake in the upper watershed had caused nitrogen concentrations to drop quickly in the mid-1980s. This decline was estimated to approximately offset the increased nitrogen discharges that occurred from the cities of Raleigh and Durham in the 1990s. In addition, although the amount of nitrogen being discharged from the large municipal sewage treatment

FIGURE 25.2. ESTIMATED NEUSE RIVER ESTUARY NITROGEN LOAD.



plants had increased, the form of the nitrogen had changed. With improvements in sewage treatment occurring in the 1980s and 1990s the nitrogen being released changed from ammonia, a reduced form, to nitrate, an oxidized form. Under the right conditions nitrate can be converted to nitrogen gas, which volatilizes from the river and enters the atmosphere. Thus, it was concluded that some of the additional nitrogen that was being discharged into the river was lost to the atmosphere before reaching the estuary. The net result of many simultaneous changes was that the amount of nitrogen in the estuary had not shown any recent, discernible changes that might account for the problems the estuary was experiencing.

The absence of a discernible nitrogen increase in the estuary illustrates that, despite general agreement in the scientific community that recent nitrogen increases were causing the problems in the estuary, the past behavior of the system was not well-understood. Although nitrogen increases were being observed in similar coastal ecosystems, circumstances specific to the Neuse caused nitrogen levels to remain approximately constant. The *Pfiesteria* versus dissolved oxygen debate indicates a disagreement among scientists regarding the current behavior of the ecosystem, with opposing schools of thought regarding the proximal cause of the ongoing fishkills. And, although there was apparent misunderstanding of the past behavior and disagreement about the current behavior, the challenge for ecological risk assessment was to predict how the estuary would respond in the future under conditions for which no data were available. Thus, it is reasonable to believe that predictions of the future will be uncertain, reflecting our partial, or even mistaken, understanding of the past and current ecosystem behavior.

The situation in the Neuse is fairly typical of risk assessment situations at the ecosystem scale. Usually there are many simultaneous alterations occurring in the ecosystem, and it is only their net effect that has been detected. Although only a few dominant changes may actually affect ecosystem behavior, disentangling the effects and relative importance of the individual changes can be difficult, leading to a scenario of "dueling scientists"—each espousing different hypotheses—sometimes resulting in a very confused public, and decision makers unsure of whom to believe. There are also typically conflicting constraints, resulting because stakeholders differentially value different features or services provided by the ecosystem. The simultaneous consideration of the various stakeholder concerns often leads to the search for an optimal strategy, one that balances the costs and benefits of the various management alternatives. But evaluating that optimal strategy, *quantifying* the optimal nitrogen level for the Neuse in this example, is a difficult problem.

The ideal way to quantify the optimal nitrogen level for the Neuse would be to do a series of experiments adding nitrogen to the estuary at a range of levels and monitoring the results. But ecosystem-scale experimentation of this sort, while

extremely revealing, is usually impractical (Carpenter and others, 1995). The experimental manipulations required are too large, and the number of people affected if such experimentation could be done is too great.

Another way to learn how the Neuse might respond to differing nitrogen levels is to experiment on a smaller scale, either in the laboratory (*microcosms*) or in small enclosures in the ecosystem (*mesocosms*). In fact, microcosm and mesocosm experiments are often used to learn about some aspects of ecosystem behavior, but extrapolating the results from small-scale experiments to whole ecosystems is tenuous. Many processes that occur in ecosystems cannot be meaningfully captured in small enclosures. In addition, small enclosures often introduce artifacts—that is they may result in behavior that is highly unlikely in the real ecosystem. Thus, we are usually limited in our ability to conduct experiments to estimate optimal ecosystem management strategies.

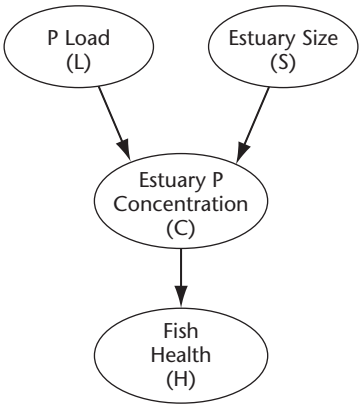
A third alternative for estimating the effect of managing nitrogen inputs to the estuary is to develop a mathematical model that captures our best understanding of ecosystem behavior. Models are useful for forecasting future ecosystem behavior under various management alternatives; they also synthesize our current knowledge of ecosystem behavior and thus help identify our biggest knowledge gaps and decision-sensitive uncertainties. In addition to being tools for prediction, models can be regarded as devices for doing numerical experiments when real experiments are infeasible.

But just like microcosm and mesocosm experiments, models have inherent limitations. Models are approximations of system behavior. While we know a lot about the overall processes that occur in ecosystems, *quantifying* these processes, that is, estimating the rates at which they occur in a given ecosystem, can be challenging. And as previously indicated, some important aspects of processes occurring in the Neuse River and Estuary were not well-understood by scientists and researchers working in the watershed.

Because of the high degree of uncertainty surrounding the specific behavior and likely responses of the estuary to reduced levels of nitrogen, it was appropriate to select a modeling framework that would readily accommodate uncertainty and would also provide a mechanism for assimilating new information or data from the ecosystem as it became available. Bayes theorem provides such a framework, so the modeling approach chosen to forecast the response of the estuary to nitrogen management was a Bayesian probability network or *Bayes net*.

A Bayes net begins with a graphic depiction of the associations among the most important variables in the ecosystem. The graph represents our knowledge of the ecosystem's cause-and-effect relationships. The nodes (ovals) of the graph indicate ecosystem processes and the arrows depict causal relationships or dependencies (see Figure 25.3).

FIGURE 25.3. GRAPHICAL REPRESENTATION OF THE NEUSE RIVER ESTUARY BAYESIAN NETWORK.



The ellipses represent measurable system variables and the rounded rectangles indicate underlying sub-models. The arrows depict causal relationships among the variables and sub-models.

Each dependency indicated by an arrow represents a conditional probability distribution that describes the relative likelihood of each value of the down-arrow node, conditional on the values of the nodes that are up-arrow. For example, the probability of fish health is conditional on the estuary's pollutant concentration. If the pollutant concentration is low, the probability that fish are in good health is high; conversely, if the pollutant concentration is high, the probability that fish are in good health is low. Similarly, the estuarine pollutant concentration is conditional on both the pollutant load and the estuary size. This graphic model can then be easily translated into simple relationships that follow basic rules of probability. Figure 25.3 implies that the joint distribution of the variables *L, S, C, and H* can be factored as:

$$P(L,S,C,H) = P(H|C)P(C|L,S)P(L)P(S) \qquad (25.2)$$

where *P(L,S,C,H)* is the joint probability of *L,S,C,* and *H, P(H|C)* is the probability of *H* given specific values of *C, P(C|L,S)* is the probability of *C* given specific values of *L* and *S, P(L)* is the probability of *L,* and *P(S)* is the probability of *S.* The kinds of probabilistic relationships described by this equation are well-understood and explained in any text on probability and statistics (e.g., Degroot, 1986). They provide a basis for predicting changes in the down-arrow nodes and the associ-

ated uncertainty in those changes as a result of changes in the up-arrow nodes that may occur as a result of management actions.

The Bayes net framework is extremely flexible; probabilistic information for the processes at each node can be derived in several ways:

- From detailed, process-based (mechanistic) models
- From data-based (empirical) models
- From expert elicitation (Morgan and Henrion, 1990)
- From any combination of the three previous sources

Mechanistic models are typically based on theory and use differential equations to describe ecosystem behavior at relatively fine scales of spatial and temporal detail. Empirical models are usually more aggregated in time and space and use observed data from the ecosystem to estimate overall ecosystem behavior. Expert elicitation is a method that has been used in economic and social sciences but not widely employed in the natural sciences. It is a structured means of querying experts to extract their knowledge about a topic and expressing this knowledge probabilistically. A particular utility of the Bayes net approach is that it can incorporate information from all of these sources. This is especially useful for developing ecosystem models because it is often the case that different kinds of information, representing different scales of resolution, will be available for any given system.

Model Development

The first task of our modeling study in the Neuse Estuary was to identify measurable ecosystem variables that were meaningful to stakeholders and public officials (Borsuk, Higdon, Stow, and Reckhow, 2001). *Stakeholders* are people who live in or near the watershed or have some direct interest in the services provided by the ecosystem. The first step was to discover the ecosystem services or attributes that would be used by the public and decision makers to evaluate the success of the nitrogen management program. While this may seem like an obvious starting point for the modeling process, it is often overlooked in the rush to gather and analyze data or write computer simulation programs (Reckhow, 1994). Inadequate attention to this step may lead to an incomplete analysis or an analysis of the wrong problem with respect to important policy interests or the interests of the affected community.

We identified potential stakeholders from various sources including a list of permitted wastewater dischargers, literature searches, attendance records from prior

Neuse-related meetings, and word of mouth. We also solicited names from extension and rural-development agencies to contact segments of the public who might otherwise be excluded. We sent packets of introductory materials to those individuals identified in our search and invited their input through phone interviews, surveys, and public meetings. We held four public meetings at locations throughout the watershed and conducted in-depth interviews with participants selected to span a range of interests and perspectives, including: the owner of a seafood restaurant, an elderly lifelong resident of a small coastal town, a fishing guide, a corporate attorney, and a group of summer-camp employees.

The results of our interviews and surveys (Exhibit 25.1) showed that the public cares about attributes of water quality and ecosystem services beyond those generally predicted by traditional water-quality simulation models. These included water-quality measures such as water clarity, taste, lack of odor, levels of chlorophyll *a* and dissolved oxygen, and the presence or absence of algal toxins. Important biological quality indicators included algae levels and the presence of excessive, submerged aquatic vegetation, as well as abundance, diversity, and health of fish and shellfish. Concerns regarding human health included the presence of fecal coliform bacteria and toxic microorganisms such as *Pfiesteria piscicida*.

EXHIBIT 25.1. ECOSYSTEM ATTRIBUTES OF CONCERN TO NEUSE RIVER STAKEHOLDERS.

Water quality

- Oxygen levels
- Chlorophyll *a* levels
- Taste
- Odor
- Water clarity
- Sandy bottom
- Algal toxins

Biological quality

- Algal blooms
- Fish and shellfish abundance and health
- Species diversity
- Human-induced fishkills
- Submerged aquatic vegetation

Human health

- Fecal coliform
- Toxic microorganisms

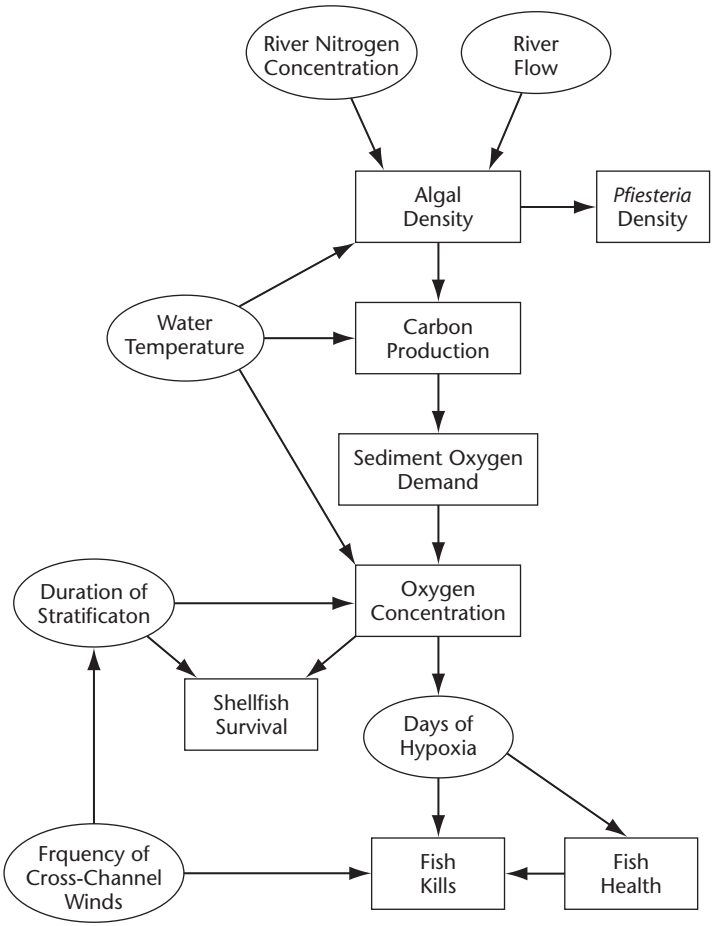
Development of the causal diagram linking nitrogen inputs to attributes and ecosystem services identified by the stakeholders began with a comprehensive survey of the relevant scientific literature. With the primary attributes of interest defined by the stakeholder process, it was natural to begin by identifying the nodes immediately preceding them in the causal chain, then nodes preceding them, and so on, back to the model inputs, including nitrogen loading. This process was successful in producing a network linking causes and effects that represented the current published opinion of scientists studying the Neuse, but the exact quantitative nature of the relationships was not clear. Therefore, the scientists themselves were consulted for additional information.

Using our literature-based graphic model as a starting point for discussion, we held a series of meetings with researchers to explain the Bayesian network approach and to get their input on the causal diagram. Almost invariably they were intrigued by this alternative way of modeling the system and provided extensive information on available data sources and additional contacts. However, all the scientists also had their own pet processes that they wanted to see included in the model, usually related to the focus of their own research. These ranged from the role of algal grazers in controlling algal density to the effect of a mid-estuary gyre. For the purposes of completeness, these were all tentatively included, resulting in a graphical model with 35 nodes and 55 arrows! Clearly, some simplification was necessary to make the problem tractable and to keep it consistent with available data.

The inclusion of many important environmental variables and processes may, in principle, produce more precise predictions. If the values of those variables and the rates of the processes are well-known, predictions can be conditioned on them, thereby reducing uncertainty (Reichert and Omlin, 1997). However, if the variables are stochastic or uncontrollable and must be described by marginal probability distributions themselves, then their inclusion is not very useful for informing management decisions (Levin, 1992). Therefore, to design a simple yet realistic model, each node in the network was reviewed to determine if the variable it represented was either (1) controllable, (2) predictable, or (3) observable at the scale of the management problem. If not, then the node was removed from the network.

The simplification strategies described above were effective in reducing the network down to 14 nodes and 17 arrows (see Figure 25.4). Ecosystem attributes consistent with those identified in the stakeholder study include algal density, as measured by chlorophyll *a* concentration, abundance of the toxic microorganism *Pfiesteria,* fish population health, frequency of fishkills, and shellfish abundance. Other variables that the stakeholders would have liked to see included in the network, for example, taste, odor, aquatic vegetation, and fecal coliform concentrations, were determined to be not affected by nitrogen control, the only management action currently under consideration. Because variables

FIGURE 25.4. GRAPHICAL REPRESENTATION OF THE NEUSE RIVER ESTUARY BAYESIAN PROBABILITY NETWORK.



and relationships are only included in the model if they contribute to our ability to predict ecosystem attributes of policy relevance, the model structure can be best explained by starting with these variables and proceeding in the up-arrow direction.

The submodels for each node were developed in a variety of different ways using the best information available (Borsuk, Stow, and Reckhow, 2004a). For example, the sediment oxygen demand submodel was an empirical model that derived from simple process-based formulations. It arose from a consideration of the

rate of organic carbon decay as it sinks from the surface to the bottom of the water column:

$$\frac{dC}{dz} = -kC^n \tag{25.3}$$

where C is the organic matter concentration (mol C m^{-3}), z is the depth (m), and k is a decay coefficient ($(m^{-3}\ mol^{-1})^{n-1}\ d^{-1}$) that describes the order of the reaction (e.g., a value of 1 would be first-order and 2 would be second-order). With some mathematical manipulation the resultant model for sediment oxygen demand was:

$$SOD = a\left(\frac{L_c}{[1 + kL_c h]}\right)^b \tag{25.4}$$

where SOD is sediment oxygen demand (mol O_2 $m^{-2}\,y^{-1}$), L_c is areal carbon loading (mol C $m^{-2}\ y^{-1}$), and h is the water column depth (m). This is a relatively simple expression, but contains three coefficients, a, b, and k with unknown values. One approach for estimating values for these unknown coefficients is to use a statistical estimation procedure such as regression analysis. In this case, however, there were insufficient measurements of SOD, L_c, and h available from the Neuse Estuary to enable use of this kind of procedure. Therefore, to estimate these values we dug into the scientific literature to find data from 34 different estuaries worldwide that would allow us to estimate values for a, b, and k that were applicable for use in the Neuse Estuary (Borsuk, Higdon, Stow, and Reckhow, 2001).

The shellfish survival submodel is an example of an expert-elicitation procedure (Borsuk, Powers, and Peterson, 2002). Scientists who study estuarine clams (*Macoma balthic*) in the Neuse Estuary were asked to estimate mortality at various dissolved oxygen levels, depending on how long the period of low dissolved oxygen lasted. The results, shown in Table 25.1, indicate a large amount of population variability, especially at the higher dissolved oxygen levels. Times-to-death at 1.5 mg/L range from below 7 to over 63 days. Both the median and the spread of these estimates were greatly reduced at lower DO levels with most individuals expected to die within 14 days at complete anoxia. The experts expressed uncertainty for most of their assessments, generally corresponding to about 15 percent in either direction around their median value.

Though we went to considerable effort to develop a model that captured most of the important stakeholder concerns, the basis for nitrogen regulation turned out to be only a small component of the overall model. In this case regulatory constraints simplified the decision process; nitrogen inputs were to be brought to a level so that algal density, as measured by the concentration of chlorophyll *a* (a

TABLE 25.1. ESTIMATED MORTALITY AT VARIOUS DISSOLVED OXYGEN LEVELS.

	Dissolved	Oxygen	Concentration	(mg/L)
% Dead	1.5	1.0	0.5	0.0
5	7	3–4	2	1–2
25	14	6–7	3–4	2–3
50	14–21	14	7	4–5
75	35–49	21–28	7–14	6-9
95	49–63	28	21	10–14

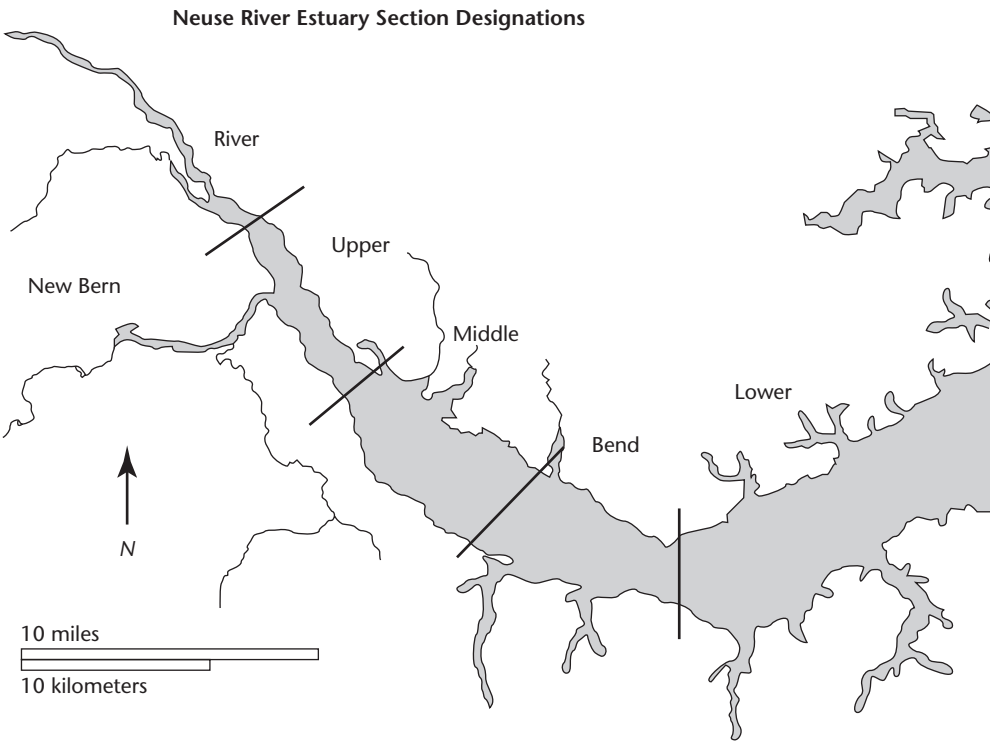
pigment found in algae), would not exceed the North Carolina state criterion of 40 ug/L. Because scientists and regulators recognized that water quality measurements, such as chlorophyll *a*, vary in time and space this criterion value is not viewed as an absolute maximum that can never be exceeded; rather it is interpreted as a 90th percentile—meaning that it can be exceeded no more than 10 percent of the time. Thus, we needed to develop a sub-model for the Bayes net that could predict the probability of exceeding a chlorophyll *a* concentration of 40 ug/L, as a function of nitrogen inputs to the estuary. For this sub-model there was an abundance of data available from the Neuse River system. Examination of the data suggested that the estuary could be divided into five segments, each exhibiting somewhat different behavior because of their relative position to the mouth of the river (Figure 25.5).

The relationship between algal density—as measured by chlorophyll *a* concentration, estuarine location, water temperature, and incoming Neuse River flow—and total nitrogen concentration was developed using a model fit to approximately five years (mid-1994 through 1999) of biweekly monitoring data (Borsuk, Stow, and Reckow, 2004b). The resultant model was specified as:

$$\ln(chl) = \beta_{0,\text{sec}} + \beta_{\text{wey}} + \beta_{1,\text{sec}}\{\ln(flow) - \phi_{\text{sec}}\} \times I\{\ln(flow) < \phi_{\text{sec}}\} + \beta_{2,\text{sec}}\{\ln(flow) - \phi_{\text{sec}}\} \times I\{\ln(flow) \geq \phi_{\text{sec}}\} + \beta_{\text{T}}(T - 20^{\circ}) + \beta_{\text{TN,sec}}(TN) + \varepsilon_{chl} \quad (25.5)$$

where $\beta_{0,sec}$ is the intercept term, allowed to differ by estuary section, β_{wey} is an additive term that was used to compensate for differences in analytical methods used by different participants in the project, ϕ_{sec} is the breakpoint of the flow relationship for each section, $\beta_{1,\text{sec}}$ and $\beta_{2,\text{sec}}$ are the slopes of the flow relationship below and above the breakpoint, respectively, for each section, β_{T} is the temperature coefficient, $\beta_{\text{TN,sec}}$ is the nitrogen coefficient for each section, and e_{chl} *is a normally distributed error*

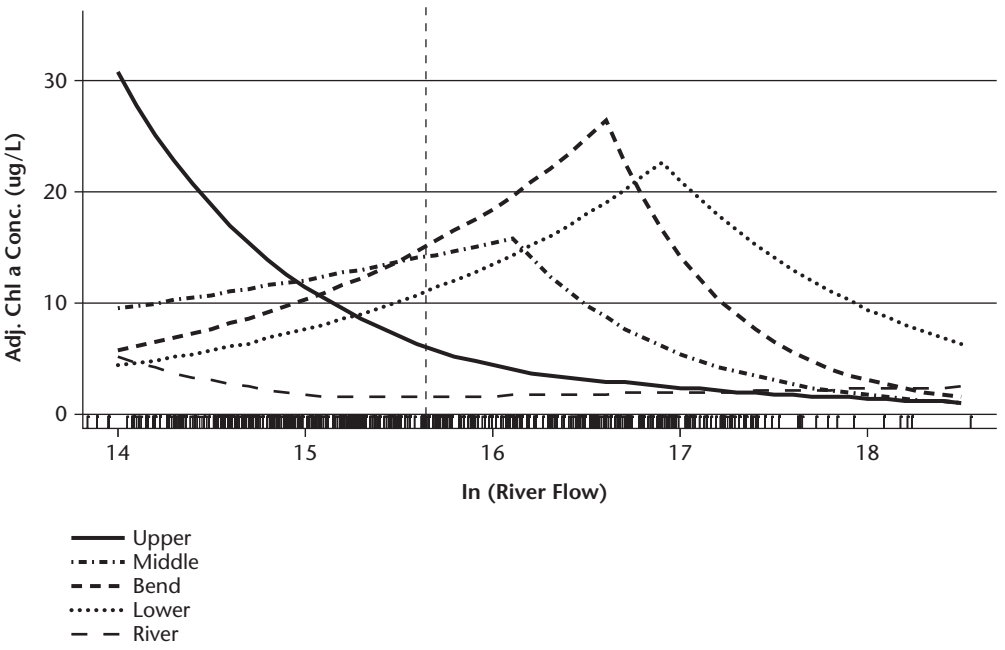
FIGURE 25.5. NEUSE RIVER ESTUARY SECTION DESIGNATIONS.



term with mean 0 and variance ε_{chl}^2. Writing temperature as the deviation from 20°C is a common way to express temperature dependencies in these kinds of models.

While this model may look fairly complicated the results were straightforward to interpret and provided some useful insights about the behavior of the estuary that had not previously been well-understood. The model indicates that there is a positive relationship between chlorophyll and nitrogen input concentration for all locations in the estuary, with the strongest relationship in the lower section, where nitrogen is most likely a limiting factor for algal growth (Qian and others, 2000). Higher river flows were found to generally exert a negative effect on chlorophyll concentration at upstream locations, possibly due to shortened residence times, lowered salinity, and increased turbidity (Figure 25.6). However, at mid- and lower estuary locations, higher flows were associated with higher chlorophyll for flow values below an empirically estimated breakpoint but with lowered chlorophyll at flows above this value. This may be the result of increased nitrogen delivery from upstream sections at intermediate flow values and a flushing effect at higher flows. A

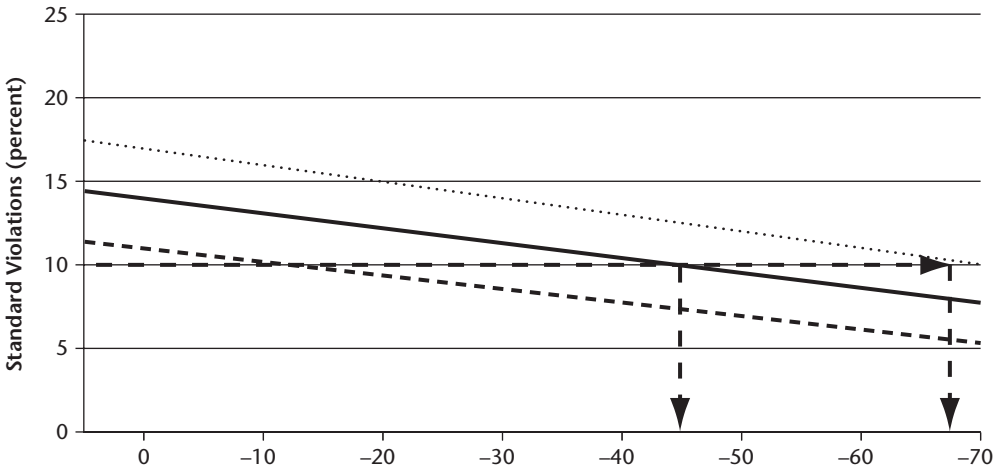
FIGURE 25.6. RELATIONSHIP BETWEEN RIVER FLOW AND CHLOROPHYLL *a* FOR EACH ESTUARY SECTION.



positive relationship between chlorophyll concentration and water temperature was found for all estuarine sections. As measured by the R^2 value, the model was found to resolve 55 percent of the variation in log-transformed chlorophyll concentration—a level of accuracy comparable with more complex simulation models (Stow, Borsuk, and Reckhow, 2003). Or alternatively, 45 percent of the variation in log chlorophyll *a* was not explained by this model—consistent with our understanding that there will be considerable uncertainty in our forecasts of future conditions.

The importance of the uncertainty in our model predictions becomes more apparent when the results are translated into management actions that will be required to meet the 40 ug/L chlorophyll *a* criterion. In Figure 25.7 we show the nitrogen load reductions that would be required to achieve a specified percent of violation of the chlorophyll *a* standard. These reductions are expressed as a percent of the average nitrogen load from 1991–1995. The median model prediction is depicted by the solid line, while a 90 percent predictive interval, representing the uncertainty in our prediction, is shown by the dotted line below. There is a 5

FIGURE 25.7. N REDUCTIONS RELATIVE TO 1991–1995.



percent probability of being above the upper bound (the top dotted line) of the 90 percent predictive interval, and a 5 percent chance of being below the lower bound (the bottom dotted line), while there is a 50 percent chance of being above or below the median. The dashed line shows that to achieve a level of 10 percent standard violations with 50 percent certainty (represented by the point where the median crosses the 10 percent line) would require a nitrogen load reduction of approximately 45 percent. Alternatively viewed, with a 45 percent nitrogen reduction there is a 50 percent risk of not meeting the standard. To reduce this risk to 5 percent (the chance of being above the upper bound of the 90 percent predictive interval) would require a nitrogen reduction of approximately 68 percent.

Figure 25.7 actually depicts a range of risks that could be incurred. With no action, represented by a 0 percent reduction, the risk is almost 100 percent. Alternatively, to incur very low risks, large reductions are required. These large reductions will almost guarantee that the standard will be met, but are likely to be very expensive, or perhaps be unrealistic to actually implement. So with all these considerations in mind—what is the best course of action?

Up to this point in the analysis our ecosystem risk assessment was largely a scientific endeavor; the role of science is to evaluate what is known about the ecosystem and use our best understanding to predict the probability of certain outcomes based on a range of management alternatives. But the choice of what

risk is acceptable requires a *value-judgment,* not a scientific decision. This choice involves a consideration of many trade-offs that include the ecological risks and benefits of different outcomes, the costs of management actions and the likelihood that they can be successfully put into action, and whether or not the decision will be supported both politically and popularly. The choice of acceptable risk is a *policy decision,* not a scientific one. While it is informed by good science it is a decision for those who have been charged with making decisions for the public—typically these are elected officials and their delegated representatives.

In the case of the Neuse estuary, representatives from the State of North Carolina decided on a management goal of a 30 percent nitrogen reduction. While the decision represents a fairly high risk, according to the model results (Figure 25.7) of not meeting the chlorophyll *a* standard there were other factors in addition to our risk assessment that influenced the final decision. Prior to our assessment there was already an existing state rule mandating a 30 percent nitrogen reduction. This decision had been made, in a somewhat ad hoc manner without a formal risk assessment, several years earlier when the public outcry over fishkills began. Additionally, state officials felt that the high degree of uncertainty associated with our model might be reduced with accumulating data from ongoing monitoring in the estuary as the 30 percent nitrogen reduction mandate began to take effect. This process, monitoring ecosystem responses to management actions and iteratively updating model predictions and subsequent management actions as we "learn by doing," is known as "adaptive management."

Adaptive Management

The results of the Neuse Estuary model underscore the inherent difficulty in making precise ecosystem forecasts. In this particular circumstance there was a wealth of data available on which to base the model. In many other ecosystem risk assessment situations the data available on which to base assessments and forecasts may be sparse. Yet, the need for decision-making remains. Deferring a decision to take management action pending further data collection is itself a decision to maintain the status quo, and results in no new information. Viewing environmental decision-making as a one-time event that will either succeed or fail depending on the predictive accuracy of a model can lead to management paralysis as decision makers wait for better predictions. However, a large amount of uncertainty may be unavoidable, even with continued data collection and model development. Therefore, the "wait and see" approach will be less valuable than we intuitively expect. If instead we view decision making as an ongoing, flexible process, preliminary actions can be taken that will improve our knowledge of sys-

tem response and make simultaneous progress toward management objectives. The true response of a natural system to management can only be learned through experience.

This "learning by doing" approach is a pragmatic attempt to deal with growth, change, new information, and imprecise forecasting. This strategy of adaptive management had its origins in the early 1970s when the deliberate attempt to manage the state of ecosystems was a relatively new endeavor (Holling and Chambers, 1973). During that time it was increasingly recognized that ecosystems can exhibit idiosyncratic behavior which small-scale experiments are unlikely to reveal. Mathematical models can be helpful to synthesize our knowledge and predict ecosystem behavior—but as our Neuse model illustrates, models only capture a proportion of ecosystem behavior. Thus, the idea developed that management actions themselves should be regarded as an experiment that, if well-designed and monitored, will provide new knowledge about the behavior of the ecosystem that can be used in an ongoing process to refine future management actions. Adaptive management is not an ad hoc game of trial and error, but rather an articulated succession of judgment-based decisions, followed by implementation, feedback, and adjustment (Holling, 1978; Walters, 1986; Lee, 1993). A flexible, updatable model that quantifies information on uncertainty can serve as the organizing principle behind this set of actions. Once the management actions are implemented careful monitoring of the way the system responds can provide new data and information that can be used to update the model.

In the case of the Neuse estuary, as management actions cause nitrogen levels to decline, the influence of nitrogen will become clearer as it begins to vary more independently from the other confounding factors that affect chlorophyll *a* concentration. As ongoing monitoring provides more data to document these changes the existing models will be updated to assimilate the new data, using Bayes theorem. The incorporation of new data, which represents a greater range of ecosystem behavior, into the models will allow us to sharpen our forecasts, revaluate the risks, and update our management actions in an interactive and informed manner.

Thought Questions

1. Why is establishing cause and effect relationships difficult at the ecosystem scale?
2. What are the limitations of small-scale experiments for ecosystem risk assessment?
3. What role do models play in ecosystem risk assessment?
4. Why is it important to include stakeholders in environmental decision making?
5. What are the benefits of "adaptive management"?

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CHAPTER TWENTY-SIX

THE OHIO COMPARATIVE RISK PROJECT

Michele Morrone

Learning Objectives

Students who complete this chapter will be able to

1. Demonstrate an understanding of the Ohio Comparative Risk Project
2. Identify the workgroups and risk assessment methods employed by each of the groups in the project
3. Identify the methods for involving the public in the Ohio Comparative Risk Project
4. Discuss the policy implications of the Ohio Comparative Risk Project

The EPA showed its commitment to exploring the use of comparative risk by providing grants to state and local governments to participate in comparative risk projects. The Ohio Environmental Protection Agency (Ohio EPA) submitted a proposal to conduct a project and was awarded a $100,000 grant from EPA in 1993. The Ohio General Assembly matched these federal funds with state dollars and established additional funding for Ohio EPA to disseminate grants to local governments and organizations to conduct additional projects.

The author of this chapter is the project manager of Ohio's Comparative Risk Project

In a show of support for the Agency's comparative risk efforts, Ohio Governor (as of 2006, Senator) George Voinovich signed Executive Order 98–48V officially establishing the Ohio Comparative Risk Project in March 1994. This Executive Order required all state agencies to be involved in ranking relative risks in Ohio. On the same day the Executive Order was signed, a kickoff meeting was held in Columbus with more than two hundred stakeholders in attendance. Part of this meeting was spent brainstorming environmental issues that participants felt were most important to examine in the course of the risk-ranking effort.

Issue List Development

The list of environmental threats compiled at the kickoff event was the starting point for developing the project's working list of issues. Participants in the project worked with the seven-hundred-plus issue list to reduce redundancies and to identify a manageable group of key issues that could be adequately addressed by the project's volunteers within the available time. On August 18, 1994, the chairs of the three main work groups met to negotiate a working list of environmental issues that would serve as a basis for research efforts and ultimately for the risk ranking. In order to organize the research for the project, the negotiating team developed eleven general problem categories:

1. Indoor air quality
2. Outdoor air quality
3. Land use and development
4. Habitat loss and degradation
5. Surface and ground water quality
6. Drinking water at the tap
7. Food safety
8. Waste management
9. Natural resource use
10. Environmental awareness and access to information
11. Environmental management

Each of the eleven problem categories contained several potential threats. For example, mobile source emissions are a potential threat categorized in the outdoor air quality problem category. Abandoned industrial sites are a potential threat in the land use and development problem category, and tire management is a potential threat in the waste management category. In all, forty-five potential threats were grouped into the eleven categories.

Although the issues list was extensive, it was impossible for this volunteer effort to include every environmental issue of concern to Ohioans. Moreover, project participants recognized that the list represented, at best, a snapshot of concerns, which were constantly shifting and changing due to developments in Ohio. For instance, in the months after the working list of issues was established, radioactive waste handling—an issue identified as a component of waste management but not included as one of the specific threats on the ranking list—became an issue of great public interest. During this time, the Ohio General Assembly considered legislation on locating a low-level radioactive waste storage facility in Ohio. Those working on the project explained that the mere inclusion of an issue on the working list did not indicate that the issue presented a significant risk and the absence of an issue from the list should not be interpreted to indicate that the issue was of no concern.

Project Structure

As discussed previously, the Ohio Comparative Risk Project followed a traditional format of including a coordinating group and several technical work groups.

Public Advisory Group

The Public Advisory Group (PAG) was the governing body of the Ohio project. This group consisted of more than twenty volunteers representing business and industry, government agencies, academia, and, with some reluctance, environmental groups. The PAG was assembled using an application process more for the sake of organization than selection. The project manager from the Ohio EPA worked for several months promoting the project and gathered information from potential participants. All of those who expressed an interest in serving on the PAG were invited to do so.

The environmental activist community in the state remained suspicious about the project and were quite vocal in their criticism of the project's intent. This criticism was grounded in the association of comparative risk with the conservative republicanism discussed in Chapter Eight. Even with this suspicion, a couple of environmental activists did agree to serve on the PAG, and their participation was absolutely critical to enhancing the credibility of the effort.

The PAG met monthly for more than two years during the risk-ranking phase. They reviewed work coming from the technical work groups, coordinated the massive public outreach component of the project, and developed the methodology for ranking the environmental issues according to the risks they posed in Ohio.

After the risk-ranking phase, the PAG assumed an even greater role in developing policy recommendations based on the ranked list of environmental issues. This took an additional year of meetings and resulted in a document that was somewhat controversial, but not as influential as the risk ranking.

Technical Work Groups

Three technical work groups were extremely important in gathering data about risks to human health, ecosystems, and quality-of-life in Ohio. These work groups were responsible for researching the current state of the science relative to the environmental issues being examined. They were composed of volunteer environmental professionals representing industry, academia, regulatory agencies, and citizens. All three work groups assessed the risks from the forty-five potential threats.

Risk Assessment Methods

The work groups developed their own methodologies for assessing the risks, drawing on work by other states that had completed similar efforts. The discussion below summarizes the methods employed by the ecosystem, human health, and quality-of-life work groups in their analysis of risk.

Ecosystem Risk Assessment

The ecological risk assessment methods were based loosely on ecosystem risk assessment guidance from the EPA (1992) and the work of other states such as California (California Comparative Risk Project, 1994), but focused on Ohio data. The stressors were evaluated based on the state ecological region, or ecoregion, most affected. Ohio has five distinct ecoregions: (1) Western Allegheny Plateau (WAP) in the southeastern area of the state, (2) Erie-Ontario Lake Plain (EOLP) located in northeast Ohio, (3) Huron-Erie Lake Plain (HELP) in northwest Ohio, (4) Eastern Corn Belt Plain (ECBP) comprising a swath from the center of the northern border of Ohio diagonally to the southwestern part of the state, and (5) Interior Plateau (IP) in the extreme southwest corner of the state (Omernik and Gallant, 1988).

The ecosystem work group used the method employed by the California Comparative Risk project. Stressors were rated on a scale of 1 to 5 according to the severity or magnitude of the stress on the ecosystem (intensity), the percentage of the ecosystem affected by the activity (extent), how long it would take the ecosystem to recover from the effect of the stressor (reversibility), the evidence that the effect will occur (uncertainty), and the quality of the data (level of confidence) (see Table 26.1). A low rating indicated stressors with little or no potential impact on the environment, while higher scores indicated more severe impacts.

TABLE 26.1. EVALUATION CRITERIA OF ENVIRONMENTAL STRESSORS.

Criteria	Definition	Scale
Intensity	The ecological severity of the effect.	1 = non-lethal effects on individual organisms 2 = loss of individual organisms 3 = non-lethal effects on whole populations 4 = loss or exclusion of populations 5 = complete destruction of exosystem
Extent	The proportion of the ecosystem type affected.	1 = less than 1% of ecosystem affected 2 = 1 to 5% of ecosystem affected 3 = 6 to 10% of ecosystem affected 4 = 11 to 50% of ecosystem affected 5 = 51 to 100% of ecosystem affected
Reversibility	The time required for the system to recover.	1 = less than 1 year 2 = 1 to 5 years 3 = 6 to 20 years 4 = 21 to 70 years 5 = not recoverable
Uncertainty	The certainty that the effect will occur or the probability that the event producing the stressor will occur.	1 = no direct evidence of effect 2 = effect possible based on understood biological principals 3 = effect is probable based on experience with similar situations 4 = some effects have been measured 5 = effect documented to occur
Level of Confidence	The reliability of the data upon which the ranking criteria are based.	1 = high confidence 2 = medium-high confidence 3 = medium confidence 4 = low confidence 5 = no confidence

Source: California Comparative Risk Project (1994).

As an example of how the ecosystem analysis worked, consider the environmental problem category of natural resource use. Mining is an activity or potential threat in this category related to power production. A stressor associated with mining is acid mine drainage. In Ohio, the majority of mining takes place in the southeast, the location of the WAP ecoregion, so acid mine drainage is evaluated using the above criteria for this portion of the state.

Human Health Assessment

The human health assessment is modeled after standard risk assessment methods employed by the federal government (National Research Council, 1983). The analysis included an assessment of the types of health effects (e.g., cancer, noncancer, chronic, acute) associated with the risk and the human health pathways of exposure in Ohio. The human health work group estimated the number of Ohioans who would be affected by the risk, and special populations such as children and the elderly were examined relative to adverse affects of the risk. Geographic concerns were also noted, since issues such as mining only affect a specific region of the state.

In each human health technical paper, the author discussed the data used in the analysis. Included in the discussion was the current state of research relative to the risk, dose-response research, presence of Ohio data, level of conservatism in assumptions, and the basis of the health effects determinations (laboratory versus in situ data). The outline for the human health assessment can be found in Exhibit 26.1.

Quality-of-Life Assessment

The quality-of-life work group faced the greatest challenge in their analysis of risks. The purpose of quality-of-life assessment was to evaluate the adverse effects of the environmental risks on intangibles such as peace of mind and future generations. Using experience from other states, this work group developed six criteria: (1) peace of mind, (2) sense of community, (3) economic impact, (4) aesthetics, (5) fairness, and (6) future generations. For each environmental issue under study, the quality-of-life group assessed the impact that the issue had on the six criteria, for example, how mining might affect peace of mind and future generations.

The quality-of-life group relied heavily on the extensive public opinion data gathered on environmental issues in Ohio. Public outreach data were used to weight the quality-of-life criteria so that those issues having the greatest effect on future generations would rank the highest.

Public Involvement

The Ohio Comparative Risk Project involved substantial public outreach as thousands of Ohioans were invited to voice their opinions about the threats from environmental issues in the state. A goal of the project was to use both science and values to rank environmental risks, and the data gathered from the public influenced the final risk ranking by the public advisory group. The final ranking was

EXHIBIT 26.1. OUTLINE OF REPORTS FOR THE HUMAN HEALTH ASSESSMENT.

I. Introduction
   A. Hazards/severity
   B. Types of health effects (cancer, noncancer; chronic, acute)
   C. Hazards (indicator chemicals, physical hazards such as fires)
   D. Human health pathway (ingestion, inhalation, absorption)

II. Population
   A. Overall estimate (size of Ohio's population exposed to hazards in II)
   B. Special populations at risk from the hazards in II (children, the elderly, asthmatics)
   C. Special geographic concerns (regions or communities in the state at special risk from the hazards in II) (e.g., southeastern Ohio, urban areas)

III. Information/discussion of data sources
   A. Information on human exposure to health stressors (current state of the research (and identifying how humans are exposed)
   B. Dose-response (research identifying a link between dose of a chemical and human health response)
   C. Presence or absence of actual state data on incidence of illness or death (current data linking exposure to health risk in Ohio)
   D. Level of conservatism in assumptions
   E. Information based mainly or only on animal model (presence of longitudinal human health studies or mainly laboratory studies)

IV. Other considerations
   A. Time imminence of threat (current, future, or ongoing)
   B. Interconnectedness with other problems
   C. Reversibility of health threat
   D. Evidence of trend

based primarily on risk to human health, followed by an equal consideration of risks to ecosystems and quality of life. Examples of public participation techniques employed in the Ohio Project are found in Table 26.2.

Risk Ranking

The three technical work groups produced separate rankings of the issues based on their focus (i.e., human health, ecosystem, or quality of life). The PAG took the separate rankings provided by the technical groups, conducted telephone

TABLE 26.2. PUBLIC INVOLVEMENT TECHNIQUES IN OHIO COMPARATIVE RISK PROJECT.

Type	Event	Participants
Informal voting: Involved as display at an event in which interested people voted with stickers or fake $100 bills.	Earth Day, 1994	200
	State Fair, 1995	5,855
Facilitated discussions: Generally small groups with open discussion about environmental issues; at the close of the meetings participants would vote on issues with stickers.	Ohio Department of Natural Resources meetings	401
	Conservation groups	132
	Student groups	515
	Ohio Alliance for the Environment	107
	League of Women Voters	140
	Business/industry	183
	Community groups	183
	Public advisory group	54
	Ohio Farm Bureau	4,765
Public opinion poll: Conducted by a survey research firm via telephone.	Phone poll	134
Total participants in structured outreach events		12,669

interviews with other environmental professionals, and reviewed the public outreach data. They then developed a set of criteria for evaluating the potential threats. These criteria included a weighting system so that those issues that posed the greatest threat to human health would be ranked in the highest group, followed by ecosystem and then quality-of-life risks. The human health weighting was based largely on concerns raised by members of the public who were most interested in addressing environmental issues that could affect their health. The weighting scheme is as follows:

- *Greater weight.* High human health risk, high ecosystem risk and either medium human health risk or high quality-of-life risk, high quality-of-life risk and medium human health risk

- *Medium weight.* Medium human health risk, high ecosystem risk, high or medium quality-of-life risk
- *Lesser weight.* Low human health risk, medium or low ecosystem risk, low quality-of-life risk

To group the issues, the PAG then produced an integrated list using letters rather than relative labels such as "high," "medium," or "low." The PAG chose to use A, B, and C in the ranking process rather than high, medium, and low because the ranking process was intended to provide insight into relative, not absolute, degrees of risk. Those issues in Group A represent greater risk than those in Group B and Group C, but not necessarily the greatest risks in Ohio.

State of the Environment Report

Aside from the ranked list of environmental issues in Ohio, a major outcome of the first phase of the project was the first ever *State of the Environment Report* for Ohio. This five-hundred-plus page report explains the risk-ranking process, details technical information about all of the risks examined during the course of the project, summarizes the public outreach component, and contains five chapters from local projects that were completed simultaneously with the state project.

The *State of the Environment Report* proved to be a valuable tool for the director of Ohio EPA to use during budget testimony, and it has been used in several classes in Ohio colleges. In addition to the report, several members of the PAG formed an additional subcommittee to develop a CD-ROM based on the report and the comparative-risk work. The CD-ROM, *Protecting Your Environment*, has been distributed free of charge to more than twenty thousand interested parties, including schools, public libraries, and interested members of the public. The CD-ROM has proved to be one of the best outcomes of the comparative risk project and is a unique environmental education tool that has wide appeal.

Policy Recommendations

Perhaps the weakest component of the Ohio Comparative Risk Project was the policy recommendations. This is consistent with other comparative risk projects across the country. The PAG remained together after the risk ranking and spent an additional twelve months developing policy suggestions based on how environmental issues were evaluated during the ranking process. Surprisingly, this part of the comparative risk project proved to be more contentious than the risk ranking.

Throughout the policy-development phase there was serious debate and discussion about several of the issues. When it became clear that the PAG was not

going to reach consensus about what policy to recommend for issues related to natural resource use, the chair of the PAG asked for a minority report. This minority report was authored by several members of the PAG, mainly those affiliated with environmental activist groups. The result was a weakened document that was then passed to Governor Voinovich, who was beginning his bid for a seat on the U.S. Senate.

As the policy recommendations were completed, the administration of the state of Ohio changed. Governor Voinovich was elected to the U.S. Senate and Governor Taft replaced the directors of most of the state agencies, including the Ohio EPA. This change in administration, combined with the weakened state of the policy document due to the minority report, led to the ultimate collapse of the Ohio comparative risk project. Indeed, only one of the specific policy recommendations, having to do with environmental education, was carried out.

As a direct result of the Ohio Comparative Risk Project and the policy recommendations, Ohio EPA created an Office of Environmental Education; the director of the Comparative Risk Project was named its first chief. This move highlighted the importance of improving educational opportunities for all Ohioans. Part of the responsibilities of the office included administering the Ohio Environmental Education Fund (OEEF), which provides grants for environmental education. The grant guidelines were revised to encourage projects to focus on those issues identified in the Comparative Risk Project as important.

Thought Questions

1. What do you think was a major obstacle to completing the Ohio Comparative Risk project? Was it politics, the reliance on volunteers, or the lack of buy-in from the environmentalist community? How could a future project overcome these obstacles?
2. Why do you think the Ohio Comparative Risk Project had limited impact on environmental policy in the state? What was the one success story that resulted from the project?

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CHAPTER TWENTY-SEVEN

COMMUNITY-BASED RISK ASSESSMENT

DDT Contamination in Triana, Alabama

Padma Tadi-Uppala

Learning Objectives

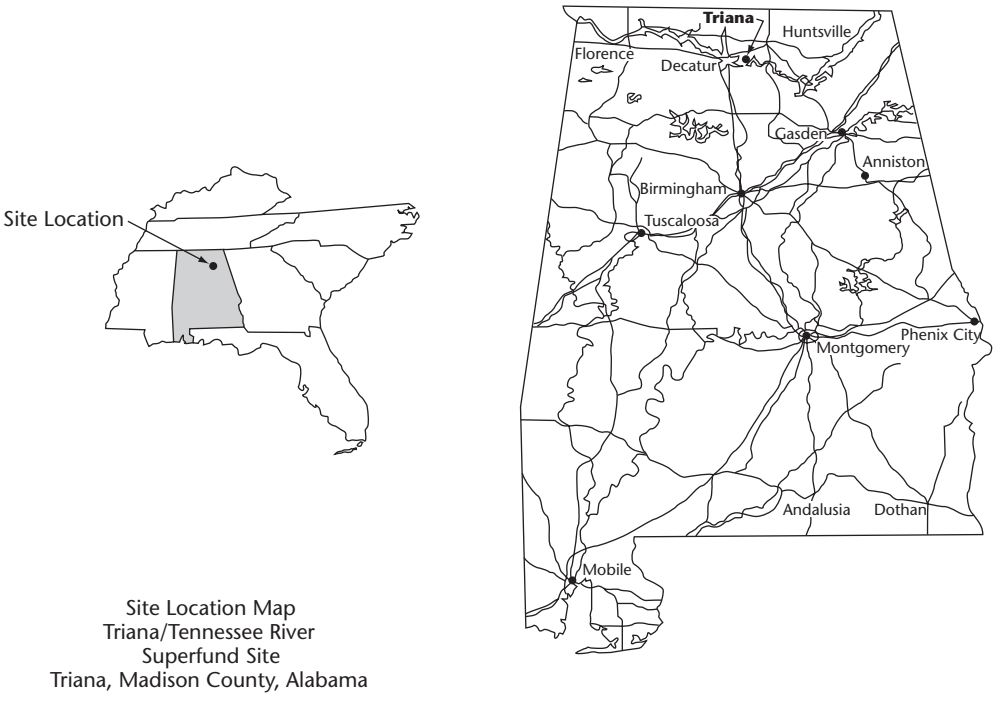
Students who complete this chapter will be able to

1. Understand the relation between human health and ecological risk assessment
2. Understand the process of bioaccumulation of DDT in the environment
3. Estimate the lifetime risk of humans exposed to DDT through consumption of DDT-contaminated fish
4. Understand the concept of "environmental justice" among minority populations

The community of Triana in Madison County, Alabama, provides an ideal situation to study the influences of social, cultural, and environmental factors on the health of the residents. This town has been referred to as the unhealthiest town in the United States (see Figure 27.1) (Reynolds, 1980).

The Honorable Clyde Foster, Mayor of Triana (1964–1984), Mavlene Freeman, Mayor of Triana 1996–present, and Community Representative Joe Fletcher helped me with the information on DDT contamination in Triana. Dr. Renate Krause, Dr. Hal Marlow, Dr. Sam Soret, and Guru Uppala provided valuable suggestions and editing. Research sponsored by The U.S. Army Medical Research Material Command; Grant Number: DAMD17-98-1-18138.

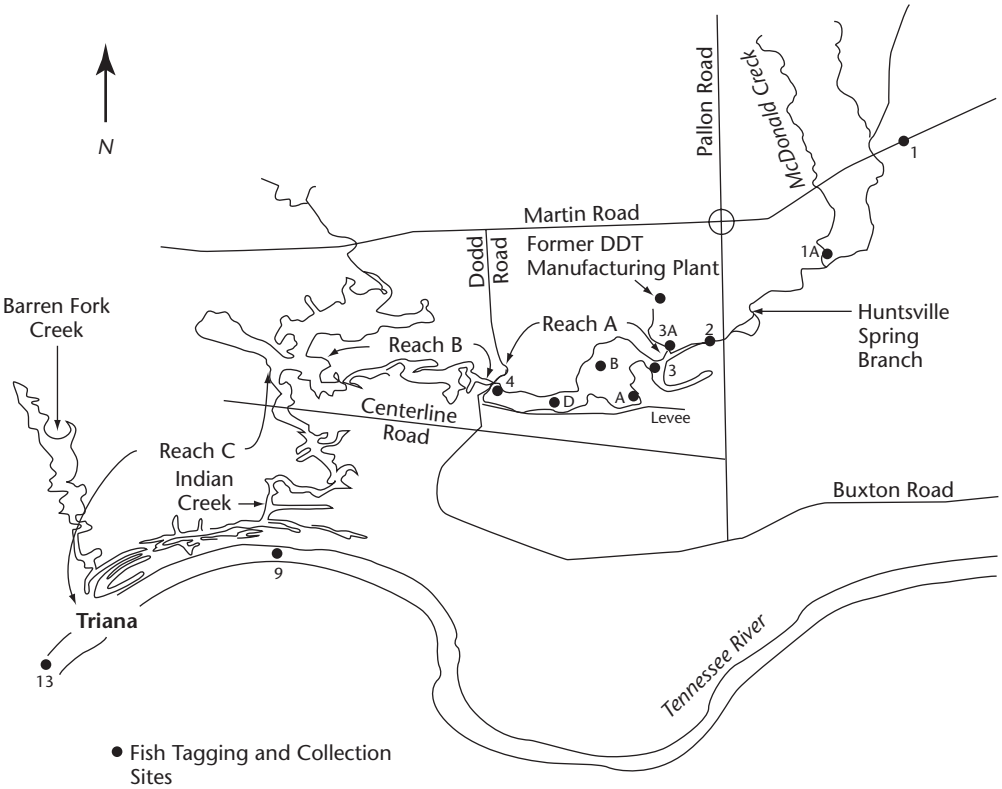
FIGURE 27.1. SITE LOCATION MAP TRIANA/TENNESSEE RIVER SUPERFUND SITE, TRIANA, MADISON COUNTY, ALABAMA.



Source: USEPA Document Control No. 4400-24-ACYT

Some of the residents were found to have been contaminated with the highest levels of DDT ever recorded (Environmental Protection Agency, 1993). Residents of Triana, predominantly African American, have been eating fish from a local river contaminated with DDT for nearly 50 years. The Olin Corporation at the U.S. Army's Redstone Arsenal in Huntsville, Alabama, manufactured DDT between 1947 and 1970. Manufacturing, handling, and disposal practices at the facility led to the discharge of DDT residues through Redstone Arsenal's drainage system into the Huntsville Spring Branch–Indian Creek system, which enters the Tennessee River. Although cleanup efforts have been attempted (Williamson, 1995), exposure to contaminants is still a major concern (see Figure 27.2).

FIGURE 27.2. TRIANA/TENNESSEE RIVER SITE, HUNTSVILLE SPRING BRANCH, INDIAN CREEK SYSTEM.



Source: USEPA Document Control No. 4400-24-ACYT

The Centers for Disease Control and Prevention (CDC) conducted a study in 1979, which confirmed an average total DDT serum level of 159.4 parts per billion (ppb). At least 27 percent of the participants in the Triana Study had total DDT levels 10 times the U.S. geometric mean (16.7 ppb) (Centers for Disease Control and Prevention, 1980). During the laboratory analysis, many specimens appeared to have polychlorinated biphenyls (PCBs) as well as DDT. While the normal levels for PCBs range from 5 to 20 ppb among the general population, they ranged from 4 to 97 ppb with a mean serum level of 17.2 ppb among the Triana residents.

Background

DDT is an organochlorine insecticide that was used for agricultural and nonagricultural applications in the United States and worldwide beginning in 1939. Although DDT use was banned in the United States in 1972, it is still used in certain parts of the world to control vector-borne diseases such as malaria. DDT and its metabolite DDE, as well as PCBs, are known animal carcinogens and suspected human carcinogens. Both DDT and PCBs have been shown to be tumor promoters. Agencies such as International Agency for Research in Cancer (IARC) (IARC monograph, Vol. 53, 1991), National Institute of Environmental Health Sciences (NIEHS) (Seventh Annual Report on Carcinogens), and the U.S. Environmental Protection Agency (EPA) (risk assessment) classify DDT as a chemical anticipated to be carcinogenic in humans. Several reports since 1991 suggest that DDT may be a risk factor for breast cancer. Recently several in vitro animal and epidemiological studies have indicated that DDT and PCBs are associated with cancer of the lung, liver, and pancreas. In spite of the controversies between DDT and risk for breast cancer, several studies in recent years have suggested an association between DDT and risk for breast cancer (Charlier and others, 2003; Aronson and others, 2000; Hoyer and others, 1998).

DDT studies have indicated a tumor-promoting potential in human breast tissue. It was shown that DDT could stimulate cell proliferation in a dose-dependent manner and encourage growth-arrested breast cancer cells to enter into a growth cycle; it could also inhibit gap-junctional intercellular communications, enhance breast cell growth, and increase unscheduled DNA synthesis. It was also shown to induce micronuclei and hyperdiploidy/polyploidy in the mammary cells of pubertal rats (Tadi-Uppala and others, 2005). The mechanism by which DDT may cause breast cancer is through estradiol metabolism as explained below. Estrogenic action of DDT has been shown to occur by binding to and activating estrogen receptors. Estradiol metabolism proceeds by hydroxylation at one of the two mutually exclusive sites at c-2 and c-16 alpha. The catecol pathway yields the estrogenic 2-hydroxyestrone, which inhibits breast cell proliferation; in contrast, the alternative pathway yields the genotoxic 16-alpha hydroxy estrone. DDT and PCBs were shown to significantly increase the ratios of these metabolites. Although classified as an epigenetic carcinogen, it is possible for DDT to exert its carcinogenic effects through interaction with other factors or synergistically with other weak estrogens such as PCBs or other metabolites of DDT. The incidence of breast cancer may be intensified due to other factors such as social and cultural causes in the low-income, medically underserved Triana community.

Exposure

Preliminary epidemiology studies among 162 Triana residents indicate that the prevalence of all cancers combined among study subjects was 23 percent, and cardiovascular disease was about 75 percent (Jacobs, Kahn, Stralka, and Phan, 1998). The prevalence of breast cancer among women was 18 percent, based on 17 cases. The occurrence of breast cancer was significantly associated with fish consumed from the DDT-contaminated ponds or rivers ($p = 0.0001$). The prevalence odds of breast cancer among those exposed to DDT compared to the non-exposed was 2.4 (95 percent confidence interval, 0.85–5). Of the 17 breast cancer cases or their surrogates interviewed, 4 had a family history of breast cancer. Of the remaining 13 breast cancer cases with no family history of breast cancer, 3 cases reported other hormone-related cancers (prostate, pancreas, and ovary among immediate family members) (Tadi-Uppala and others, 2000).

Table 27.1 indicates the DDT serum levels of 43 Triana residents from the 1980 CDC study.

Thought Questions: Population Risk Estimates

1. Given the data below regarding the exposure of Triana residents to DDT, estimate the lifetime cancer risk of adults who ate fish daily for 20 years.

   The DDT production facility operated from 1947 to 1970 and released approximately 408.8 tons of DDT to surface waters, which drain to the Tennessee River.

   Best predictors of DDT exposure were the amount of fish consumed and the age of consumer. In 1979, the Tennessee Valley Authority (TVA) showed that fish taken from the Spring Branch revealed DDT amounts as high as 200 parts per million (ppm), 40 times the federal limit.

   Most Triana residents ate fish daily for all three meals. The estimated mean consumption rate for all fish for the U.S. population of the 48 conterminous states was 15.65 grams/person/day (Jacobs, Kahn, Stralka, and Phan, 1998).
2. If you were an EPA official, would you be concerned about your findings? Why or why not? For which parts of the calculations would you need definite data?
3. The case study is an example of the much-debated topic on environmental estrogen/endocrine disrupters such as DDT that might cause cancer and have

TABLE 27.1. SERUM LEVELS OF DDT IN TRIANA RESIDENTS.

ID Number	Sex	Approximate Age	DDT Level (ppb)
10000	M	57	538
10001	F	59	419
10002	M	76	351
10003	M	61	673
10004	F	63	796
10005	F	72	452
10006	M	71	361
10007	M	56	533
10008	F	62	426
10009	M	41	855
10010	M	48	344
10011	F	34	433
10012	F	7	219
10013	M	37	2,447
10014	M	35	388
10015	F	57	532
10016	M	5	643
10017	F	37	561
10018	F	68	414
10019	M	54	425
10020	M	55	524
10021	M	27	366
10022	M	60	681
10023	M	84	510

TABLE 27.1. SERUM LEVELS OF DDT IN TRIANA RESIDENTS, Cont'd.

ID Number	Sex	Approximate Age	DDT Level (ppb)
10024	M	14	219
10025	M	56	639
10026	M	43	1,185
10027	M	77	677
10028	M	71	599
10029	M	48	97
10030	M	51	452
10031	M	38	1,261
10032	M	76	1,314
10033	M	55	328
10034	M	65	955
10035	M	13	182
10036	F	53	916
10037	M	64	440
10038	M	60	418
10039	F	71	512
10040	F	42	235
100041	M	85	3,300
100042	M	46	270

Source: Centers for Disease Control and Prevention (1980).

deleterious effects on reproductive health. Given the situation, what is the estimated lifetime risk for breast cancer in countries continuing the use of DDT?

4. What is the risk for mental and cardiovascular disease among Triana's children at age 60 if they continue to live in Triana?

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