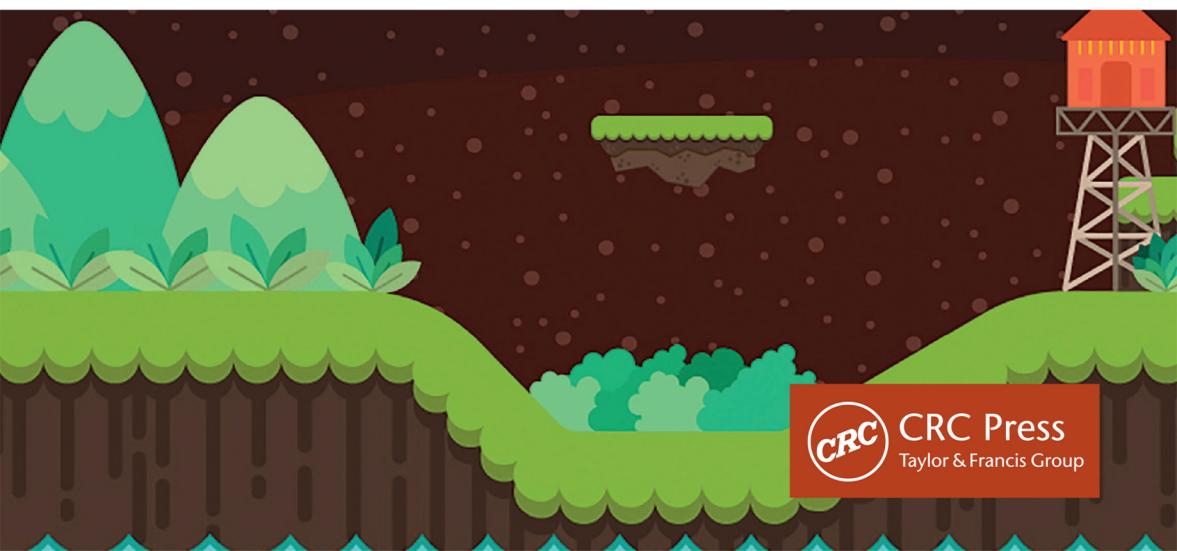


# ENVIRONMENTAL RISK ASSESSMENT

A TOXICOLOGICAL APPROACH

SECOND EDITION

Ted Simon



CRC Press  
Taylor & Francis Group

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**Ted W. Simon**



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*This book is dedicated to my grandchildren,  
Elizabeth, Charlie, Georgia and Ezra, with  
the hope that the world they inherit will  
be nurturing, beautiful, and safe.*



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## Foreword

As we approach the third decade in the 21st century, toxicological and risk assessment science face a crossroads. In many programs, overreliance on outdated default assumptions and policies based upon ossified 1970s knowledge continues, leading to generation of phantom risks and misdirected risk management actions under the guise of precautionary decision-making. Risk management actions that are not rooted in modern knowledge of biology, toxicology, and risk assessment can be costly, time-consuming, and take resources away from other pressing needs—all without affording any true risk reduction.

Knowledge is a powerful driver of transformation. We now know more than ever before about biology, how chemical exposure occurs, and the mechanisms, pathways, and dose-dependent changes that can lead to toxicity. It's time to unshackle the chains of 50-year-old default approaches for risk assessment and harness all of our current 21st-century knowledge to improve the methods for conducting safety evaluation of products and for evaluating risks from environmental exposures, including exposures from releases to air, water, and soil.

Having confidence in the safety profile of chemicals and understanding potential risks of exposures to chemicals in products and via the environment is essential for regulatory and product stewardship decision-making. The social license of the global chemical enterprise, industry sustainability, and the introduction of chemically derived advanced technologies all depend on the scientific understanding of chemical hazards, exposures, and risks. Scientific knowledge and innovation not only drive transformational advances in product development, but they should also catalyze transformational advances in the manner in which chemical hazards, exposures, and risk are evaluated.

Ted and I have worked together for close to ten years now on projects at the cutting edge of this transformation. In this edition, not only does Ted do a stellar job of explaining and illustrating the basics of risk assessment and risk communication, but he also clearly presents the advanced approaches grounded in modern scientific understanding that should supersede the 1970s-based defaults. This book will enable students to understand both the older default approaches and the thinking and data supporting the transition in risk assessment.

**Dr. Richard A. Becker**  
*Director, Long Range Research Initiative,  
American Chemistry Council*



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## Preface

As the developed world moves further into the 21st century, what is becoming increasingly clear is that societal decisions must be based on an honest and forthright appraisal of the state of relevant knowledge. More often than not, these decisions relate to so-called wicked problems for which no easy answers exist. Unfortunately, these decisions almost always become highly politicized.

Much of the methodology and knowledge generally used in environmental risk assessment today dates from the 1980s and 1990s. Environmental risk assessment has become highly dependent on the use of default values for a range of factors in both exposure and toxicity—defaults are appropriate when existing data are inadequate, and it is important for risk practitioners to understand the basis and appropriate use of default values. For example, the linear no-threshold hypothesis for chemical carcinogens was derived from early 20th-century work on radiation mutagenesis and has been used for the past 25 years. However, recent investigations of radiation mutagenesis and the increasing knowledge about fundamental biology and nature of cancer suggests that this hypothesis is based on flawed assumptions and is inconsistent with the biology.

Happily, this situation is changing—the recent publications from the US National Academies of Sciences titled *Toxicity Testing in the 21st Century: A Vision and a Strategy* and *Science and Decisions: Advancing Risk Assessment* have the potential to engender significant progress. In order for future practitioners to understand the effect of this coming change, they must know what was done in the past and what the future may hold in store.

Key issues in risk assessment are those that either contribute appreciably to quantitative estimates of risk (a risk driver) or add to the uncertainty of those estimates (an unknown). Hence, this book serves to provide students with sufficient knowledge and confidence to enable them to probe the science underlying key issues in environmental risk for themselves rather than accepting so-called conventional wisdom or the opinion *de jour*.

Realizing the need to use relevant scientific information as the basis of decisions, having confidence in one's own knowledge and one's ability to learn, and possessing the humility to accept the limitations of humankind's knowledge are the hallmarks of a great scientist—the kind who can provide an unbiased and science-based appraisal of risk and uncertainty that best serves the decision-makers in today's complex society.

The aim of this book is to provide a text and reference that will enable students of risk assessment to approach the future with confidence about the state of their knowledge. No aspect of environmental risk assessment should be a “black box” for any practitioner. Environmental risk assessment courses are taught in either public health or civil/environmental engineering programs. The science of risk analysis is part and parcel of many disciplines. Hence, students from these two diverse academic backgrounds as well as other areas of study can become proficient in the science of risk analysis—engineering students will likely need to put greater effort into learning

about toxicology and epidemiology, whereas public health students will likely need to work harder on learning about environmental sampling and analysis, hydrogeology, and soil science. This textbook cannot cover all aspects of risk analysis, and one of the hallmarks of a good practitioner is sufficient engagement with the subject to seek out relevant information. For the sake of honesty, it is vitally important to acknowledge one's areas of ignorance and seek help from others as needed—doing so most often requires mustering one's humility.

Democratic societies in the 21st century have become invested in risk assessment as a tool for informing important societal decisions. The ability to conduct environmental risk assessments is a marketable skill, and with hard work, this skill can provide the practitioner a rewarding career. To provide practical experience in performing risk assessments as a start to developing one's skills, fully worked examples of specific human health and ecological risk assessments including the environmental sampling data are provided. In addition, an electronic workbook with more exercises/examples is provided at [www.crcpress.com/9780367250973](http://www.crcpress.com/9780367250973).

Regarding these examples and others in this book, there are no “correct” risk assessments—there are only those that comport with the judgments of the decision-makers who use these analyses as a decision tool. Are the risk analyses helpful in supporting a regulatory choice? One of the central tensions in risk assessment today is the gap between regulatory guidance and the state of the science. The datasets and examples provide the opportunity for students of risk assessment to explore this science/policy gap for themselves.

## CHAPTER DESCRIPTIONS

Chapter 1 presents an introduction to the field and a history of environmental risk assessment in the United States and elsewhere.

Chapter 2 discusses problem formulation and hazard identification as the two initial steps in risk assessment. Problem formulation is necessary to ensure the scope of a risk assessment matches the size of the problem addressed. Hazard identification, although inexact, provides a means of deciding when to investigate a perceived problem further.

Chapter 3 provides a number of computational tools and brief discussions about aspects and use of statistics as part of the science of risk analysis.

Chapter 4 provides a narrative and examples of exposure assessment—how do receptors, generally humans, come into contact with contaminated environmental media? Both qualitative and quantitative aspects are discussed.

Chapter 5 deals at length with hazard characterization and dose–response assessment. Because this book concentrates on the toxicological aspects of risk assessment, this chapter is central to the book. It provides both students and instructors a look back and a look forward. Methods for dose–response assessment are changing rapidly, and as noted, it is vital to know the past in order to understand the future. Many examples are provided.

Chapter 6 on risk characterization presents two detailed case studies that demonstrate complete environmental risk assessments as might be written by a regulatory agency, a regulated entity, or a contractor employed by either of the former. These two examples allow students to hone their skills in using the various tools of environmental risk assessment. In addition, some briefer examples of risk characterizations are provided to illustrate “thinking outside the box” for application of risk assessment to specific questions.

Chapter 7 on ecological risk assessment discusses the development of the guidance on ecological risk assessment and provides an example. Discussions on harmonization of ecological and human health risk assessment have been ongoing for years, but these two activities remain separate. This chapter introduces the subject.

Chapter 8 on bias and conflict of interest presents a number of issues in the realm of risk policy, societal decision-making, and the role of science in society. The thorny issues such as bias, conflict of interest, and the appropriate use of the precautionary principle are thought starters for your own considerations. You likely have strong opinions yourself about these issues.

Chapter 9 on emerging issues is necessarily incomplete. Three issues in risk assessment that loom on the horizon are discussed—epigenetics, pharmaceuticals in the environment, and climate change.

## GOALS FOR THIS BOOK

My hope is that this book will enable students of risk assessment to approach the future with confidence in their skills and knowledge. As a scientist acting in the role of risk assessor, you will be called on to answer difficult and at times impossible questions.

None of us likes dealing with uncertainty, the “poor redheaded stepchild” of science—we all know it’s there, but no one wants to acknowledge it. In many situations, the most honest answer to one of those impossible questions is “I don’t know.” It takes humility and courage to answer in this way when sitting in a meeting and everyone else there thinks you are the smartest guy or gal in the room. Indeed, many of the decision-makers (your clients as a risk assessor) will be looking to you for answers. The best way to serve them is absolute honesty.

The goals of this book are fourfold: (1) to provide a summary of the history, the current methodologies and practices, and likely future of environmental risk assessment; (2) to provide the tools and opportunities for practice, and thus enable students to develop and conduct their own environmental risk assessments; (3) to provide students the ability to understand and potentially address the gaps in the relevant knowledge base supporting environmental risk assessment; and (4) to imbue these students with confidence in their abilities to understand and perform complex risk assessments, humility regarding the extent of their knowledge, and a healthy skepticism that is the hallmark of any good scientist.

## HOW TO LEARN RISK ASSESSMENT

In 1992, I was teaching biology at a small chiropractic college in Atlanta, Georgia. Not to mince words, it was a terrible job, and I was looking for another from the first day. I was there six months until I got a call from an EPA contractor that supplied onsite personnel to the Agency's regional office in Atlanta, Georgia.

The first time I ever heard the term “risk assessment” was when I arrived for work the first day. That first year at EPA, I felt as if I were drinking from a firehose much of the time.

This textbook represents something I would have liked back then to put the various things I was learning into some sort of perspective. I hope it works that way for the instructors and students who use it.

## TERMINOLOGY AND UNITS

A sincere attempt was made to define all terms and acronyms. SI units are generally used.

## EXERCISES AT THE ENDS OF THE CHAPTERS

These exercises are meant to stimulate thought and discussion. The field is changing, and today’s student will be tomorrow’s leader. The opportunity to consider some of the issues in risk assessment in a high-trust, low-concern situation such as a university classroom will prove a valuable experience. I have taught a risk assessment class at the University of Georgia on an occasional basis since 2004. One of the exercises the students found most informative was a mock risk communication/public meeting exercise in which many divergent points of view were expressed.

## ELECTRONIC MATERIALS

After discussions with university colleagues during the writing of this book, I became aware of the need for and utility of specific examples. Hence, environmental datasets and descriptions of situations needing a risk assessment are provided in this workbook. The datasets are provided as Excel spreadsheet files with accompanying narrative. From the worked examples in Chapters 4, 5, 6, and 7, students will have sufficient background to work through the workbook exercises. Again, there are no right answers—only risk assessments that comport with regulatory guidance and/or scientific information to a greater or lesser extent.

Additional material is available at [www.crcpress.com/9780367250973](http://www.crcpress.com/9780367250973).

## Acknowledgments

For showing me just how huge, the science of risk analysis can be, I will always be indebted to Dr. Rick Becker of the American Chemistry Council, who graciously agreed to write the foreword for this book. For getting me started in risk assessment, I want to thank Julie Fitzpatrick, now retired from EPA's Office of the Science Advisor, who was my coworker at EPA during the 1990s and remains a friend today.

I want to thank Dr. James Klaunig for making clear the need for examples.

Finally, I cannot find the words to express my thanks to my wife Betsy for her continuing encouragement in everything I do.



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## CHAPTER 1

# An Introduction to Risk Assessment with a Nod to History

What a piece of work is a man! how noble in reason! how infinite in faculty!  
in form and moving how express and admirable! in action how like an Angel!

**William Shakespeare, *Hamlet*, Act II, Scene 2**

At the outset of the 21st century, technology and industrialization have provided advantages for much of the world's population—but technology is a double-edged sword. Twenty-first-century technology affords us many benefits, including advances in medical care and pharmaceutical products, cell phones, microwave ovens, and mass transit—but, as a downside, industrialization creates a legacy of waste and unintended consequences. Humans enjoy the benefits of technology, but must also deal with accompanying and often unforeseen hazards.

The purpose of risk assessment and the underlying science of risk analysis is to support societal decision-making. Risk assessment is the means by which democratic societies attempt to understand the adverse and unintended consequences of technology. Risk management is the use of risk assessment information to control or abate these consequences.

Ideally, both the risk assessment and risk management will be conducted in a way that takes into account the interests of all stakeholders—this is no more than fair! In risk assessment, the central issue embodied in the ideal is how we as a society take into account both the variation in human exposures to environmental hazards or stressors and the variation in human susceptibility to injury or illness.

### 1.1 RISK ASSESSMENT: DOES CONSISTENCY ACHIEVE THE GOAL OF FAIRNESS?

One way to be fair in risk assessment is consistency. Risk assessment sits at the uneasy interface of science and policy. Almost all decisions about risk assessment methods require considerations of issues in both policy and science. Science is constantly changing, whereas the pace of policy change at times seems glacial

in comparison. Tension between the old and the new in the science of risk analysis will always exist. Risk analysis is an applied science useful for decision support of various activities, including exposure to chemicals, medical procedures, finance as well as other human endeavors; risk analysis can also be considered a pure science producing knowledge about means to assess, characterize, communicate, and manage risk.<sup>1</sup>

Some risk assessment practitioners have come to see this tension between old and new as a scientific culture war—a battle between those who would preserve the status quo, clinging to old ways for consistency’s sake, and those who heartily embrace new ideas and new information. Since the field of risk assessment began with 17th-century mathematician Blaise Pascal’s development of probability theory to ameliorate his winnings at games of chance,\* there has been tension between those who view the best available science as a new and challenging opportunity and those who view change as an anathema. This conflict between new and old lies at the heart of modern environmental risk assessments. Ralph Waldo Emerson noted that “a foolish consistency is the hobgoblin of little minds.”<sup>2</sup> Consistency, however, is a way to create the perception of fairness.

If the goal of consistency were achieved by nothing more than using the same default values for exposure and the same toxicity criteria in every environmental risk assessment, then this consistency would indeed be foolish and likely unfair. This makes the job of a risk assessor tough—one must understand not only the science but also the policy goals, and use this knowledge of both in an honest and forthright manner. A commitment to rigorous intellectual honesty in the evaluation of the data and scientific knowledge used in a risk assessment allow one move away from “foolish consistency” while still achieving fairness.

Two types of ethics are at play in risk assessment—ethics of the mind that justifies an action by reference to intention, and ethics of the consequence that justifies an action by reference to the results or consequences. The commitment to intellectual honesty involves the ethics of intention, whereas the actual goal of the risk assessment is clearly associated with the ethics of consequence. Speaking truth regardless of the consequences is an example of the ethics of intention. Philosopher Immanuel Kant’s categorical imperative arises from the decision to act morally, to do good, as a compelling moral obligation. Kant noted that people may perform good deeds for bad reasons (e.g., egotism, attaining social prominence, etc.), and, based on the ethics of intention, the deeds would have no moral worth.<sup>3</sup>

On the other hand, the ethics of consequence is expressed as utilitarianism that supports material benefit (e.g., money, pleasure, food, survival) as an appropriate end. In *Leviathan*, Thomas Hobbes opined that utilitarianism requires man to recognize and accede to a sovereign authority. Utilitarianism on an individual level gives every man or woman the right to anything in the world. The resulting conflict would result in lives that are “solitary, poor, nasty, brutish and short.” The social contract underlying a democratic society is based on surrendering individual utilitarianism for that of the larger society.<sup>4</sup>

\* Success at poker requires skills in both risk assessment and risk management.

The ethics of consequence seems the basis of environmental regulation—there is no intrinsic common good in setting a maximum contaminant level in drinking water at a particular level; instead, the common good arises from the protection inherent in the regulation. Often, environmental regulation seeks democratic balance between competing agendas using risk assessment as one of many sources of decision support information. However, many view the risk assessment process as obfuscating, antagonistic to environmental protection, and inimical to stakeholders who lack sufficient expertise. The result is the two types of ethics have become tightly woven in an oft-confusing fashion in the practice of risk analysis.<sup>5</sup>

Scientific knowledge is constantly increasing, maybe 5% per year, maybe more.<sup>6</sup> Changes in policy occur more slowly, thus science will always be ahead of policy. For example, knowledge of the genetic code and the structure of DNA led not only to use of forensic DNA analysis, but also to the growing field of genomics and its use in medicine. Epigenetics is another growing area of biological knowledge that is just beginning to be incorporated in human health risk analysis. Such information is relevant to differences in susceptibility to the health effects of environmental chemicals; to date, most risk assessments have not attempted to incorporate consideration of genomics or epigenetics.

These genomic studies reveal the remarkable ability of humans and other species to modulate gene expression in a subtle and context-dependent way and thus produce biologically appropriate responses to the ever-changing internal and external stimuli living organisms experience.<sup>7,8</sup> A similarly large degree of variation manifests in the range of human behavior and resulting exposure characteristics; this variation is clearly evident in time–activity studies in children.<sup>9–11</sup>

Epigenetics refers to potentially heritable alterations in DNA structure, chromosome structure, and modifications of gene/protein expression without a change in the DNA sequence. These changes fall into three broad categories—DNA methylation, histone modifications, and non-coding microRNAs (miRNAs) that alter gene expression and nucleosome positioning.<sup>12,13</sup> Epigenetic regulation can also be influenced by environmental exposures.<sup>14–17</sup> Epigenetic alterations associated with environmental exposures may play a causal role in disease; however, as noted, the use of epigenetic data in risk assessment remains a subject of investigation, and the value of such data has yet to be determined.<sup>13–15</sup>

Given the range of human variability, how can one account for this range in the exposure and toxicity assessments in an honest way that is fair to all stakeholders? The amelioration of the scientific knowledge base underpinning risk assessment is inevitable—why would one not want to avail oneself of all this information?

Of course, some risk assessments are better than others, and some risk-based decisions are better than others. As scientists and risk assessment practitioners, we use the tools provided by toxicologists, chemists, statisticians, and others to understand the exposures and effects of environmental stressors and account for human variability in both these aspects. Our efforts inform decision-makers so that they can balance the competing interests of many stakeholders and hold the ideal of fairness paramount. In the simplest and best terms, risk assessors transform information into knowledge so that the decision-makers can act with true wisdom.<sup>18–20</sup>

Risk assessment is a predictive activity—the practitioners attempt to predict potential consequences using the knowledge at hand and the principles of probability. Risk assessments are predictive by their nature, and as such, are also probabilistic. For at least the last decade, the term “probabilistic risk assessment” has been used to refer to risk evaluations that include a statistical and quantitative treatment of either variability or uncertainty or both; however, it is important for risk assessment practitioners not to lose sight of the inherently probabilistic nature of their activities.

The culture war of the old and familiar versus the new and innovative will likely continue to intensify. There will be many examples in this book that make clear that the cultural divide in risk assessment was evident throughout its history and will likely continue.

Some of this cultural divide is due to the difference between the goals of science versus the goals of government regulation. Regulation seeks resolution of competing agendas by affecting human behavior—the pressure brought to bear on regulators for decisions is very often unrelated to science; societal or political factors may play a greater role and potentially lead to peremptory, episodic, and ill-considered actions.

Science, on the other hand, investigates and attempts to explain observed phenomena in a cautious and incremental fashion. Risk assessment is the attempt to utilize science to inform these societal decisions—hence, risk assessment uses science, but is a tool of regulation.

Scientists today stand at the threshold of a new biology—one that integrates genomics, proteomics, metabolomics, transcriptomics, epigenetics, computational methods, and systems biology in an attempt to reach a new understanding applicable to toxicology, risk assessment, medicine, and other human endeavors. This new science is recognized as the only feasible way to attempt to obtain toxicity information on the approximately 80,000 chemicals in commerce today.<sup>19</sup> However, an understanding of the predictive value of this new science for risk assessment remains elusive.<sup>21,22</sup>

The largest hurdle to progress in risk assessment remains the emphasis on consistency and the relatively slow pace with which change occurs in the regulatory practices in government. An example is the Integrated Risk Information System (IRIS), part of the National Center for Environmental Assessment of the US Environmental Protection Agency (EPA). IRIS is a collection of quantitative toxicity reference values that are used nationally and internationally for regulatory purposes. In the period from 2000 to 2009, a growing reluctance to accept new science among the IRIS leadership at that time led to a highly controversial assessment for formaldehyde and a review of the entire program by the National Research Council (NRC) in response to a request from Congress.

### **1.1.1 Formaldehyde: A Cautionary Tale**

In 1991, formaldehyde had been classified by EPA as a probable human carcinogen. A draft assessment in 2010 indicated that formaldehyde caused nasopharyngeal cancers, lymphohematopoietic cancers, and leukemias.

The 2010 draft assessment derived a draft inhalation unit risk (IUR) factor of 6.6E-05 per  $\mu\text{g}/\text{m}^3$ , a fivefold increase over the previous IUR of 1.3E-05 per  $\mu\text{g}/\text{m}^3$ . An IUR is the cancer risk associated with an air concentration of 1  $\mu\text{g}/\text{m}^3$ . Formaldehyde is produced by the body as an essential metabolite of serine, glycine, methionine, and choline.<sup>23</sup> The normal concentration in human breath ranges up to 2  $\mu\text{g}/\text{m}^3$ , and thus, according to the 2010 draft assessment, the calculated risk from this normal concentration would be 1.4 in 10,000, above the regulatory threshold of 1 in 10,000.<sup>24</sup>

The NRC review panel was highly critical of the IRIS formaldehyde review, claiming that the document failed to support a link with leukemias and respiratory cancers. The panel also criticized the methods used, noting “the assessment was not prepared in a and logically consistent fashion, lacks clear links to an underlying conceptual framework and does not sufficiently document methods and criteria used to identify evidence for selecting and evaluating studies.”<sup>25,26</sup>

Fallout from the formaldehyde assessment included several Congressional hearings to examine the IRIS program and an additional NRC review to assess the scientific and procedural merits of changes planned by EPA and to suggest modifications as appropriate.<sup>26</sup>

EPA’s IRIS program has embarked on another formaldehyde assessment but a draft has yet to be released. A workshop was held in April 2014 to discuss the scientific issues with stakeholders. Very recent epidemiologic and mechanistic studies are available. A link between formaldehyde and leukemias remains controversial, with well-regarded scientists on both sides of the issue.<sup>27-31</sup> In March of 2019, EPA postponed the release of a new formaldehyde assessment, and the outcome remains uncertain.

### **1.1.2 A Future Look Back**

One wonders if risk assessment practitioners in 2100 and later will characterize today’s regulatory risk assessors as Luddites, much as we think of the naysayers who protested the building of the Liverpool–Manchester railroad in 1825:

the railway would prevent cows grazing and hens laying. The poisoned air from the locomotives would kill birds as they flew over them and render the preservation of pheasants and foxes no longer possible. There would no longer be any use for horses; and if the railways extended, the species would become extinguished, and oats and hay would be rendered unsalable commodities.<sup>32</sup>

How similar are the attitudes of today’s regulators toward this new science? In the fullness of time, how will history judge modern society and the risk a with regard to their open-mindedness and acceptance of new science. As a society, we cannot turn back the clock, no matter how much we might long for a simpler and less complex time. Science and technology have changed the world in both large and small ways, and risk assessment is the best decision tool to apportion the burdens of the technology we all enjoy in a democratic manner.

## 1.2 KNOWLEDGE VERSUS FEAR: THE PRECAUTIONARY PRINCIPLE AND UNINTENDED CONSEQUENCES

In 1980, under Public Law 96-528 passed by the US Congress, the National Research Council of the National Academies of Sciences (NAS) undertook an effort to strengthen the reliability of and objectivity of the scientific assessment underlying the federal regulatory policies on carcinogens and other public health hazards. The report produced by the NRC was titled *Risk Assessment in the Federal Government: Managing the Process*.<sup>33</sup> When released in 1983, this book had a red cover and came to be known as the “Red Book.”

Carcinogens were a focus of the “Red Book”, likely because of the fear of cancer ingrained in western society.<sup>34</sup> For many years, treatments for cancer were horrific and generally disfiguring—if they worked at all.<sup>35</sup> This fear is reflected in the adoption of the Delaney Clause by the US Congress in 1958 that states no food additive that has been shown to induce cancer in man or experimental animals can be considered safe.<sup>36</sup>

The precautionary principle is an example of the ethics of intention in risk assessment and was created to encourage policies that protect human health and the environment in the face of uncertain risks. The precautionary principle was first given voice in the Rio Declaration of 1992:

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.<sup>37</sup>

The dictum of better safe than sorry might sound like good advice, but acting before sufficient information is available to support the decision or failing to consider all the available information may actually make matters worse. The precautionary principle is intended to address scientific uncertainty and to act, when needed, despite this uncertainty. This underlying belief is that such an approach is needed because scientific evidence will always be incomplete.

However, many who apply the precautionary principle act out of fear and the perception that “something needs to be done right away.” The actions intended by the precautionary principle should be in proportion to the scope of the problem. When actions are taken in haste, the application of the precautionary principle runs head-on into the law of unintended consequences. Chapter 8 will provide much additional discussion.

The prominent role given risk assessment by government agencies and international bodies over the past 20 years confirms that, as a policy, societal decisions are best served by the unbiased application of scientific knowledge. As a tool of these decisions, risk assessment occupies the interface between science and policy. In the next section, the history of risk assessment in the United States will be examined in detail.

## 1.3 THE HISTORY OF ENVIRONMENTAL RISK ASSESSMENT IN THE UNITED STATES

In 1969, the 91st US Congress enacted the National Environmental Protection Act (NEPA), and President Richard M. Nixon signed the Act into law on January 1, 1970.

NEPA requires that every agency in the executive branch of the United States government take steps to implement the policies set forth in the Act. NEPA created the Council on Environmental Quality in the Executive Office of the President with the responsibility of ensuring that other federal agencies met their obligations under NEPA.

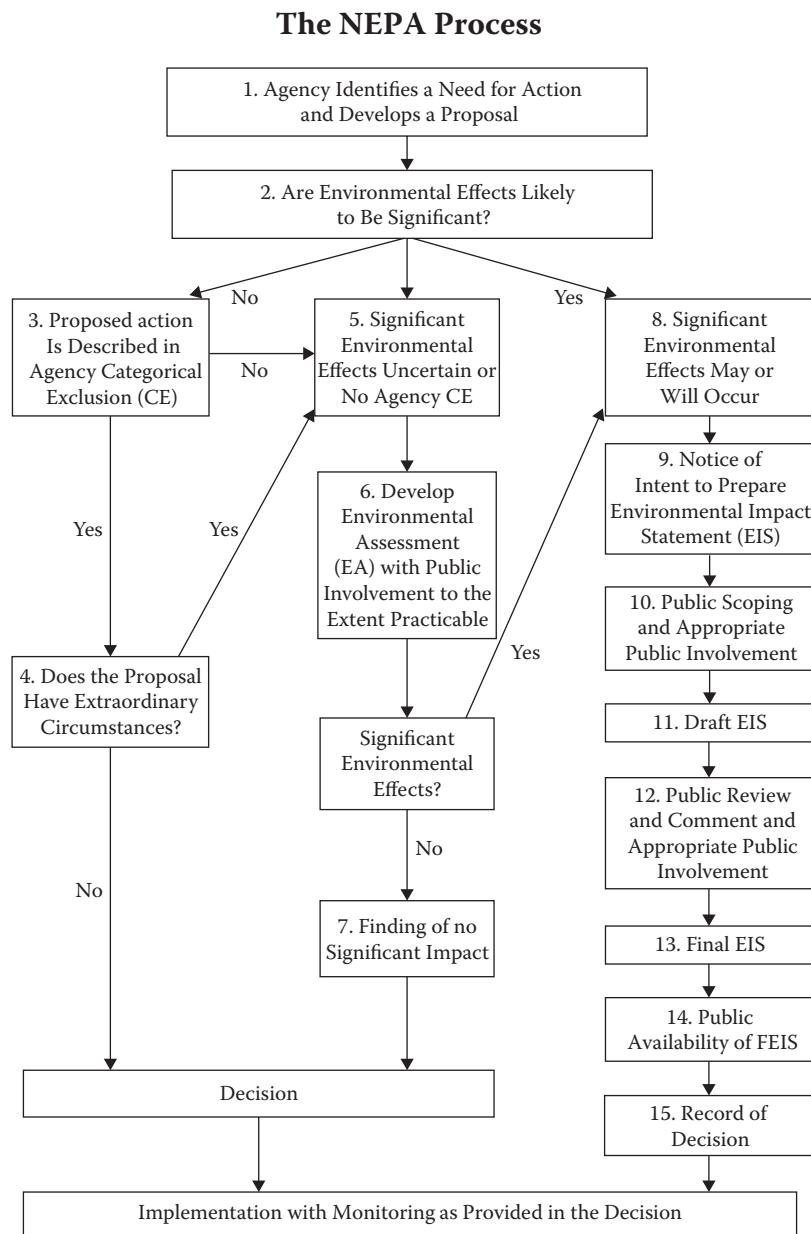
### 1.3.1 Risk Assessment under NEPA

The NEPA process involved evaluation of the environmental impact of any proposed action. Some actions, such as minor facility renovations or improvement of existing hiking trails were categorically excluded from the process. Actions without a categorical exclusion would undergo an environmental assessment, the results of which would be reported in an environmental impact statement. Section 101 of the Act conveys the ambition and desire for protection of the environment:

The Congress, recognizing the profound impact of man's activity on the interrelations of all components of the natural environment, particularly the profound influences of population growth, high-density urbanization, industrial expansion, resource exploitation, and new and expanding technological advances and recognizing further the critical importance of restoring and maintaining environmental quality to the overall welfare and development of man, declares that it is the continuing policy of the Federal Government, in cooperation with State and local governments, and other concerned public and private organizations, to use all practicable means and measures, including financial and technical assistance, in a manner calculated to foster and promote the general welfare, to create and maintain conditions under which man and nature can exist in productive harmony, and fulfill the social, economic, and other requirements of present and future generations of Americans.

(42 USC § 4331)<sup>38</sup>

Figure 1.1 shows a schematic for the NEPA process. Box 6 in the middle of the diagram refers to “Environmental Assessment.” A stated policy goal of NEPA is to “attain the widest range of beneficial uses of the environment without degradation, risk to health or safety, or other undesirable and unintended consequences.”<sup>38</sup> This is likely the first explicit mention of environmental risk assessment by the US government. Hence, the “Red Book,” as the first risk assessment document of the United States government, was necessary for implementation of NEPA.



**Figure 1.1** Schematic of the NEPA process. Box 6 in the middle of the diagram mentions “Environmental Assessment.” This is the first mention of anything related to environmental risk assessment from the US government.

### 1.3.2 The Events of the Late 1960s Facilitated the Passage of NEPA

NEPA was passed by the Senate in a unanimous vote on July 10, 1969 and passed by the House of Representatives by a vote of 372–15 on September 23, 1969. Clearly, NEPA received bipartisan support.

The American mindset in the late 1960s provided the backdrop leading up to the passage of such a far-reaching Act as NEPA. Indeed, the passage of NEPA today seems unlikely, and the history is well worth our attention.

On March 18, 1968, presidential candidate Robert F. Kennedy spoke at the University of Kansas as follows:

Too much and too long, we seem to have surrendered community excellence and community values in the mere accumulation of material things. Our gross national product ... if we should judge America by that—counts air pollution and cigarette advertising, ... It counts the destruction of our redwoods and the loss of our natural wonder in chaotic sprawl ... the gross national product does not allow for the health of our children, the quality of their education, or the joy of their play. It does not include the beauty of our poetry or the strength of our marriages, the intelligence of our public debate or the integrity of our public officials. It measures neither our wit nor our courage; neither our wisdom nor our learning; neither our compassion nor our devotion to our country; it measures everything, in short, except that which makes life worthwhile. And it tells us everything about America except why we are proud that we are Americans.<sup>†</sup>

Two notable events in 1968 united political will and likely had bearing on the enactment of NEPA. These events were:

- April 4, 1968—Dr. Martin Luther King Jr. was assassinated in Memphis.
- June 6, 1968—Robert F. Kennedy was assassinated in Los Angeles.

On December 13, 1968, Garrett Hardin published his famous article “The Tragedy of the Commons” in *Science*.<sup>39</sup> Hardin wrote:

The rational man finds that his share of the cost of the wastes he discharges into the commons is less than the cost of purifying his wastes before releasing them. Since this is true for everyone, we are locked into a system of “fouling our own nest,” so long as we behave only as independent, rational, free-enterprisers ... but the air and waters surrounding us cannot be readily fenced, and so the tragedy of the commons as a cesspool must be prevented by different means, by coercive laws or taxing devices that make it cheaper for the polluter to treat his pollutants than to discharge them untreated.<sup>39</sup>

In 1969, two environmental disasters occurred. These also likely facilitated the passage of NEPA.

- January 31, 1969—an offshore oil well near Santa Barbara, California blew out, spilling 235,000 gallons of oil that covered 30 miles of beach with tar.

<sup>†</sup> This speech, from March 18, 1968, can be heard in its entirety on YouTube at [www.youtube.com/watch?v=z7-G3PC\\_868](https://www.youtube.com/watch?v=z7-G3PC_868).

- June 22, 1969—the Cuyahoga River in downtown Cleveland burst into flames five stories high from chemical and oil pollution.

With the passage and signing of NEPA on January 1, 1970 the practice of environmental risk assessment was first codified into law.

## 1.4 HOW MUCH RISK IS ENOUGH?

The Occupational Safety and Health Act was also passed in 1970, and established the Occupational Safety and Health Administration (OSHA). OSHA based its early regulatory decisions on whether or not a hazard was identified—a qualitative criterion. In 1978, the American Petroleum Institute challenged OSHA's benzene lifetime permissible exposure limit. This case went all the way to the Supreme Court. The court ruled that OSHA must establish that the chemical poses a “significant” risk before establishing a standard. The court wrote:

Some risks are plainly acceptable and others are plainly unacceptable. If for example, the odds are one in a billion that a person will die from cancer by taking a drink of chlorinated water, the risk clearly could not be considered significant. On the other hand, if the odds are one in a thousand that regular inhalation of gasoline vapors that are 2 percent benzene will be fatal, a reasonable person might well consider the risk significant and take the appropriate steps to decrease or eliminate it.<sup>40</sup>

OSHA chose a risk level of  $10^{-3}$  or “one in a thousand” as an appropriate standard for the workplace. The court identified acceptable risk as somewhere in the million-fold risk range from “one in a billion” to “one in a thousand.” OSHA ended up choosing  $10^{-3}$  as an acceptable risk, the upper end of the range stated by the court.

In 1958, the US Congress passed the Delaney Clause to the Food, Drug and Cosmetic Act of 1938. This clause banned the use in food of “any chemical additive found to induce cancer in man, or, after tests, induce cancer in animals.” In 1959, just after the passage of the Delaney Clause, there occurred the Thanksgiving Day turkey scare because Arthur Sherwood Flemming, then Secretary of Health, Education, and Welfare, announced publicly in early November that aminotriazole, a weed killer that causes thyroid cancer in laboratory rats, had been discovered in some grocery store cranberries. Flemming asked the National Cancer Institute (NCI) to help establish a “safe” level of carcinogens in food. The NCI used a definition of safety of “one in a hundred million” or  $10^{-8}$  from a 1961 publication by Nathan Mantel, a biostatistician at NCI. The purpose of the article was to develop guidelines for the number of animals required to establish the safety of a chemical.<sup>40</sup>

The US Food and Drug Administration (FDA) approved diethylstilbestrol (DES) in 1954 for use as a growing/finishing food additive for cattle. In 1971, a

report appeared in the *New England Journal of Medicine* about the occurrence of vaginal tumors in young women born to mothers who had received diethylstilbestrol during pregnancy.<sup>41</sup> This discovery also increased the fear of carcinogens in food.

Because of the economic impact of the Thanksgiving Day cranberry scare, FDA felt it had the ability to define a “safe” level of carcinogens in food—in direct contradiction to the Delaney Clause. FDA used Mantel’s value of one in a hundred million ( $1 \times 10^{-8}$ ) in its proposed rule in the Federal Register in 1973, but increased this level to “one in a million” ( $1 \times 10^{-6}$ ) in the 1977 Final Rule. There was also considerable controversy leading up to FDA’s ban of DES for use in cattle production in 1979.<sup>42-44</sup>

The Proposed Rule for the National Contingency Plan for Oil and Hazardous Substances identified a risk range of  $10^{-7}$  to  $10^{-4}$  as acceptable for Superfund cleanups. When the Final Rule was promulgated in 1990, the risk range was changed to  $10^{-6}$  to  $10^{-4}$ .

EPA clarified the use of  $10^{-4}$  as the upper end of the target risk range in a memorandum in 1991 titled *Role of the Baseline Risk Assessment in Remedy Selection*.<sup>45</sup> This guidance document identified  $10^{-4}$  as a “soft brightline” as follows:

The upper boundary of the risk range is not a discrete line at  $1 \times 10^{-4}$ , although EPA generally uses  $1 \times 10^{-4}$  in making risk management decisions.<sup>45</sup>

Although this memorandum attempted to introduce flexibility into the Superfund remedy selection process, risk managers may not always be aware of this flexibility.

In 1998, EPA’s Assistant Administrator of the Office of Solid Waste and Emergency Response (OSWER), Tim Fields, released a memo titled *Approach for Addressing Dioxin in Soils at CERCLA and RCRA Sites*.<sup>46</sup> It stated:

Based on presently available information, and using standard default assumptions for reasonable maximum exposure scenarios, the upper-bound lifetime excess cancer risk from residential exposure to a concentration of 1 ppb dioxin is approximately  $2.5 \times 10^{-4}$ , which is at the higher end of the range of excess cancer risks that are generally acceptable at Superfund sites. The calculated upper-bound excess cancer risk associated with a lifetime commercial/industrial exposure to 5 ppb, or the lower end of the range recommended for commercial/industrial soils, is approximately  $1.3 \times 10^{-4}$ , which is also within the CERCLA [Comprehensive Environmental Response, Compensation and Liability Act] risk range.<sup>46</sup>

Hence, the upper end of the CERCLA risk range of  $1 \times 10^{-4}$  could be interpreted as somewhere between  $10^{-4}$  and  $10^{-3}$ . In essence, this represents a return to the Supreme Court’s definition of acceptable risk as “one in a thousand” from the benzene decision.

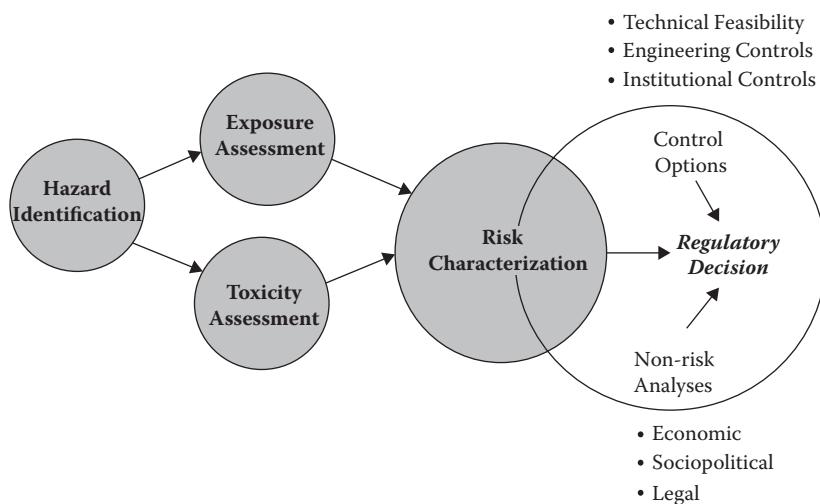
## 1.5 RISK ASSESSMENT RECOMMENDATIONS FROM THE US NATIONAL ACADEMIES OF SCIENCES AND OTHER GOVERNMENT ENTITIES

### 1.5.1 The Environmental Risk Assessment Paradigm as Defined in *Risk Assessment in the Federal Government: Managing the Process*, the National Research Council's 1983 "Red Book"

The "Red Book" defines risk assessment as the use of the factual base to define the health effects of exposure of individuals and populations to hazardous materials and situations. Risk assessment contains the following four steps:

- **Hazard identification**—whether a chemical or other stressor can be causally linked to a particular adverse health outcome;
- **Dose–response assessment**—the relationship between the magnitude of exposure and the likelihood of occurrence of the identified hazards;
- **Exposure assessment**—the extent, frequency and magnitude of human contact with the chemical or stressor;
- **Risk characterization**—a description of the nature and magnitude of the risk associated with the situation being considered, including both qualitative and quantitative risk descriptors and the uncertainties attendant in these descriptors.

Figure 1.2 shows this four-part scheme along with other factors that influence environmental decisions.



**Figure 1.2** Schematic of the Risk Assessment paradigm from the "Red Book" with non-risk decision factors also shown. As noted in the narrative, the "Red Book" highlighted the need for separation between risk assessment and risk management.

In addition to setting out the paradigm shown in Figure 1.2, the “Red Book” strongly advocated for the separation of risk assessment from risk management. The first recommendation made was as follows, and occurs on page 151:

Regulatory agencies should take steps to establish and maintain a clear conceptual distinction between assessment of risks and the 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.<sup>33</sup>

Value judgments are needed to weigh the tradeoffs between the potential for adverse health consequences and economic, political, and social considerations. These judgments about non-science issues are the proper function of government in a democratic society. The clear motivation for this recommendation was to place a firewall between these value judgments and the scientific information and science-policy judgments that are the purview of the risk assessment. Above all, science requires integrity, and the writers of the “Red Book” foresaw and attempted to forestall the potential for economic or political factors of risk management to affect the scientific considerations of risk assessment.

The second recommendation on page 153 was:

Before an agency decides whether a substance should or should not be regulated as a health hazard, a detailed and comprehensive written risk assessment should be prepared and made publicly accessible. This written assessment should clearly distinguish between the scientific basis and the policy basis for the agency’s conclusions.<sup>33</sup>

A written assessment would permit stakeholders to voice agreement or disagreement in an informed manner. The selected risk management alternative will be based on both science and policy considerations—it is highly appropriate for the regulated community or other stakeholders to disagree with the interpretation of the science, the policy considerations, or the value judgments. However, the scientific information, the data upon which the risk assessment is based, is generally not up for debate.

The third recommendation was for review of risk assessments by an independent scientific panel with members selected for their scientific and technical competence. The “Red Book” recommended that panel members be selected from the private and public sectors, universities and government research agencies. Personnel from the agency conducting the risk assessment or employees of an entity with a substantial interest, economic or other, in the societal decision should not be members of the scientific review panel.

The NRC went on to recommend that inference guidelines be developed to create a degree of uniformity in the risk assessment process. The “Red Book” specifically suggested that guidelines be developed for cancer risk assessment and for exposure assessment. In addition, inference guidelines should be periodically updated and revised. The writers of the “Red Book” were wise in that they were aware of the conflict between old and new and they recognized the need for both consistency and progress.

### **1.5.2 The Clean Air Act (CAA), EPA's 1989 Risk Assessment Guidance for Superfund (RAGS), and Other Guidelines**

In 1970, the US Congress passed the Clean Air Act (CAA) regulating emissions from both mobile and stationary sources of air pollution. EPA was authorized to establish National Ambient Air Quality Standards to protect public health and welfare. Before 1990, risk assessment was used to establish standards for six common classes of pollutants—sulfur oxides, particulate matter, carbon monoxide, nitrogen oxides, hydrocarbons, and photochemical oxidants such as ozone and formaldehyde. The 1990 Clean Air Act Amendments authorized EPA to regulate the emissions of 189 toxic chemicals that were considered carcinogenic, mutagenic, or toxic to reproduction or development. Section 112 of the CAA required EPA to set emission standards for hazardous air pollutants to protect public health with “an ample margin of safety.” The regulatory standards were not based on risk, but rather the maximum achievable control technology (MACT).<sup>47</sup> Hence, EPA interpreted Section 112 to place technology-based regulation in a primary role and health-based risk assessment in a secondary role.

The National Resources Defense Council (NRDC) sued EPA in the District of Columbia Circuit Court of Appeals, seeking to compel the agency into a zero emissions policy for air pollutants considered carcinogenic. In the choice of technology-based regulation, EPA had adopted a generic method for determining whether the emissions of a specific pollutant would meet the bar of an “ample margin of safety.” NRDC argued that this decision rendered all potential carcinogens as having an “ample margin of safety.” In 1987, the court upheld the NRDC claim, indicating that the intent of Section 112 was protection of public health and that EPA’s generic method was inadequate.

In the interim, EPA was active in implementing the recommendation in the “Red Book” for development of uniform inference guidelines. In 1986, EPA’s Risk Assessment Forum released the first version of the *Guidelines for Carcinogen Risk Assessment*, the *Guidelines for Mutagenicity Risk Assessment*, and the *Guidelines for Human Health Risk Assessment of Chemical Mixtures*.<sup>48–50</sup> In 1989, EPA’s Office of Solid Waste and Emergency Response that regulates under the Comprehensive Environmental Response, Compensation and Liability Act, more commonly known as Superfund, produced comprehensive guidance on the application of risk assessment to hazardous waste sites—*Risk Assessment Guidance for Superfund (RAGS), Part A*.<sup>51</sup> Although, in the years to come, parts B–F of *Risk Assessment Guidance for Superfund* were released, this 1989 document has become commonly known as “RAGS.” The generic quantitative risk equations for carcinogens and non-carcinogens are shown in Box 1.1.

The 1990 Amendments to the Clean Air Act rewrote Section 1212 to enhance the role of risk assessment. Rather than assuming that the MACT would result in an acceptable level of risk, the 1990 Amendments codified a tiered approach such that a risk assessment would always be performed; if the MACT standard resulted in a risk of greater than one in a million for the most highly exposed individual, then a residual risk standard would be also developed. Hence, risk assessment would play a central role in the Clean Air Act regulation.

**BOX 1.1 GENERIC RISK EQUATIONS FROM RAGS<sup>32</sup>****Carcinogenic Risk**

$$\text{Risk} = \text{CSF} \times (\text{CR} \times \text{ED} \times \text{EF}) / (\text{BW} \times \text{AT}) \quad [1.1]$$

**Non-cancer Hazard Quotient**

$$\text{HQ} = (1/\text{RfD}) \times (\text{CR} \times \text{ED} \times \text{EF}) / (\text{BW} \times \text{AT}) \quad [1.2]$$

where CSF = Cancer Slope Factor

RfD = Reference Dose

HQ = Hazard Quotient

CR = Contact Rate

ED = Exposure Duration

EF = Exposure Frequency

BW = Body Weight

AT = Averaging Time

The *Carcinogenic Risk* is expressed as a unitless probability; the assumption is that the dose–response relationship for carcinogens is linear in the low dose region and even one molecule of a substance poses some risk, albeit vanishingly small. The *Hazard Quotient* (HQ) is the ratio between the reference dose (RfD) and the average daily dose (ADD); an HQ value less than one indicates that it is unlikely even for sensitive populations to experience adverse health effects.

From 1984 until 1992, EPA developed three versions of uniform guidelines on exposure. *Final Guidelines for Exposure Assessment* was published in the Federal Register in 1992.<sup>52</sup> These guidelines were detailed and specific, and distinguished between various types of dose terms (Box 1.2). The recognition of internal dose and

**BOX 1.2 DOSE TERMS USED IN EPA'S 1992 EXPOSURE GUIDELINES<sup>50</sup>**

**Exposure Dose**—contact of a chemical with the outer boundary of a person, e.g., skin, nose, mouth;

**Potential Dose**—amount of chemical contained in material ingested, air inhaled, or applied to the skin;

**Applied Dose**—amount of chemical in contact with the primary absorption boundaries, e.g., skin, lungs, gastrointestinal tract) and available for absorption;

**Internal Dose**—amount of a chemical penetrating across an absorption barrier or exchange boundary via physical or biological processes;

**Delivered Dose**—amount of chemical available for interaction with a particular organ or cell.

delivered dose enabled the use in risk assessment of physiologically based pharmacokinetic (PBPK) models that were commonly used in pharmacology and drug development. These models are also known as Absorption/Distribution/Metabolism/Excretion (ADME) models, and will be discussed briefly at the end of this chapter and at length in Chapters 3 and 5.

### **1.5.3 *Science and Judgment in Risk Assessment: The National Research Council's 1994 "Blue Book"***

Part of the 1990 Clean Air Act Amendments directed EPA to engage the National Academies of Sciences to review EPA's methods for estimating carcinogenic potency of chemicals and methods for estimating exposure to both hypothetical and actual maximally exposed individuals. *Science and Judgment in Risk Assessment* was released by the National Research Council in 1994 and was known as the "Blue Book."<sup>18</sup>

One of the major observations of the "Blue Book" was the desire of most people to "understand whether and how much their exposures to chemicals threaten their health and well-being."<sup>19</sup> The "Blue Book" also noted some common themes that cut across various aspects of risk assessment and suggested strategies for improvement. These common themes were:

- the use of default options or values;
- validation of data, models and methods;
- information and data needs;
- accounting for uncertainty;
- dealing with variability;
- aggregation of risks.

#### **1.5.3.1 *Epa's Use of Defaults per the "Blue Book"***

The "Blue Book" concluded that the practice of using default options was reasonable when there is doubt about the choice of values or models. Essentially, the NRC concluded that the use of defaults was a necessary evil. Regarding Section 112 of the CAA, the "Blue Book" noted that scientific disagreements fostered both concern and skepticism about risk assessment, and the use of defaults could potentially ameliorate this situation.

The "Blue Book" also indicated that the scientific or policy basis of each default should be clearly articulated. Last, the "Blue Book" called for a clear and transparent process for choosing to depart from default options that includes full public discussion and peer participation by the scientific community.

#### **1.5.3.2 *Validation of Models, Methods, and Data***

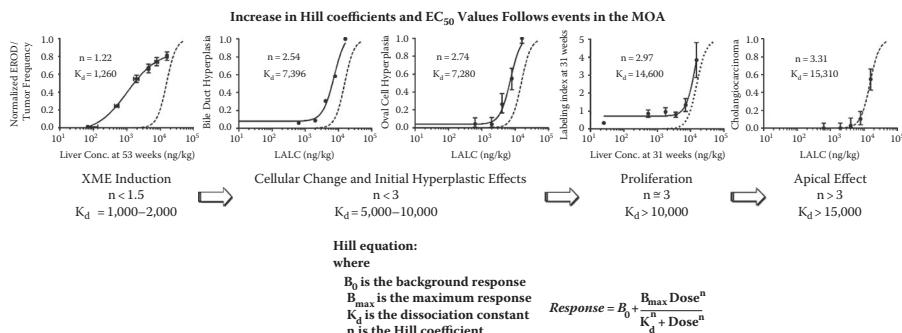
The "Blue Book" called on EPA to establish the predictive accuracy of the methods and models used in risk assessment, with greatest priority given to the scientific basis of the default options. Regarding exposure models and data, the "Blue Book"

indicated EPA should consider both population mobility and time–activity relationships. Regarding the toxicity assessment, the “Blue Book” indicated that EPA should continue to use laboratory animal bioassay data as needed, but should not automatically assume that chemicals that cause cancer in animals necessarily also do so in humans.

In an almost prescient fashion, the “Blue Book” discussed mode of action (MOA) without using the term. MOA has come to be central to dose–response assessment. The term MOA was first used in the 1990s as a means of providing a structured approach to understanding the process of cancer induction in test animals and the relevance of this process to humans.<sup>53</sup> MOA is described in Table 1.1, and Figure 1.3

**Table 1.1 Common Concepts and Terms in Risk Assessment**

Concept	Definition
Cancer Risk	In RAGS, EPA indicates that the presumption of a threshold for carcinogenic chemicals is inappropriate. Hence, any non-zero dose will provide some quantifiable prediction of the likelihood of cancer. The methodology underlying this type of risk assessment is to obtain a measure of the statistical upper bound of the slope within the low dose region of the presumed dose–response relationship. The slope represents the linear relationship between risk and dose and is in the units of risk per dose.
Cancer Slope Factor	RAGS defines this as a plausible upper bound estimate of the probability of cancer per unit intake of a chemical over a lifetime. The most common unit of the CSF is the reciprocal of mg chemical per kilogram body weight per day or (mg/kg/d)–1.
Hazard Quotient	The ratio of a single substance exposure level over a specified time period (e.g., chronic) to a reference dose for that substance derived from a similar exposure period.
Hazard Index	The sum of more than one hazard quotient for multiple substances and/or multiple exposure pathways. The HI is calculated separately for chronic, subchronic, and shorter-duration exposures.
Reference Dose	An estimate (with uncertainty spanning perhaps an order of magnitude or greater) of a daily exposure level for the human population, including sensitive subpopulations, that is likely to be without an appreciable risk of deleterious effects during a lifetime.
Mode of Action	A sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in the formation of cancer or other adverse effects.
Key Event	An empirically observable causal precursor step to the adverse outcome that is itself a necessary element of the mode of action. Key events are required events for the MOA, but often are not sufficient to induce the adverse outcome in the absence of other key events.
Associative Event	Biological processes that are themselves not causal necessary key events for the MOA, but are reliable indicators or markers for key events. Associative events can often be used as surrogate markers for a key event in a MOA evaluation or as indicators of exposure to a xenobiotic that has stimulated the molecular initiating event or a key event.
Modulating Factor	A biological factor that modulates the dose–response behavior or probability of inducing one or more key events or the adverse outcome.



**Figure 1.3** Mode of action for the production of cholangiocarcinoma in female Sprague-Dawley rats by 2,3,7,8-tetrachlorodibenzodioxin (TCDD). Tumor induction involves the key events of induction of xenobiotic metabolizing enzymes (XME), cellular and hyperplastic tissue changes, cell proliferation, and the apical event of tumors. Cholangiocarcinoma is a tumor that arises from liver stem cells likely residing near the bile ducts. The Hill model shown at the bottom of the figure was used to model the dose response of all key events and tumor occurrence. Higher values of the dissociation constant indicate an effect with a higher threshold. Higher values of the Hill coefficient indicate a more steeply rising dose response. TCDD binds to and activates the aryl hydrocarbon receptor, producing changes in gene expression including induction of cytochrome p450 1A1 (CYP1A1), as shown in the left-hand panel. The later effects of hyperplasia and proliferation occur at higher thresholds and with a steeper dose response. The apical effect of cholangiocarcinoma has the highest threshold and steepest response of all the effects shown.

shows the use of MOA to determine human relevance of key events. The “Blue Book” indicated on page 141 that animal tumor data should not be used as the exclusive evidence to classify chemicals as carcinogenic to humans if “the mechanisms operative in laboratory animals are unlikely to be operative in humans.”<sup>18</sup>

### 1.5.3.3 Information and Data Needs

The “Blue Book” pointed out that EPA had not defined the types, quantities, and qualities of data needed for risk assessment. There should also be standards for the collection of environmental data to ensure that the data collected support the risk assessment to the greatest extent possible. Indeed, this recommendation led to the development of data quality objectives.

Because the “Blue Book” was written to address issues regarding the Clean Air Act, much of the document is relevant to air rather than other environmental media. The Toxic Release Inventory (TRI) Program is a database of material released during manufacturing and storage; basically, the amounts of chemicals in finished products are subtracted from the amounts purchased and held in inventory, and this difference is assumed to be released. If available, direct measurements of releases may also be used. The information was self-reported by the regulated entity, and EPA had no way to check on the accuracy of the information.

In 1992, Amoco, EPA, and the Commonwealth of Virginia agreed to conduct a multi-media assessment of releases at the Amoco refinery at Yorktown, Virginia.<sup>54</sup> One purpose of this study was to assess the accuracy of TRI data, and the study revealed that the TRI data were not accurate. This fact is hardly surprising given that the preparation of TRI reports did not generate revenue for the regulated entity; since the regulators at EPA had no way to check, accuracy was sacrificed in favor of timely completion of the paper work for regulatory compliance.

#### **1.5.3.4 Accounting for Uncertainty**

EPA did not account for the uncertainties inherent in risk assessment in either a qualitative or quantitative fashion. Hence, the “Blue Book” suggested that EPA develop guidelines for uncertainty analysis and the contributions of the various sources of uncertainty to the total uncertainty in a risk assessment.

Many EPA risk assessments were presented as a single point-estimate of risk—the entire risk assessment was boiled down to a single number, hardly a nuanced or transparent presentation. In 1992, F. Henry (Hank) Habicht II, the Deputy Administrator of EPA from 1989 until 1992, wrote a memorandum, *Guidance on Risk Characterization for Risk Managers and Risk Assessors*.<sup>55</sup> Habicht wrote quite eloquently as follows:

Specifically, although a great deal of careful analysis and scientific judgment goes into the development of EPA risk assessments, significant information is often omitted as the results of the assessment are passed along in the decision making process. Often, when risk information is presented to the ultimate decision-maker and to the public, the results have been boiled down to a point estimate of risk. Such ‘short hand’ approaches to risk assessment do not fully convey the range of information considered and used in developing the assessment. In short, informative risk characterization clarifies the scientific basis for EPA decisions, while numbers alone do not give a true picture of the assessment.<sup>55</sup>

The “Blue Book” included the Habicht memo in its entirety as Appendix B. This memo was the first official statement from EPA that the standard operating procedure for risk assessment failed to convey the full picture of risks, especially when the results of a complex and time-consuming assessment were transmitted to decision-makers and the public as a single number.<sup>56</sup>

#### **1.5.3.5 Understanding and Dealing with Variability**

One size fits all? This maxim is patently untrue for most aspects of human life, with the possible exception of tube socks. For ski boots and fishing waders, the lack of veracity is obvious. The idea of human variation is captured most eloquently of all in the quotation from Shakespeare’s *Hamlet* at the beginning of this chapter.

Before 1994, EPA had chosen to regulate based on estimated risk to the maximally exposed individual—the worst-case scenario in which a hypothetical individual experienced a 70-year, 24-hour per day exposure to the maximum estimate of the long-term average concentration. The “Blue Book” indicated that this could be used as a bounding estimate, but was a poor choice for the basis of regulation. Instead, the suggestion was to select an individual at the 90th percentile of exposure or above as a reasonable “high-end” estimate.

The “Blue Book” also recommended that EPA begin to use frequency distributions of both exposure and susceptibility to express the range of human heterogeneity and incorporate a range of values from these distributions to obtain a set of risk estimates more informative than a single-point estimate.

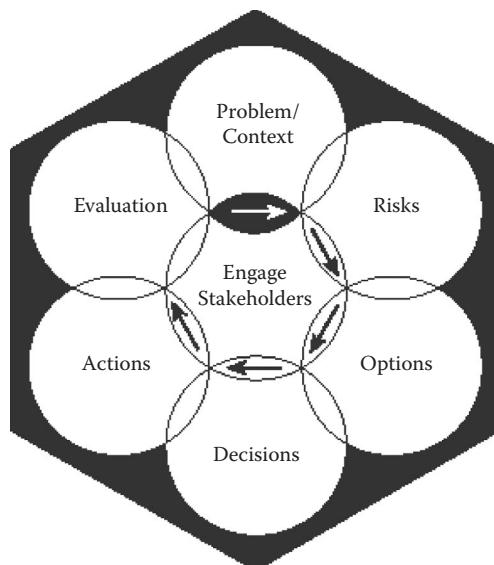
#### **1.5.3.6 Aggregation of Risks**

The “Blue Book” also called for consideration of how to account for separate but related causes of risk such as the occurrence of multiple chemicals from a single source. Aggregation of both exposures and effects was discussed. These concepts are still being debated today as questions arise about synergy of effects and whether multiple sub-threshold exposures to chemicals operating via a common mode of action or common adverse effect should be considered in terms of additivity of dose or additivity of effect.<sup>57</sup>

#### **1.5.4 Framework for Environmental Risk Management: The 1997 Federal Commission Report**

The “Blue Book” also advocated the formation of a joint Presidential/Congressional Commission on Risk Assessment and Risk Management. The 1997 report of this commission, *Framework for Environmental Health Risk Management*, dealt with risk management to a much greater extent than risk assessment and provided yet another diagram of the interface between the risk assessment and risk management (Figure 1.4).<sup>20</sup> One of the major points made by the commission report was that inclusion of various stakeholders in the decision process generally led to better decisions, and that government officials and other risk managers should take into account the economic, social, cultural, ethical, legal, and political ramifications of their decisions in addition to considerations of risk to human health or the environment.

In addition, the report specifically called for analysis of costs, benefits, and potential unintended consequences of environmental decisions. The report provided a controversial example. Assume a new regulation bans a commonly used but potentially carcinogenic pesticide, resulting in a significant price increase of fruits and vegetables. Those who can afford the price increase will enjoy the benefit of reduced health risks, but others who cannot afford the higher prices will suffer poorer nutrition and increased cancer risk associated with a diet low in fruits and vegetables. Below is a historical example of this disparity.



**Figure 1.4** Risk assessment/risk management framework developed by the joint Congressional/Presidential Commission in 1997.

#### 1.5.4.1 Bias and Scientific Misconduct: Another Cautionary Tale

Lake Apopka is located in central Florida, near Orlando. In the 1940s, the lake was famed for excellent largemouth bass fishing. In 1941, a levee was built in order to develop the shallow wetlands on the north side of Lake Apopka into a muck farm, the rich soil of which supported commercial growing of vegetables. In 1980, pesticides manufactured by the Tower Chemical Company were spilled in Lake Apopka. Following the spill, reproductive abnormalities were observed in male alligators in Lake Apopka.<sup>58</sup>

In 1996, Stephen Arnold, a postdoctoral fellow in the laboratory of John McLachlan at Tulane University, was the lead author on a paper in *Science* claiming that pesticides and hydroxylated PCBs that are weakly estrogenic when acting alone, but could synergize with a thousand-fold increase in potency.<sup>59</sup> The following year, John McLachlan, the senior author, retracted the article from *Science*, indicating the inability to reproduce the results.<sup>60</sup> Following an investigation, Arnold resigned from Tulane. In 2001, the Department of Health and Human Services found Steven Arnold guilty of scientific misconduct “by providing falsified and fabricated materials to investigating officials at Tulane University in response to a request for original data to support the research results and conclusions reported in the *Science* paper.”<sup>61</sup>

The general concern for endocrine disruption spurred legislative committees to accelerate their work to enact provisions for endocrine disruption into law. The Tulane results likely had an effect on pushing the Food Quality Protection Act

(FQPA) into law.<sup>62</sup> The FQPA specifically required EPA to consider exposure of children to multiple substances. The House Commerce Committee, chaired by Rep. Tom Bliley (R-Va.), wrote into the FQPA an additional tenfold margin of safety for the pesticide chemical residues to be applied for infants and children.<sup>63</sup>

Neither legislators nor EPA personnel seemed at all troubled that part of the FQPA was based on inaccurate science. One sad outcome of this chain of events is likely the dearth of fresh produce in so-called “food deserts,” low-income neighborhoods that lack an accessible grocery store; hence, the tenfold factor may have served to increase the occurrence of obesity, type 2 diabetes, and related health problems.<sup>64–66</sup>

The Federal Commission report was an attempt to persuade EPA to consider the economic aspects of risk. The report was very clear that both risk–risk and risk–benefit tradeoffs must be considered. The report included among potential adverse consequences:

- reduced property values or loss of jobs;
- environmental justice issues, such as disregard for dietary needs, preferences, or status of a particular group, or prioritizing cleanups in affluent areas;
- potential harm to the social fabric and “life” of a community by relocating people away from a highly contaminated area.

How should risk issues be balanced against economic issues? In western society, life is considered “priceless”—the reason, of course, why slavery and murder are illegal.

For risk–benefit analysis, economists have developed a measure of the worth of a human life called the value of a statistical life (VSL). The VSL is very different than the value of an actual life. The VSL can be estimated by statistical regression analysis of the wages of different occupations versus the risk of injury or death associated with the occupations. Another way to estimate the VSL is to ask people about their willingness to pay for a reduction in risk. EPA used the central estimate of \$7.4 million in 2006 dollars as the VSL for cost–benefit analysis.<sup>67</sup>

#### **1.5.4.2 Realism, Cost, and the Separation of Risk Assessment and Risk Management**

EPA’s 1992 *Final Guidelines for Exposure Assessment* describe three tiers of exposure assessment. The first tier is a preliminary evaluation to produce bounding estimates. This preliminary evaluation described in the guidelines is similar to the majority of risk assessments conducted, in that conservative assumptions are used to ensure that cleanups will be protective. The second tier of exposure assessment is the refinement of these preliminary risk descriptors by incorporation of site-specific considerations. The third tier of exposure assessment includes a probabilistic component and explicitly acknowledges human variability. The upper end of the distribution of risk should be characterized and high-end estimates of individual risk, such as the hypothetical Reasonable Maximum Exposure (RME) individual, should

fall at the 90th percentile or above. Additionally, the exposure guidelines provide a detailed and cogent discussion of uncertainty assessment that concludes:

It is fundamental to exposure assessment that assessors have a clear distinction between the variability of exposures received by individuals in a population, and the uncertainty of the data and physical parameters used in calculating exposure.<sup>68</sup>

The exposure guidelines were a prescient document, and soon after their publication, EPA Regional Offices in Denver and Philadelphia issued guidance on the appropriate use of probabilistic methods in risk assessment.<sup>69</sup>

In 1995, Administrator Carole Browner issued the far-reaching *Memorandum on EPA's Risk Characterization Program*. This memo called for disclosure of the scientific analyses, uncertainties, assumptions, and science policy choices underlying the decisions made in the course of risk assessment and risk management. The memo endorsed the core values of transparency, clarity, consistency and reasonableness (TCCR).<sup>70</sup>

The Risk Assessment Forum's 1995 *Guidance on Risk Characterization* that accompanied the Browner memo pointed out the importance of distinguishing between variability and uncertainty. Similar to the Habicht memo, the *Guidance on Risk Characterization* also took the agency risk assessors to task for oversimplifying the results of their risk assessments:

Often risk assessors and managers simplify discussion of risk issues by speaking only of the numerical components of an assessment. ... However, since every assessment carries uncertainties, a simplified numerical presentation of risk is always incomplete and often misleading.<sup>56</sup>

In December 2000, the Science Policy Council of the EPA issued the *Risk Characterization Handbook*. This document also echoed the message of the Habicht memo, pointing out how risk characterization communicates the results of the risk assessment, including key findings, uncertainties, strengths, and weaknesses of the analysis, to decision-makers and stakeholders in a conscious, deliberate, and transparent way. This document also emphasized the core values of TCCR.<sup>71</sup>

#### **1.5.4.3 EPA Addresses Variability and Uncertainty**

In the spring of 1997, EPA Deputy Administrator Fred Hansen released a memorandum, *Policy for Use of Probabilistic Analysis in Risk Assessment*. According to the policy statement of the memorandum, probabilistic analysis techniques, “given adequate supporting data and credible assumptions, can be viable statistical tools for analyzing variability and uncertainty in risk assessments.”<sup>72</sup> Along with this policy statement, the Risk Assessment Forum released the *Guiding Principles for Monte Carlo Analysis* that discussed 15 principles for conducting a sound probabilistic analysis. Notably, this document called for an explicit problem formulation for any such assessment.<sup>73</sup>

#### 1.5.4.4 Compounding Conservatism

EPA released the policy memo and the *Guiding Principles* document in response to calls for an increased role of science in EPA's decision-making. One of the most vocal critics of EPA's risk assessment methodology during the 1990s was Dr. David Burmaster of Alceon in Cambridge, Massachusetts. Burmaster was, frankly, a man ahead of his time and became frustrated during the early 1990s when EPA risk assessors turned a deaf ear to his requests that they consider probabilistic risk analysis.<sup>74-76</sup> As early as 1993, Burmaster was clearly aware of the culture war between old and new discussed earlier in this chapter and its effect on the practice of risk assessment. He wrote in a perspective feature in the journal *Risk Analysis*:

An unfortunate trend—created in the name of policy consistency—has replaced the science in risk assessment with simplistic policy assumptions that have the effect of making risk assessments even more conservative. Too many risk assessors with advanced degrees are being forced to use (and to defend in public) contrived and biased methodologies to conform to EPA policy guidance. These methodologies cannot be defended as good science, and they subvert the Agency's stated risk management policies aimed at protecting the public health against reasonably expected future exposures ....<sup>77</sup>

The degree of conservatism compounds dramatically for deterministic point estimates of risk constructed from upper percentiles of input parameter.<sup>78</sup>

One can actually do a very simple calculation to estimate the degree of conservatism in a risk assessment. An example is shown in Box 1.3, suggesting that the default methodology for cancer risk assessment is very conservative on a numerical basis.

#### BOX 1.3 ESTIMATING THE PERCENTILE OF CONSERVATISM IN A RISK ASSESSMENT

The basic equation we will use is:

$$\text{Risk} = \text{Exposure} \times \text{Toxicity} \quad [1.3]$$

To estimate the percentile of conservatism in a risk assessment, we will use the following equation, where P means percentile:

$$P_{\text{conservatism}} = 1 - (1 - P_{\text{exposure}}) \times (1 - P_{\text{Toxicity}}) \quad [1.4]$$

Looking back at Box 1.1, we can see that the contact rate (CR), exposure frequency (EF), and exposure duration (ED) are exposure factors that are usually set at high-end values representing the 95th percentile. Hence, the percentile of conservatism for exposure would be:

$$P_{\text{Exposure}} = 1 - (1 - 0.95) \times (1 - 0.95) \times (1 - 0.95) = 0.999875 \quad [1.5]$$

The Toxicity term we will consider is the cancer slope factor. For cancer slope factors, the 95th percentile lower confidence limit on the dose at the point of departure (POD) is currently used. Previously, the 95% upper confidence limit on the slope in the low dose region was used. Hence, the conservatism of the Toxicity term will be assumed to be 95%.

The overall percentile of conservatism can be estimated using the products of the percentiles for exposure and toxicity:

$$P_{\text{Conservatism}} = 1 - (1 - 0.999875) \times (1 - 0.95) = 0.9999375 \quad [1.6]$$

This calculated RME risk at greater than the 99.99th percentile cannot likely be distinguished from maximum risk in terms of the degree of health protectiveness or conservatism.

### 1.5.5 Circular A-4 from the Office of Management and Budget

There were other more powerful critics of EPA at that time—notably John R. Graham, then head of the Harvard School of Public Health Center. Graham later became head of the White House Office of Management and Budget (OMB). In 2003, under Graham's leadership, the OMB issued guidelines strongly advocating the use of formal quantitative uncertainty analysis for regulatory decisions with economic effects of over \$1 billion.<sup>79</sup> Circular A-4 was written by Dr. Nancy B. Beck, in 2019 appointed Deputy Assistant Administrator of EPA's Office of Chemical Safety and Pollution Prevention. Circular A-4 points out that discovery of which decision yields the greatest net societal economic benefit provides useful information to decision-makers. The methodology recommended includes analysis of risk–benefit–cost tradeoffs, even when economic efficiency is not the primary public policy objective, be applied to decisions in many areas. The document discusses three basic elements for a good regulatory analysis:

- a statement of the need for the proposed action;
- an examination of alternative actions;
- an evaluation of benefits and costs of the proposed action and any alternative actions.

Circular A-4 was an effort to provide a more reasoned alternative to the precautionary principle.

### 1.5.6 *Science and Decisions: Advancing Risk Assessment: The National Research Council's 2009 “Silver Book”*

In 2009, in response to a request from EPA, the National Research Council published this report that immediately became controversial because of the recommended approach to dose–response. Due to the burgeoning amount of scientific data,

regulators were seeking risk analyses of difficult and complex situations, including multiple chemical exposures, variation in susceptibility, cumulative risk assessment, life-cycle impacts, cost–benefit considerations, and risk–risk tradeoffs. In order to meet these demands, the report focused on recommendations to improve both the quality of the technical analysis in risk assessments and the utility of risk assessments for decision-making.

### **1.5.6.1 *Improvements in Problem Formulation***

One area of concern to the authors of the report was problem formulation, discussed at length in Chapter 2 of *Science and Decisions*. The document urged a greater focus on the upfront stages of risk assessment—planning, scoping, and problem formulation.<sup>80</sup>

The report also recommended consideration of uncertainty and variability in all phases of risk assessment. In 2001, EPA’s Superfund Program released *Risk Assessment Guidance for Superfund (RAGS) Volume III—Part A: Process for Conducting Probabilistic Risk Assessment* that actively discouraged the application of probabilistic methods to dose–response assessment.<sup>81</sup> Of course, including variation in exposure only in a probabilistic risk assessment gives only part of the picture.<sup>5</sup> Hence, *Science and Decisions* encouraged inclusion of quantitative estimates of uncertainty and variability at all key computational steps in a risk assessment.

### **1.5.6.2 *Replacing Defaults with Data***

Back in 1983, the “Red Book” recommended the use of uniform inference guidelines, as discussed earlier in this chapter. This recommendation resulted in a number of advances such as the Cancer Guidelines; the recommendation also resulted in the proliferation of default values for many widely used quantitative factors in risk assessment. Over time, these default values became “set in stone” and the original thinking and scientific basis of these numbers was more often than not forgotten. In many risk assessments, the ascendancy of the defaults often trumped measured values that were directly applicable to the problem at hand.<sup>80,82</sup>

The 2009 NRC report recommended using alternative assumptions or values in lieu of the default if the alternative can be demonstrated to be superior.<sup>80</sup> The committee also indicated that many defaults without any seeming basis had become ingrained in risk assessment practice. Often, regulators are hesitant to abandon defaults, especially when data indicate that the default is overly conservative/protective.<sup>83</sup>

### **1.5.6.3 *Controversies around “Silver Book” Recommendations for Dose–Response Assessment***

For a number of years, EPA has been attempting (or saying it is) to “harmonize” non-cancer and cancer risk assessment. In 1997, a colloquium organized by EPA’s

Risk Assessment Forum concluded that EPA needed to “push the envelope” in terms of consideration of mode of action, and such consideration was likely the means of harmonization.<sup>84,85</sup> One of the goals of benchmark dose modeling is harmonization of the cancer and non-cancer approaches.<sup>86</sup>

The NRC committee also wanted to address the scientific limitations with current approaches to dose–response assessment, as presented in Chapter 4. The committee reasoned that because of background exposures and ongoing disease processes, variations in susceptibility would exist within the human population. Hence, a give dose of a substance could cause disease of specific magnitude or severity in a given fraction of the population. Further, variation would exist in the population in terms of both severity and incidence. The distinction between incidence and severity first appeared as a “straw man” proposal for redefining the reference dose in a 2002 paper by Dr. Dale Hattis. The proposal was to set the reference dose so that the incidence of a minimally adverse effect would be 1 in 100,000 or less in the general population and 1 in 1000 in a defined sensitive subpopulation.<sup>87</sup>

Another dose–response theme in the “Silver Book” was that background exposures and ongoing disease processes could also contribute to both severity and incidence. These variations could contribute to the appearance of a linear dose–response at the population level.<sup>88</sup> For example, there is evidence both for and against low dose linearity in the incidence of cardiovascular and respiratory mortality associated with exposure to particulate matter, even though the causes of these deaths include multiple factors, including weather.<sup>89–93</sup> Similarly, a no-effect level cannot be determined for the dose–response between blood lead concentration and reduction in IQ.<sup>94,95</sup>

EPA’s dose–response paradigm throughout the 21st century has yet to harmonize cancer and non-cancer outcomes—instead, an arbitrary and artificial separation is made. The slope factor methodology for cancer risk assessment that yields quantitative estimates of risk is available on both an individual and population basis, notwithstanding the patently incorrect assumption of low dose linearity. Cancer risk estimates, correct or not, can therefore be used in cost–benefit analyses and consideration of risk–risk tradeoffs. These estimates ignore severity, and the cancer dose–response models assume that cancer is a dichotomous or yes/no outcome.

For non-cancer assessment, a hazard index based on a reference dose (RfD), as used in current practice for non-cancer assessments, provides no such quantitative information. One cannot quantify risk either above or below the reference dose in a way that enables quantitative risk comparisons. The regulatory cancer risk range of 1E-06 to 1E-06 can represent a regulatory target at the population level, but for non-cancer hazard, no similar quantity can provide insight into the magnitude of population risk that might be considered acceptable—the “bright line” of a Hazard Index (HI) value of unity provides no insight at all as to the likelihood of adversity.

The uncertainty factors used for low dose extrapolation and interspecies extrapolation represent a mixture of uncertainty and variability, thus their use is contrary to

EPA's 1997 *Policy for the Use of Probabilistic Analysis in Risk Assessment*.<sup>72</sup> The "Silver Book" suggested the use of distributions to represent uncertainty; although this idea has received considerable research attention, the practice has not been accepted by regulatory agencies.<sup>96–99</sup> At present, the utility of non-cancer assessment is limited and hinders the ability to conduct analyses of risk–risk tradeoffs, to weigh costs and benefits, or to provide transparency in decisions.

The "Silver Book" recommended a unified approach to dose–response, using MOA to determine the shape of the dose–response curve in the low dose region. The exploration of a possible default value for interindividual variation in cancer susceptibility was also recommended. The examples provided in the "Silver Book" did not explicitly demonstrate the linear low dose extrapolation would be used for both cancer and non-cancer dose–response. However, the NRC report suffered from being less than clear about the specifics of low dose extrapolation, and this lack of clarity engendered a great deal of comment within the risk assessment community.<sup>100–106</sup>

The "Silver Book" described three conceptual models for dose response whether or not the low dose response was linear on an individual or population level. Notwithstanding this controversy, there remains great benefit in providing a dose–response assessment resulting in quantitative estimates of toxicity appropriate for use in a decision-analytic approach that can determine the societal value of a range of risk management options.

### **1.5.7 World Health Organization International Programme on Chemical Safety (WHO-IPCS) Guidance Document on Evaluating and Expressing Uncertainty in Hazard Characterization**

By hazard characterization, what is meant is an approach to quantify uncertainty and/or variability in toxicity as a function of human exposure. This document defines a framework based on four principles with their basis in the original "straw man" proposal by Hattis<sup>87</sup> that distinguished the population incidence of an adverse health effect from the severity of that effect in an individual. These four principles are:

- individual and population dose responses are not the same;
- for all health outcomes, both cancer and non-cancer, the magnitude or severity of effect for a given individual changes with that individual's dose;
- toxicological equivalence means that an equal change in the severity of a defined effect, i.e., an "effect metric," will occur across a population experiencing toxicologically equivalent or equipotent doses; the level of adversity may still vary across the population because of other factors;
- extrapolating to a toxicity reference dose from a point of departure requires accounting for lack of knowledge (uncertainty) and population heterogeneity (variability) in the effect metric.

Based on these four principles, probabilistic methods would be used to estimate both the equipotent human dose (HD) at a given effect metric (M) in humans and the

incidence of disease (I) in the target population. The resulting dose level is defined as  $HD_M^I$  or the human equipotent dose at severity M and incidence I.<sup>107,108</sup>

## 1.6 RISK ASSESSMENT AS PRACTICED INTERNATIONALLY

The events in the United States that led to the passage of NEPA and the formation of the Environmental Protection Agency were the first of their kind and influenced events in other countries. This section will consider risk assessment methodology and its use in regulation in China, Europe, and Canada. The point is to show commonality of methods rather than to conduct an exhaustive comparison of the differences. The influence of the methodology developed in the United States will be apparent.

### 1.6.1 Will Risk Assessment in China Point the Way for the Developing World?

The average growth rate of China's Gross Domestic Product over the past 20 years has been 9.7%. With 22% of the world's population, environmental impacts in China have the potential to affect the rest of the world.<sup>109</sup> In 1990, the State Environmental Protection Administration (SEPA) of the People's Republic of China required the performance of environmental risk assessments for potential environmental pollution accidents. Before 2004, environmental risk assessments in China were conducted using guidance documents from other countries. In 2004, SEPA issued its *Technical Guidelines for Environmental Risk Assessment for Projects*.<sup>110</sup>

Much of the guidance currently being developed in China is copied from US guidance; for example, the Beijing Municipal Environmental Protection Bureau issued *Technical Guidelines for Environmental Site Assessment* and the Ministry of Environmental Protection (MEP) of the People's Republic of China, which replaced SEPA, issued *Guidelines for Risk Assessment of Contaminated Sites*. Both documents were based on EPA's *Soil Screening Guidance*.<sup>110-112</sup>

Similar to the "Red Book"<sup>33</sup> and RAGS,<sup>51</sup> the MEP guidelines indicated five steps for environmental risk assessment:

- damage identification;
- exposure assessment;
- toxicity assessment;
- risk characterization;
- expected value of soil remediation.

The majority of the values for exposure assumptions, e.g., incidental soil ingestion, inhalation rate, etc., were obtained directly from EPA guidance. What was dissimilar to EPA guidance was the incorporation of risk management considerations into the risk assessment. The MEP thus has taken the same position as the United States Office of Management and Budget in Circular A-4.<sup>79</sup>

One aspect of the toxicity assessment that will be discussed in a later chapter is the growing awareness that assumption of the linear no-threshold hypothesis for chemical carcinogens is very likely incorrect and not based on biological knowledge.<sup>113–117</sup> The assumption stems from the acceptance of claims of a linear no-threshold dose–response hypothesis for radiation. This hypothesis was widely accepted in the 1950s and 1960s, but of late, the explosion of biological knowledge due to genomics, proteomics, computational, and systems biology strongly suggests that this hypothesis is incorrect.<sup>114,115,117</sup> In China, because of the desire of the government to maintain economic growth, the linear no-threshold hypothesis is being considered very carefully—China is at an early stage in the development of an environmental regulatory framework and wishes to base such a framework on the best available science.

National guidance in China has matured quickly—that guidance is not, however, being implemented on a local level, likely due to the rapid economic development. Local agencies are apparently failing in their administrative and regulatory responsibilities.<sup>118</sup>

## 1.6.2 Risk Assessment in the European Union

REACH stands for the Registration, Evaluation, Authorization, and Restriction of Chemical Substances under regulation EC 1907/2006 of the European Parliament. The European Union promulgated a far-reaching regulatory initiative in 2006. With the ever-increasing ability of analytical chemistry to measure ever lower levels of chemicals in the human body, the ubiquity of these chemicals in our bodies, albeit at vanishingly tiny levels, has increased public concern because of the perceived hazards associated with these chemicals.<sup>119–123</sup>

REACH has specified that the task of providing information has been placed onto industry. The European Chemicals Agency (ECHA) has developed detailed guidance on information requirements and chemical safety assessment from available data. The ECHA guidance provides 12 categories of information:

1. physicochemical properties;
2. skin/eye irritation, corrosion or respiratory irritation;
3. skin or respiratory sensitization;
4. acute toxicity;
5. repeated dose toxicity;
6. reproductive or developmental toxicity;
7. mutagenicity and carcinogenicity;
8. aquatic toxicity;
9. degradation and biodegradation;
10. bioconcentration and bioaccumulation;
11. effects on terrestrial organisms;
12. toxicokinetics.

REACH soon realized that due to the number of untested chemicals in commerce (~80,000), the data requirements would be impossible to fulfill for each chemical.

Hence, ECHA has led the way in developing guidance for the use of alternate toxicity testing methods such as quantitative structure–activity relationships, *in vitro* testing, and read-across.<sup>124–126</sup>

For chemicals produced in amounts greater than 10 tons per year, REACH requires a chemical safety report (CSR). The CSR consists of six elements:

1. human health hazard assessment;
2. human health hazard assessment for physicochemical properties;
3. environmental hazard assessment;
4. persistent, bioaccumulative, and toxic (PBT) and very persistent, very bioaccumulative (vPvB) assessment;
5. exposure assessment;
6. risk characterization.

The last two steps are performed only if the first four suggest the substance should be classified as dangerous.<sup>127</sup>

Step 1, the human health hazard assessment, determines a “derived no-effect level” (DNEL) based on all relevant and available data. DNELs are developed for each route of exposure (oral, dermal, inhalation) and each observed adverse endpoint.

Step 2, the human health hazard assessment for physicochemical properties, considers flammability, explosivity, and oxidizing properties as well as the potential for safety hazards of this nature to occur.

Step 3, the environmental hazard assessment, determines the environmental concentration thought to have no impact, the “predicted no-effect concentration” (PNEC). PNECs are developed for water and sediment in marine and freshwater environments. If necessary, PNECs for air or food chain exposure may also be developed.

Step 4, the evaluation of persistence and bioaccumulation, involves data on biodegradability, octanol-water partition coefficient, and environmental toxicity.

If the substance is determined to be dangerous under European Commission Regulation 1272, then steps 5 and 6, exposure assessment and risk characterization, are conducted.<sup>127</sup>

These last two steps are iterative, and REACH permits a conservative exposure assessment to be replaced with a more realistic one if it can be shown that exposure control can be achieved.

Working under the aegis of the World Health Organization, the idea of “integrated risk assessment” was developed. The goal was to apply the science of risk analysis to bring together the disciplines and practice of ecological and human health risk assessment. WHO defined integrated risk assessment as “a science-based approach that combines the processes of risk estimation for humans, biota and natural resources in one assessment.”<sup>128</sup> The process was then tested and refined based on four case studies.<sup>129</sup>

### 1.6.3 Risk Assessment in Canada

Canada has taken a pragmatic approach to health risk assessment. Health Canada has recognized that the socioeconomic and physical environment, early childhood experiences and events, personal health practices, and biology are determinants of health. Other determinants of health include age, gender, income, education, literacy, and genetics.<sup>130</sup>

In 1990, Health and Welfare Canada published a preliminary framework for risk assessment and risk management.<sup>131</sup> In 1993, Prime Minister Kim Campbell split this department into two parts: (1) Health Canada and (2) Human Resources and Labor Canada. The next year, Health Canada published a revised framework, *Human Health Risk Assessment for Priority Substances*.<sup>132</sup> In 2000, Health Canada again revised the framework. Health Canada's *Decision-Making Framework for Identifying, Assessing and Managing Health Risks* is generally based on the 1993 revision and the US Presidential/Congressional Committee Framework (Figure 1.4).<sup>133</sup> The framework can be grouped into five phases:

- issue identification;
- risk and benefit assessment;
- identification and analysis of risk management options;
- selection and implementation of an option;
- monitoring and evaluation of outcomes.

This framework also emphasized the need for stakeholder involvement at all stages of the process. This emphasis was the essence of the 2000 revision.

In 1999, a report titled *Risk, Innovation and Values: Examining the Tensions* from the Treasury Board of Canada Secretariat explored the competing pressures on public sector risk managers regarding decisions with uncertainty outcomes.<sup>134</sup> These competing pressures include the value of innovation versus the value society places on a chosen level of certainty. The report suggested that change was inevitable and risk managers should adopt innovation as a regular thought process. This would actually require a sea change for managers whose traditional way of thinking emphasized caution and for whom the whole notion of managing risk had become synonymous with avoiding risk.

Since 2004, Health Canada has released a plethora of guidance documents that deal with both preliminary and more advanced risk assessment methods, risk communication, and other aspects of risk assessment. These guidance documents can be found online at [www.healthcanada.gc.ca](http://www.healthcanada.gc.ca).

The decline in the influence of EPA's IRIS program has likely spurred development of these guidance documents as well as, in 2010, a compendium of toxicity reference values.<sup>135</sup>

## 1.7 WHAT HAPPENS WHEN THINGS GO RIGHT

In this section, we will first consider the events at a Superfund decision and cleanup that occurred in the early 1990s. Communication between EPA, the

public, and other stakeholders was handled with care and respect. We will then consider some of the aspects of communicating risk and uncertainty to varied audiences.

### 1.7.1 The Sangamo-Weston Superfund Site

From 1955 until 1977, the practice at a capacitor manufacturing plant in Pickens, South Carolina was to discharge untreated wastewater into Towns Creek. PCBs used in the manufacturing process migrated downstream into Twelve Mile Creek, a major tributary of Lake Hartwell. Located on the border of Georgia and South Carolina, Lake Hartwell occupies 56,000 acres and provides for public recreation, flood control, and hydropower generation. The US Army Corps of Engineers impounded the lake between 1955 and 1963. Approximately 300,000 people visit the lake each year for recreation. Many of the lake visitors harvest and consume fish from the lake.<sup>136</sup>

The PCB-contaminated sediment from the Sangamo-Weston facility was prevented from reaching the lake for a time by the dams of three small hydroelectric plants on Twelve Mile Creek. Periodic flushing of the sediment in the impoundments behind the dams discharged the PCBs further downstream until approximately 730 acres of the lake bottom sediment in the Seneca River arm were contaminated. The PCBs entered the food chain and became concentrated in the fish living in Lake Hartwell. High levels of PCBs were detected in fish collected from Lake Hartwell in 1976.

Within the Superfund program, remediation is based on risks to the hypothetical receptor experiencing “reasonable maximum exposure”, defined as the highest exposure that is reasonably expected to occur at a site.<sup>51,137</sup> The National Oil and Hazardous Substance Pollution Contingency Plan (National Contingency Plan, or NCP; 40 CFR 300) is the regulation under which the Superfund program operates. The preamble to the NCP indicates that a major objective of the risk assessment is “to target chemical concentrations associated with levels of risk that will be adequately protective of human health for a particular site.”<sup>136,137</sup>

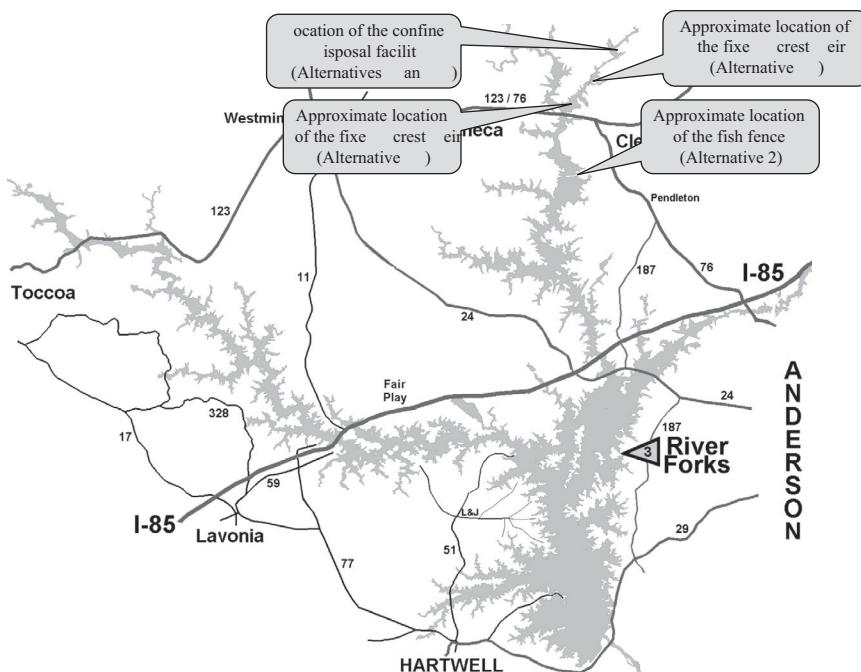
Acceptable cancer risks defined by CERCLA are between  $10^{-4}$  and  $10^{-6}$ , with a preference for the lower end of the risk range.<sup>137</sup>

Lake Hartwell is a popular inland fishing destination. As part of the CERCLA actions at Sangamo-Weston, a risk assessment was conducted for fish consumption. The cancer risk associated with the fish ingestion pathway for the RME receptor was as high as 1 percent or  $10^{-2}$  for some areas of the lake. At its time in the early 1990s, the risk assessment was quite sophisticated and included data from a site-specific creel and fish consumption survey and probabilistic estimates of exposure and risk.<sup>138</sup>

Eight remedial alternatives were proposed for cleanup. These included institutional controls with public education and fish and sediment monitoring and continuance of an existing fish advisory. Details of the various remedial alternatives are shown in Table 1.2. Figure 1.5 shows the locations of the Twelve Mile Creek and Seneca River Arms of the various alternatives.

**Table 1.2 Remedial Alternatives for the Sangamo-Weston Superfund Site**

Remedial Alternative	Cost in 1994\$	Description
Alternative 1—No Action	\$130,000	This alternative was evaluated to serve as the basis for comparison with other active cleanup alternatives. Under this no-action alternative, no further remedial actions for the contaminated sediments or fish at the site would be conducted. This alternative would not affect the existing health advisory issued by South Carolina Department of Health and Environmental Control, which would be expected to continue the advisory until polychlorinated biphenyl (PCB) concentrations in fish tissue declined to levels below 2 mg/kg (FDA tolerance level). The advisory currently warns against the consumption of fish from the Seneca River Arm of Hartwell Lake above the Highway 24 bridge and fish larger than 3 lb throughout the entire lake. The advisory would be modified if warranted by future trends regarding PCB levels in fish. Maintenance of the fish advisory is assumed to entail periodic replacement of existing signs that advise against fish consumption.
Alternative 2A—Institutional Controls	\$3,208,000	This alternative would consist of four parts: (1) continuance of the existing fish advisory, (2) a public education program on fish handling and cooking techniques for reducing the intake of PCBs, (3) fish and sediment monitoring, and (4) regulation and periodic flushing of the sediment from behind the dams on Twelve Mile Creek.
Alternative 2B—Fisheries Isolation	\$4,244,000	This alternative involved construction of a barrier or fish fence to prevent the movement of migratory species, Striped Bass, hybrid bass, and walleye, into the contaminated upper Seneca River Arm of the Lake. The barrier would be constructed from the water level down the lake bottom and would not impede boat traffic.
Alternative 3A—Capping	\$51,139,000	This alternative would isolate PCB-contaminated sediments by placing an 18-inch clean sediment cap over the areas with the highest contamination. The cap thickness was designed to minimize the impacts on sediment dwelling biota such as <i>Hexagenia</i> mayflies. The cap would be placed with a barge and hydraulic sand spreader.
Alternative 3B—Sediment Control Structure	\$53,591,000	This alternative proposed building a fixed-crest weir near the mouth of the Twelve Mile Creek Arm to maintain a constant pool elevation in this arm and prevent sediment erosion and transport.
Alternative 3C—Optimal Capping/Sediment Control Structure	\$34,049,000	In this alternative, a fixed-crest weir would be built further upstream on Twelve Mile Creek and the sediment downstream of the weir would be capped.
Alternative 4—Confined Disposal Facility	\$46,909,000	This aggressive alternative would involve re-routing a 1600-foot section of Twelve Mile Creek and dredging sediment with PCB concentrations > 1 mg/kg. The dredge spoils would be placed in a confined disposal facility.
Alternative 5—Stabilization	\$581,957,000	The upper portion of Twelve Mile Creek would be dewatered and the sediment excavated. The lower portion would be dredged. The dredge and excavation spoils would be stabilized with cement and placed in the confined disposal facility.



**Figure 1.5** Map of Lake Hartwell showing the Sangamo-Weston Superfund remedial alternatives. See narrative for details.

Within the Superfund Program, the Proposed Plan is a description of the site, the risks, and EPA's preferred alternative. EPA chose Alternative 2B, Fisheries Isolation, and presented the Proposed Plan at a public meeting in Clemson, South Carolina on April 19, 1994. Unwavering public opposition toward the fish fence was voiced at this meeting and in the public comments received. EPA concluded that the public consensus supported Alternative 2A—Institutional Controls—and chose it as the final remedial action.

One likely reason for EPA choosing Alternative 2A was cost; this remedy was chosen less than a year before the formation of the National Remedy Review Board (NRRB). Any Superfund remedy costing more than \$25 million must be reviewed by the National Remedy Review Board to ensure that the risk management decision is consistent with Superfund law, regulation, and guidance. The NRRB was formed in 1995 with the intention of controlling remedy costs and promoting consistent and cost-effective decisions.<sup>139</sup>

The public input to the risk management decision at Sangamo-Weston was an example of how the process could work when stakeholders are consulted and their input valued—exactly what the 1997 Federal Commission report advocated. Among the reasons the effort was successful are the care and thought that went into the risk assessment and that the opinion of the public living in the Lake Hartwell area was taken into account.<sup>136</sup>

### 1.7.2 Good Communication Is the Reason Things Go Right

In the 1990s, the US Nuclear Regulatory Commission developed a report on the Fukushima Dai Ichi Power Plant that predicted the scenario that led to the explosion there in 2011. Japanese scientists in the Nuclear and Industrial Safety Agency warned the Tokyo Electric Power Company in 2004 and cited this report; but the company failed to adopt any measures that would have prevented or mitigated the explosion or its aftereffects.<sup>140</sup>

A 2012 report from the National Research Council notes that likely the most difficult challenge for the science of risk analysis is effective communication of both results and uncertainties. Meeting this challenge is an absolute requirement for a successful risk analysis. This document goes on to define “wicked problems” as those affected by many interacting factors, encompassing various spatial scales and lengthy time scales. In addition, such “wicked problems” tend to be socially complex with no clear solution apparent and require scientific expertise from multiple disciplines.<sup>141</sup>

The erosion of trust by the public and the sharp increase in messaging via social media have created misperceptions about the risk of exposures to environmental substances, everyday household products, and even healthy foods.<sup>142</sup> In stressful situations, the ability to understand complex information is affected, and for many, belief in a particular scenario or outcome depends primarily on confirmation bias.<sup>143</sup>

Each of the four aspects of risk assessment identified in the “Red Book”—hazard identification, exposure assessment, dose–response assessment, and risk characterization—have associated uncertainty. Problem formulation should attempt to foresee, as much as possible, these uncertainties and detail a plan for addressing them and communicating the overall result to a range of audiences. Risk communication is as much a part of the science of risk analysis as is the conduct of the risk assessment.<sup>144–146</sup>

## 1.8 PERCEPTION IS REALITY: RISK COMMUNICATION AND STAKEHOLDER PARTICIPATION

Conducting a credible risk analysis rooted in the best available science and with a level of detail commensurate with the scope of the problem is a necessary part of decision-making. Communicating these results to stakeholders in the decision is, however, just as vital for successful implementation. Ideally, decision-making in a democratic society involves all those who have a stake in the decision and minimizes the downside for those stakeholders to the greatest extent possible. Not all stakeholders can initially understand the many technical complexities of high-level risk assessments. Nonetheless, they have a valid interest in the outcome and should be treated as partners. What success at risk communication truly requires is the honest appreciation of and respect for diverse viewpoints that will, of course, reflect individual experience, education, and background. The essence of successful risk communication is respect for others who may have a different outlook on the situation.

There are four aspects to risk communication—the message, the source, the channel, and the receiver:

- the message—how “risky” the situation is;
- the source—who conveys the risk information;
- the channel—the means of communication, i.e., a public meeting, television, radio, etc.;
- the receiver—the public or other stakeholders in the decision.

In 1988, EPA published *Seven Cardinal Rules of Risk Communication*, a pamphlet authored by Dr. Vincent J. Covello, Director of the Center for Risk Communication at Columbia University.<sup>147</sup> Covello has worked in this area for many years, most notably in helping General Norman Schwarzkopf craft the public dialogue regarding the first Gulf War in 1990.

These seven cardinal rules are:

1. Accept and involve the public as a legitimate partner.
2. Plan carefully and evaluate your efforts.
3. Listen to the public’s specific concerns.
4. Be honest, frank, and open.
5. Coordinate and collaborate with other credible sources.
6. Meet the needs of the media.
7. Speak clearly and with compassion.

While these cardinal rules are excellent general principles, environmental risk communication has become enormously more difficult since the 1990s due to the increasingly risk-averse nature of western societies. The scientific literature also provides many risk communication tools.

The information available to the public is often conflicting. In May of 2010, the National Cancer Institute released the 2008–2009 report of the President’s Cancer Panel, *Reducing Environmental Cancer Risk: What We Can Do Now*. The report suggested that the prevailing regulatory approach to environmental chemicals and cancer was reactionary rather than precautionary. The report also stated that the “true burden of environmentally induced cancer has been grossly underestimated”<sup>148</sup>

Michael J. Thun, vice president emeritus of Epidemiology and Surveillance Research at the American Cancer Society, immediately criticized the report. Dr. Thun stated that the report was unbalanced in its perspective for dismissing prevention efforts aimed at known causes of cancer such as tobacco, obesity, alcohol, infections, hormones, and sunlight. Dr. Thun also stated that the report did not represent the scientific consensus on environmentally induced cancer.<sup>149</sup> A number of other scientists have also suggested that this report is incorrect and misleading.

The purpose here is not to discuss the lack of veracity of the President’s Cancer Panel report, but rather to point out that this report, along with sensationalistic news reporting such as Dr. Sanjay Gupta’s series on CNN titled *Toxic Towns USA*, tend to increase the outrage many people feel about environmental risks. Dr. Peter Sandman of Rutgers University, an expert in risk communication, has written extensively

on outrage and how real communication about risk cannot begin until outrage is addressed.<sup>150</sup> Television journalism often tends to be prurient or alarmist to maintain or increase the viewing audience—at times, journalistic credibility is sacrificed for ratings.

What all this means is that the receiver—most often the public—will usually have some strongly held preconceptions about the nature and seriousness of environmental risks. An example of such a situation is provided below.

### **1.8.1 Public Perception of Hexavalent Chromium: A Cautionary Tale**

The movie *Erin Brockovich* was released in 2000 and chronicled the true story of the former beauty queen who became a legal aide and her participation in the toxic tort suit brought by the residents of Hinkley, California against Pacific Gas and Electric (PG&E). This movie thrust the issue of hexavalent chromium (Cr(VI)) in drinking water into the public and political spotlight. The suit was settled in 1996, with PG&E paying a settlement of \$333 million to 600 residents.

As of the summer of 2012, PG&E is still attempting to reach a final agreement with the residents of Hinkley and has offered them the option of selling their houses to PG&E or receiving water filters capable of removing hexavalent chromium.

As a backdrop to this legal action, a controversy had been brewing about the data relating stomach cancer to hexavalent chromium exposure first reported in the *Chinese Journal of Preventive Medicine*.<sup>151</sup> The authors claimed that stomach cancer rates were elevated among those residing near the Jinzhou Iron Alloy Plant who consumed water containing up to 20 mg/L Cr(VI). At these concentrations, the water would be bright yellow. The collection of water samples and the estimates of cancer may have been influenced by government policies in the 1970s and 1980s, when the data was collected. This influence is clearly evident in the last paragraph translated from a 1976 report from Dr. Zhang:

Our studies have concluded that, guided by Chairman Mao's philosophy and thought, in work to prevent and treat tumors, with the consistent emphasis on prevention and further propaganda and popularization of scientific knowledge on the subject of cancer prevention and remedy, building the confidence that malignant tumors are not to be feared, that malignant tumors can be beaten, to build in-depth, concrete, and broad-based epidemiological studies and research, to solve the epidemiological questions of malignant tumors, to strengthen the regular survey and treatment of common illnesses, recurrent maladies, and chronic illnesses, to make every effort to accomplish the goal of early detection and early treatment, in order to make the efforts of preventing and remedying tumors a service to the solidarity of the proletariat, is among the missions which we must make every effort to complete.<sup>151</sup>

The statistical comparison of cancer rates among those living near the plant with a comparison group was not clearly presented—neither in early reports nor in the 1987 publication.<sup>151–153</sup> These data were collected during the turmoil of the Cultural Revolution, and one can do no more than speculate about the political pressures on Dr. Zhang.

During 1995, Drs. Zhang and Li were in contact with scientists at McLaren-Hart/ChemRisk, and this contact may be the reason for the improved statistical analysis in the 1997 paper. In a letter dated June 9, 1995, Dr. Zhang wrote:

I've received the written draft you sent. After reading it, I quite agree with you. In the draft, one sentence reads "The death rate in each village does not show the positive correlation with the distance of the village to the source of pollution or the intensity of chromium pollution.<sup>154</sup>

The work was republished in 1997 in the *Journal of Occupational and Environmental Medicine* with the appropriate and clear statistical comparisons. In this updated study, no relationship could be demonstrated between distance from the plant (used as the measure of Cr(VI) concentration) and the rate of either all cancers, lung cancers, or stomach cancers.<sup>153</sup>

The correspondence between Drs. Zhang and Li and scientists at McLaren-Hart/ChemRisk revealed a discussion of nuances of interpretation among scientific peers.<sup>154</sup> Nonetheless, the relationship between these Chinese scientists and the American consulting company soon became controversial with the publication of the letters as part of the PG&E trial record.

Peter Waldman of the *Wall Street Journal* reported on December 12, 2005 about the correspondence between Dr. Zhang and McLaren-Hart/ChemRisk, and his reporting further fueled this controversy.<sup>155</sup> Following Waldman's exposé, the Environmental Working Group (EWG) got involved in chromium. Founded in 1993, EWG has a stated mission to use public information to protect public health and the environment. EWG and the *Wall Street Journal* alerted Dr. Paul Brandt-Rauf, the editor-in-chief of the *Journal of Occupational and Environmental Medicine*, to this correspondence. In response, Brandt-Rauf retracted the paper in July 2006.<sup>155-158</sup> Dr. Zhang died around 2000, and thus could obviously not contest the retraction.

Six months after the retraction of the paper, Dr. Shukun Li stepped forward to say the paper had been withdrawn unfairly and disputed the claim that she had agreed to the paper's retraction. Further, she demanded that the paper be republished. This never occurred. One possible reason is that Brandt-Rauf indicates the communication with Dr. Li was conducted through a translator and some miscommunication may have occurred.<sup>159</sup>

The correspondence and relationship between Dr. Zhang and the McLaren-Hart scientists was characterized by Waldman as a cautionary tale about "what can happen when the line between advocacy and science blurs."<sup>155</sup> But perhaps Waldman had a stake here as well—was he building his career with a sensational story?

Truth is not absolute in science—a scientist may change his interpretation of conclusions based on new data or updated methods, and the scientific method is an iterative process used to learn about the world. Dr. Li has publicly stated that the *Wall Street Journal* article is false and demanded that it be retracted.<sup>159</sup>

Recently, the data of Zhang and Li from the 1987 paper were reanalyzed using the entire Liaoning province as the comparison group and showed a significantly

increased rate for stomach cancer.<sup>160</sup> Further adding to the controversy, the scientists who previously worked at McClaren-Hart/ChemRisk also reanalyzed the data using the cancer rates from nearby agricultural villages that were not exposed to Cr(VI) and observed no statistical difference.<sup>161</sup> Hence, these data are hardly robust if they can be interpreted differently depending on the choice of which unexposed group serves as a control group. In short, these data have become like the elephant inspected by seven blind men—each man handles a different part of the beast, and each one comes away with a different perception.

### **1.8.2 Why the Movie *Erin Brockovitch* Changed the Public's View of Chromium**

The public perception of risk from hexavalent chromium stemming from the movie may have significantly undermined the process of scientific investigation and credible regulatory evaluation.<sup>162</sup> In one of the exercises at the end of this chapter, you will be asked to watch and comment on a video of a noted scientist testifying about hexavalent chromium before the US Senate Subcommittee on Environment and Public Works.

Many individuals fear chemical exposure, and this fear is completely understandable—there are instances of individuals being poisoned with disastrous consequences.<sup>163</sup> Some individuals are more sensitive to common odors such as perfume or tobacco smoke and may have cognitive and emotional effects associated with these odors<sup>164–166</sup> Such individuals also have a significantly higher lifetime prevalence of mood and anxiety disorders.<sup>167–169</sup>

This observation begs the question of to what extent the fear of chemicals is the result of the associated cognitive and emotional effects. Recently, a number of illness outbreaks have been attributed to psychogenic causes likely triggered by an odor.<sup>170,171</sup>

Perceptions of risk may also contribute to fear. A number of studies have noted an “awareness bias” in which individuals who perceive an environmental threat such as proximity to a landfill or industrial facility and who also worry about potential health effects associated with the perceived threat tend to report more ill health in the absence of any measurable medical or biological effect.<sup>172</sup>

The current public perception of hexavalent chromium as highly dangerous may actually be a mass psychogenic fear of chromium in the American public because of the movie *Erin Brockovitch* and the reporting of Peter Waldman of the *Wall Street Journal*.

## **1.9 ASSOCIATION VERSUS CAUSATION**

The Scottish philosopher David Hume remarked that causation could not be empirically observed, but rather is induced logically. This is a two-edged sword—one can never obtain final or absolute proof of causation or lack thereof. All there is

is an observed association between two phenomena. This is a difficulty for science that seeks to understand the world in terms of cause and effect based on observation and reasoning. Karl Popper, the 20th-century philosopher and professor at the London School of Economics, attempted to address the issue of causation by arguing against the classical scientific method that uses observation and induction. Popper noted that theories resulting from induction can be tested only indirectly, by their implications. Even a large body of experimental or observational data that confirms a scientific theory does not constitute proof—yet a single instance of a counterexample can be decisive. The central idea of Popper’s ideas about science is the asymmetry between verification and falsifiability—theories must be stated so that there exists the possibility of being falsified based on observation.

The philosophic difficulties with causation provided the intellectual background for the development of the considerations for causation of Sir Austin Bradford Hill.<sup>173</sup> These considerations are considered central to the establishment of causality because of their logic and simplicity.

Hill’s “viewpoints” or “features to be considered” are difficult to apply in any field. They provide no easy formula or guidance.<sup>174,175</sup> Hill’s considerations have been eloquently characterized as “guideposts on the road to common sense.”<sup>176</sup> Hill’s considerations necessitate rigorous scientific thinking; unfortunately, the intellectually lazy will likely apply them as a checklist or set of criteria.<sup>176,177</sup> This is not what Hill intended, and he indicates that none of the nine “viewpoints” can be required as a *sine qua non* for causation.<sup>173</sup>

The Hill considerations have been adapted for many purposes, including the assessment of the mode of action of reproductive and developmental toxins and chemical carcinogens.<sup>178,179</sup> EPA’s Cancer Guidelines specifically and correctly point out that the framework is a structure for organizing the available information.<sup>179</sup> Table 1.3 shows Hill’s original considerations and the adaptations for use in assessing human relevance of a particular mode of action in risk assessment.

**Table 1.3 Hill’s Considerations for Causation and Their Adaptation for Assessing Human Relevance of a Mode of Action**

Considerations for Causality (Hill, 1965)	Framework for Evaluating an Animal MOA (Dellarco & Wiltse, 1998; EPA, 2005; Sonich-Mullin et al., 2001; Meek et al., 2003; Seed et al., 2005)
<b>Strength of Association</b> The disease is associated with the exposure to a significant extent, as measured by valid statistical tests.	<b>Postulated MOA</b> A description of the sequence of measured events, starting with chemical administration and ending with the occurrence of the apical event.
<b>Consistency</b> If a relationship is causal, we would expect to find it consistently in different studies, in different populations, and in a range of circumstances.	<b>Key Events</b> Clear descriptions of each of the key events that comprise the MOA.

*(Continued)*

Table 1.3 (Continued)

Considerations for Causality (Hill, 1965)	Framework for Evaluating an Animal MOA (Dellarco & Wiltse, 1998; EPA, 2005; Sonich-Mullin et al., 2001; Meek et al., 2003; Seed et al., 2005)
<b>Specificity</b>	<b>Dose–Response/Biological Gradient</b>
In most cases, it is impossible to attribute a specific effect to a single cause. Causality is most often multiple.	Dose–response relationships for each key event and comparisons of these relationships between key events and with the apical event.
<b>Temporality</b>	<b>Temporality</b>
The exposure must always precede the disease.	Sequence of key events of time leading to the occurrence of the apical event.
<b>Dose Response or Biological Gradient</b>	<b>Strength, Consistency and Specificity of Association</b>
If a dose–response relationship is present, it is strong evidence for a causal relationship. However, as with specificity, the absence of a dose–response relationship does not rule out a causal relationship.	Assessment of relationships among key events, precursor, or sentinel lesions and the apical effect
<b>Biological Plausibility</b>	<b>Biological Plausibility and Coherence</b>
The putative agent produces effects in a manner that is plausible, given the currently accepted understanding of biological processes, and a theoretical basis exists for making an association between an agent and a disease.	Determination of whether key events and their sequence are consistent with current biological thinking, with consideration of species-specificity and the occurrence of the apical event.
<b>Coherence</b>	<b>Alternative MOAs</b>
The association should be compatible with existing theory and knowledge.	How likely are alternative MOAs compared to that proposed?
<b>Experiment</b>	<b>Conclusion about the MOA</b>
Can the condition be altered or prevented by an appropriate experimental regimen?	An overall indication of the level of confidence in the proposed MOA.
<b>Analogy</b>	<b>Uncertainties, Inconsistencies and Data Gaps</b>
What other factor or factors could produce the observed effects?	Identification and description of information deficiencies, inconsistencies, and contradictions in the overall data, and proposals to ameliorate data gaps.

Sources: Dellarco VL, Wiltse JA (1998) US Environmental Protection Agency's revised guidelines for carcinogen risk assessment: incorporating mode of action data. *Mutat Res* 405: 273–277; EPA (2005) *Guidelines for Carcinogen Risk Assessment*, EPA/630/P-03/001B, Washington, DC; EPA Risk Assessment Forum; Hill AB (1965) The Environment and Disease: Association or Causation? *Proc R Soc Med* 58: 295–300; Seed J, Carney EW, Corley RA, Crofton KM, DeSesso JM, Foster PM et al. (2005) Overview: Using mode of action and life stage information to evaluate the human relevance of animal toxicity data. *Crit Rev Toxicol* 35: 664–672.

More recently, modifications of Hill's considerations have been applied to mode of action, one of the key concepts in the analysis of health risks.<sup>180</sup> A quantitative scoring system for assessing various aspects of mode of action has been developed,

also extending Hill's considerations.<sup>181,182</sup> Another very recent scheme has proposed seven issues to consider in assessing the consistency of observational epidemiologic data with a causal dose-response relationship. The Hill considerations and their modifications will be revisited many times in this book.

## 1.10 KEY CONCEPTS IN MODERN RISK ASSESSMENT

The last section of this chapter will present definitions and descriptions of key terms in modern risk assessment. This list is by no means complete, but the concepts described here are those that will be encountered again—both in this book and in the practice of risk assessment. Additional terms are shown in Table 1.2.

### 1.10.1 Mode of Action

This term was first used in 1980<sup>183</sup> and defined in a regulatory context in 1998.<sup>184</sup> Since then, the concept has been used to inform the dose-response assessment of both carcinogens and non-carcinogens, and a number of frameworks for characterizing MOA has been developed.<sup>53,180,185–189</sup>

The concept of MOA was developed in the context of a framework or structured approach to evaluate the overall weight of evidence for a biologically plausible explanation of the manner in which a chemical produces an adverse effect. Key events in a carcinogenic mode of action are measurable occurrences that occur before the apical endpoint. In essence, key events are biomarkers of effect. EPA's 2005 *Guidelines for Carcinogen Risk Assessment* observes that the dose response of biomarkers or precursor effects may be used in lieu of the apical effect of cancer for obtaining a point of departure for low dose extrapolation.<sup>179</sup> MOA is also used to determine the human relevance of effects seen in animals.<sup>190,191</sup> An example of a mode of action analysis is shown in Figure 1.3.

### 1.10.2 Point of Departure

The point of departure marks the quantitative value of a response and the dose associated with this response from which extrapolation to lower doses occurs. If quantitative dose-response modeling is not conducted, the POD will usually be the no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL). For quantal or binomial data,<sup>†</sup> such as from an animal cancer bioassay, 10% is the value of the POD most often chosen. For continuous data, there has been considerable debate about the choice of POD and whether this choice should be based on statistical or biological significance.

<sup>†</sup> Quantal data is expressed as count data, usually a proportion or percentage, i.e. 4/50 animals were found to have hepatocellular adenomas. Continuous data is expressed as measurements such as enzyme activity in mg substrate per g liver per hour or the change or amount of some other physiological measurement.

### **1.10.3 Adverse Outcome Pathway (AOP)**

Adverse outcome pathways were first proposed for ecological risk assessment.<sup>192,193</sup> Quickly, the concept was adopted by practitioners of human health risk assessment. An AOP begins with a molecular initiating event and proceeds through a series of key events to an adverse outcome. The similarity with MOA is no accident. AOPs, however, are considered chemical-agnostic; in other words, an AOP is a pathway of biological events culminating in disease that may or may not be related to chemical exposure. The use of AOPs is enhanced as they begin to include quantitative descriptions of key event relationships that can be used a prediction model for dose response and timing of key events, with the goal of supporting regulatory decision-making.<sup>194,195</sup>

### **1.10.4 Biomarker**

A biomarker is physiological quantity measurable in humans *in vivo*. The best-known example is the alcohol breath test for sobriety. Because ethyl alcohol will volatilize from the blood to the air in the lungs, it can be measured in breath. Breath alcohol is not a direct measure of blood alcohol. Biomarkers can reflect either exposure or effect. The occurrence of arsenic in urine is a poor biomarker for chronic exposure to arsenic because it may reflect recent seafood consumption due to the prevalence of arsenobetaine in fish; arsenic in toenails, however, is considered more representative of long-term exposure.<sup>196</sup>

Biomarkers of effect measure some physiological variable that is altered or affected by exposure. For example, consumption of indole-3-carbinol found in broccoli, the use of the pharmaceutical proton pump inhibitor omeprazole, and exposure to the dioxin-like chemicals all increase the activity of CYP1A2, the liver enzyme that metabolizes caffeine.<sup>197,198</sup> This enzyme activity can be measured using exhaled breath or urinalysis.

### **1.10.5 Biomonitoring Equivalent (BE)**

A biomonitoring equivalent is defined as the concentration or range of concentrations of a chemical or its metabolites in a biological medium (blood, urine, or other medium) that is consistent with an existing health-based exposure guidance value such as a reference dose (RfD) or tolerable or acceptable daily intake (TDI or ADI). There is an ongoing effort to express regulatory toxicity criteria (TDIs, ADIs, RfDs) in terms of BE values so that the increasing amount of human biomonitoring data can be understood in terms of the potential for adverse effects.

### **1.10.6 Physiologically Based Pharmacokinetic Modeling**

Mathematical modeling of the distribution of chemicals in the body is also known as physiologically based toxicokinetic modeling. It is also known as ADME modeling, where ADME stands for Absorption, Distribution, Metabolism, and Excretion.

Simply, PBPK modeling is a way of dividing up the body into functional compartments into which chemicals may accumulate or be metabolized and excreted. One of the best-known PBPK models is the Widmark model—this simple one-equation model is used for retrograde extrapolation of measured blood or breath alcohol levels in forensic evaluation of potential drunk driving cases. The Widmark model assumes the body is a single compartment and that elimination of alcohol occurs by a zero-order kinetic process. What this means is that a constant amount of alcohol is metabolized and excreted per time unit.

### 1.10.7 New Approach Methods (NAMs)

In the 20th century, the primary means of obtaining quantitative toxicity data was animal testing. For example, estrogenic effects were measured by the uterotrophic assay that measured uterine growth in either immature rodents or ovariectomized females and required huge numbers of animals. Cancer bioassays conducted by the National Toxicology Program used at least ten animals per dose group in both the shorter dose-ranging study and 50 or more animals in the two-year study. Concern for animal welfare led to a desire for the 3Rs, replacement, reduction, and refinement of animal use in testing and research.

The use of these methods is the purview of the Interagency Coordinating Committee on the Validation of Alternative Methods as part of the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods.

Integrated approaches to testing and assessment provide a means by which all extant validated information about a chemical can leveraged to address a carefully defined question about hazard characterization. The information considered can include toxicity data of related chemicals, exposure routes, use cases, production volumes, and statistical prediction models.

The key point here about NAMs is that scientific confidence needs to be established in each NAM before its use in support of a hazard evaluation. Exposure information also needs to be used to ensure the hazard characterization is fit for its intended purpose and can provide context for the hazard in terms of risk.<sup>199</sup>

## 1.11 EMERGING RISKS

Environmental problems appear to be fewer, but those faced by risk analysts in the 21st century seem much more difficult. Climate change obviously comes to mind. The US National Academies of Science calls these “wicked” problems.<sup>141</sup> Such problems have many stakeholders with divergent opinions, no clear solution, and likely unknown and interlocking feedback loops that may hinder any attempts at addressing the problem.

Another significant issue is the divide between increasing knowledge of the biology and pathogenesis of cancer and the regulatory approach to cancer risk assessment that has remained essentially unchanged for the last four decades. Much more discussion on this topic will be provided in later chapters.

### 1.11.1 Climate Change

Various health regulatory authorities and others have developed assessments of the effect of climate change on health and analyses of how to develop sufficient resilience at all levels of society. Unfortunately, these assessments are not integrated into decision-making at a national level.<sup>200</sup> All five reports since 1990 from the Intergovernmental Panel on Climate Change have provided analyses of the associated health impacts. Recent guidance from the World Health Organization for conducting vulnerability and adaptation assessments (V&As) includes the following five steps:

- Formulate the frame and scope of the assessment.
- Conduct the assessment, taking into account vulnerable populations and regions as well as the current capacity of health agencies to manage these risks.
- Develop estimates of future health risks and impacts.
- Identify and prioritize policies and programs to address current and future health risks.
- Establish an iterative process to address climate-associated health risks going forward.<sup>201</sup>

Thus far, 34 countries have developed V&As and identify, unsurprisingly, vector-borne diseases and heat- or cold-related health risks.<sup>201</sup>

One of the key challenges is providing information to decision-makers in the appropriate time scale. The term in office of governmental decision-makers is likely much shorter than the time scale of the problem of climate change.

At the time of this writing, a number of Democratic presidential candidates planning to run in 2020 have touted a “Green New Deal.” If such a framework is adopted by Congress, opportunities may be plentiful for those skilled in the science of risk analysis and aware of the work already undertaken in this area.

### 1.11.2 Perfluorinated Chemicals (PFCs)

Since the 1940s, perfluoroalkyl and polyfluoroalkyl substances (PFASs) have been used in consumer and industrial applications because of their water, oil, and stain resistance. A stumbling block in developing credible toxicity factors for PFASs/PFCs is the lack of specific concordance between adverse health effects observed in humans and animals. Animals are affected to a much greater degree by PFASs/PFCs than are humans.

Extrapolation of doses from animals to humans results in significantly lower doses of PFCs in humans because of two distinct mutational events that occurred in the course of human evolution approximately 45 million years ago. About 45 million years ago, our pre-human ancestors lost the ability to synthesize ascorbic acid due to a mutational event;<sup>202</sup> about the same time, uric acid replaced ascorbate as the internal scavenger of free radicals, likely because of another mutation that resulted in the loss of the uricase gene that coded for the enzyme that metabolizes uric acid.<sup>203,204</sup> High serum uric acid levels cause renal failure, but early hominids may have adapted by sharply decreased production and concomitant reduction in renal excretion of

uric acid.<sup>205</sup> The unfortunate evolutionary consequences are the occurrence of gout, obesity, hypertension, and metabolic syndrome in 21st-century humans.<sup>206–208</sup>

Genetic variations exist for the genes encoding the renal transporters of PFASs. Gout is, of course, a genetic disease, and higher uric acid levels have been observed in association with perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS).<sup>209,210</sup> Therefore, what may have been observed in these two studies are increases in serum levels of PFOA, PFOS, and uric acid as a consequence of genetic variation—an example of so-called reverse causation—but without genotyping individuals, the source of these associations is unknown.<sup>211–214</sup>

When PFASs were first shown to be commercially useful, there was no reason to consider their renal reuptake. In fact, the physiological role for uric acid was the subject of hypotheses, and the URAT1 transporter was not identified until after 2000.<sup>215</sup> Further, uric acid and PFASs seem very different in terms of their chemical structure. No one could have foreseen this!

PFASs have garnered considerable attention from the public, scientists and regulatory agencies because of their association with a number of potentially detrimental health and environmental effects as well as their occurrence in the food supply, the environment, and humans.<sup>216</sup> Plants may accumulate PFCs, and their persistence in the environment may well translate to persistence in the food supply.<sup>217</sup> As food and water are the main sources of human exposure, the problem of PFCs appears intractable.

## 1.12 EXERCISES FOR THOUGHT AND DISCUSSION

There are, of course, no right answers to these questions below. Nonetheless, these exercises can be thought-provoking, instructive, and often entertaining.

### 1.12.1 The Current Debate about Chemical Safety

To help understand the current debate about chemical safety, please watch the videos at two websites. The first one is: <https://storyofstuff.org/movies-all/story-of-cosmetics/>. This provides the perspective of a layperson who is fearful about chemicals present in the environment, food and cosmetics. This video runs about seven minutes.

The second one is: [www.epw.senate.gov/public/index.cfm/hearings?ID=FC5A8756-802A-23AD-454A-B9EEB7BF1C36](http://www.epw.senate.gov/public/index.cfm/hearings?ID=FC5A8756-802A-23AD-454A-B9EEB7BF1C36). This is an archived webcast from the Senate Committee on Environment and Public Works titled “Oversight Hearing on the Environmental Protection Agency’s Implementation of the Safe Drinking Water Act’s Unregulated Drinking Water Contaminants Program.” Please start watching at about two hours and seven minutes and see the interaction between Dr. Steven Patierno and Senator Barbara Boxer.

Do you believe the concerns expressed in the first video are reasonable? Why or why not? If not, how would you go about edifying this individual? What did Dr. Patierno do right in his interaction with the Senator from California, and what did he do wrong?

### **1.12.2 Risk Assessment History: Robert F. Kennedy's Speech at the University of Kansas**

This speech can be heard in its entirety on YouTube at [www.youtube.com/watch?v=z7-G3PC\\_868](https://www.youtube.com/watch?v=z7-G3PC_868) and provides excellent discussion material.

### **1.12.3 Animal and Human Carcinogens**

Not all chemicals that cause cancer in laboratory animals also cause cancer in other species, including humans. For example, phenobarbital has been used as a sedative in humans since 1912 and is also used to treat epilepsy in dogs. Phenobarbital is a potent carcinogen in rodents at doses that produce sedation in humans. Gold and colleagues have developed a compendium of animal and human carcinogens. This paper is available free of charge at [www.ncbi.nlm.nih.gov/pubmed/11794380](https://www.ncbi.nlm.nih.gov/pubmed/11794380). After reading this paper, how would you decide if a chemical that has been shown to be carcinogenic in animals would also be carcinogenic in humans? When is an animal bioassay likely to produce a false positive or a false negative result?

## **FURTHER READING**

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## CHAPTER 2

# Perception, Planning, and Scoping, Problem Formulation, and Hazard Identification

### ***All Parts of Risk Assessment***

Whereas many persons live in great fear and apprehension of some of the more formidable and notorious diseases, I shall set down how many died of each: that the respective numbers, being compared with the total ... those persons may better understand the hazard they are in.

**John Graunt**

*Natural and Political Observations Made upon the Bills of Mortality*, 1663

Risk means different things to different people. If you watched the “story of stuff” video from the first exercise at the end of Chapter 1, you should now realize that the woman in this video, similar to many untrained in risk analysis, was confusing hazard identification with risk assessment. Both toxicity and exposure contribute to risk; understanding both in quantitative terms is necessary for any credible characterization of risk. Hence, low but detectable levels of chemicals known to be toxic may be present in the environment, but would not present a concern because the exposure and resulting risk are very low. Flaws in both exposure assessment and hazard characterization can confound risk characterization results.

### **2.1 WHAT IS RISK, AND HOW CAN WE ESTIMATE RISK?**

Risk perception also changes the way risk is viewed. Risks may be voluntary or involuntary. The classic example of this distinction is the individual attending a public meeting about a nearby hazardous waste site who lights up a cigarette and asks: “So what are you going to do to prevent me from getting cancer from these nasty environmental chemicals? And, by the way, why did you have this meeting on Saturday? That’s when I go skydiving.” This facetious example is provided to illustrate the difference between the perception between voluntary and involuntary

risk. This individual chose to smoke cigarettes and to jump from airplanes—both voluntary risks—but did not want to experience risk brought by the actions of others.

### **2.1.1 Three Types of Risk: Aleatory, Epistemic, and Ontological**

Aleatory risk stems from the randomness of known uncertainties. Every time I drive to the grocery store, a small but finite risk exists for a traffic accident.<sup>1</sup> This risk can be known from safety statistics of driving compiled by the Department of Transportation.

Epistemic risk stems from a lack of fundamental knowledge.<sup>1</sup> The movie *The Big Short* deals with the epistemic risk leading up to the 2007–2008 financial crisis. Many investors were unaware of the problems with mortgage-backed securities. The hazards to humans of perfluorinated chemicals, introduced in Chapter 1, remain unknown and uncertain despite the observed adverse effects on reproduction and development in laboratory animals; the majority of animal testing is not predictive of human toxicity.<sup>2,3</sup>

Ontological risk was most memorably defined by Secretary of State Donald Rumsfeld during the Iraq War as the “unknown unknowns.” These risks stem from uncertainties of which one is unaware. The philosopher David Hume noted there is no way to prove a general case from a limited set of observations. This problem of induction is compounded by inattention to one’s ignorance—for example, looking for one’s car keys at night under a street light because it’s the only place the keys will be visible.

The first two types of risk will be considered again in Chapter 6 on risk characterization. In today’s complex world, risk analysts would do well to keep ontological risk in mind, as a reminder of the limits of the science of risk analysis in predicting surprises.

### **2.1.2 Risk of Being Struck by Lightning**

Risk means different things to different people. Insurance actuaries, gamblers, toxicologists, statisticians, epidemiologists, and laypeople all use this word in different contexts. The idea of risk arose in the field of statistics; likely as a result, there are a number of ways in which numerical values for risk can be expressed. Below, the risk of being struck by lightning will be used as the first example, and the risk of being struck by lightning while swimming in an indoor pool will provide the second example.

#### **2.1.2.1 Frequentist or Actuarial Risk of Lightning**

The risk of being struck by lightning in the United States can easily be calculated based on historical values.<sup>4</sup> The average number of reported deaths per year from lightning during the period from 2001 to 2010 was 39. The average number of reported injuries over the same period was 241. From the 2000 census, the US population was 281,421,906. From the 2010 census, the US population was 308,745,538. We will assume the average for the period from 2000 to 2010 is represented by the

average of these two values, or 295,083,722. Hence, the risk of being struck by lightning can be calculated as follows:

$$(\text{Deaths} + \text{Injuries}) / \text{Population at risk} = (39 + 241) / 295,083,722 = 9.5\text{E-}07 \quad [2.1]$$

Hence, the risk of being struck by lightning is around 1 in 1,000,000. This estimate is based on the assumption that the frequency of past events reflects the likelihood of similar events occurring in the future. This is known as frequentist or actuarial risk. Insurance companies use actuarial risk in setting rates. Most accidental death policies do cover death by lightning strike, so insurance policies consider being struck by lightning and dying to be a low-risk event—a good bet, so to speak.

Several uncertainties are inherent in this lightning risk estimate—the number of reported deaths and injuries may not be accurate, as may the population estimate, but population estimate contributes less to uncertainty because this number is so large and occurs in the denominator.

### **2.1.2.2 Predicted Risk of Lightning: Using a Model**

There is another way to estimate the risk of being struck by lightning—the use a prediction model. For example, one could estimate three quantities on a yearly basis:

- average number of lightning ground strikes per year;
- average number of people at risk during a single lightning event;
- probability of a lightning strike hitting a person.

The model would be a simple multiplication of these factors

$$\begin{aligned} \text{Strikes/year} \times \text{people at risk/strike} \times \text{probability of a strike} \\ = \text{Risk of being struck by lightning} \quad [2.2] \end{aligned}$$

This simple prediction model seems quite logical until one attempts to obtain data on these quantities. There is a wide geographic variation in the number of strikes per year. For example, Singapore has one of the highest rates of lightning activity in the world.<sup>5</sup>

For this example of a prediction model, we will consider “Lightning Alley,” the area between Tampa and Orlando in Central Florida that sees more lightning than any other area in the US with as many as 50 strikes per square mile, corresponding to 20 strikes per  $\text{km}^2$ . If one assumes that the Orlando metropolitan area is a target, this area is home to 2,000,000 people and has an area of 260  $\text{km}^2$ , so one can determine the risk of being struck by lightning in Orlando.<sup>6</sup>

Multiplying 260  $\text{km}^2$  by 20 strikes/ $\text{km}^2$ , one can calculate 5200 strikes per year in the Orlando metropolitan area. If one further assumes that lightning has an equal

probability of striking any part of the area with similar frequency,\* and that a single strike affects an area of 100 m<sup>2</sup>, then the lightning strikes affect 0.2% of the area each year; 10% of the population will likely never experience this risk because they spend little to no time outside during storms. Hence, the population at risk would be 1,800,000, not 2,000,000—although the value of 2,000,000 could still be used in the denominator as representing the entire potentially affected population depending on the assumption and type of risk estimate desired. Further, if the population, similar to the assumed occurrence of lightning, is evenly distributed over the metropolitan area<sup>†</sup> and each individual has a 1% chance of being outside during a storm,<sup>‡</sup> then the prediction model would be:

$$\begin{aligned} & \text{Population at risk} \times \text{Likelihood of being outside / Entire Population} \\ & \quad = \text{Risk of being stuck by lightning in Orlando} \end{aligned} \quad [2.3]$$

$$\text{Population at Risk} = 0.2\% \times 90\% \times 2,000,000 = 3600 \quad [2.4]$$

$$\text{Susceptibility} = \text{Likelihood of being outside during a storm} = 1\% \quad [2.5]$$

$$\text{Entire Population} = 2,000,000 \quad [2.6]$$

$$3600 \times 1\% / 2,000,000 = 1.8\text{E-}05 \quad [2.7]$$

This model produces a risk estimate that is 15 times higher than that for the entire USA. Perhaps this difference reflects the increased occurrence of lightning in Orlando. There is considerable uncertainty about the assumptions used to calculate the risk estimate specific to Orlando, but there is also uncertainty about whether the simple calculation that yielded a risk of 1 in 1,000,000 for the entire USA is applicable to Orlando.

In 2011, eight people were injured by a lightning strike occurring at SeaWorld's Discovery Cove water park in Orlando. Three of these people were guests at SeaWorld, and the others were employees.<sup>7</sup> The fact that eight people were injured in a single lightning strike suggests that the population density in the Orlando area may be a factor in increasing the risk. However, the fact that Orlando is a tourist destination means that the estimated number of people at risk—i.e., the denominator—may be higher than the number of residents. In 2011, a total of 55,000,000 people visited Orlando.<sup>6</sup> Would visitors who likely spend more of their time outside be more susceptible to lightning? The number of visitors is much higher than the resident population and would likely affect calculation of both the numerator and denominator. Just how the presence of visitors would affect the risk estimate is not entirely clear because of the many assumptions used in the model.

\* “They” do say that lightning never strikes twice in the same place.

<sup>†</sup> Both these assumptions are obviously incorrect!

<sup>‡</sup> This value is based on professional judgment, which is code or risk-speak meaning that no one has any idea what the true value is.

### **2.1.2.3 Perceived Risk of Lightning**

The news report from SeaWorld suggests still another way to determine risk—perception or subjective judgment. Following this news report, many people would no doubt be concerned about the risk of lightning in Orlando; with time and fading memory, this perception would also likely fade.

If one were concerned about the risk of being struck by lightning, such news might suggest that the higher of the two very uncertain estimates is more correct. This is not necessarily true. While the uncertainties in these estimates were discussed, albeit briefly, it should be abundantly clear that one could have little to no confidence in the accuracy of either estimate.

Extrapolating from the estimate of 1 in 1,000,000 from the entire United States to Orlando seems to produce an underestimate of the risk, possibly because of the greater density of lightning in Orlando. The use of the Orlando-specific values for resident population density along with the assumption that the population is evenly distributed over this area are both incorrect. The lightning strike at SeaWorld injuring eight indicates that people tend to cluster. A tourist attraction such as SeaWorld will tend to produce such clusters. Will these clusters increase or decrease risk? Well, it all depends where people are when lightning strikes ....

### **2.1.2.4 Predicted Risk of Lightning While Swimming in an Indoor Pool**

The National Association of Parks and Recreation monthly magazine reports: “There are no *documented* reports of fatal lightning strikes at indoor swimming pools. None! Ever!” The article goes on:

The decision to close indoor swimming pools during these storms is based on irrational fears rather than objective facts. The problem with closing indoor swimming pools during electrical storms is that this policy places people at greater risk by removing them from the safe confines of swimming pools and placing them in unprotected areas like on phones, in showers, outdoors and in cars where electrical storms have killed people.<sup>8</sup>

Tom Griffiths, the first author of the report, is the president and founder of Aquatic Safety Research, LLC. The article goes on to compare lightning strikes to shark attacks, in that both are rare events.

The author of this textbook has been known to enjoy a swim at the Boundary Waters Aquatic Center in Douglas County, Georgia. This pool is well-kept and clean; the lifeguards and managers are pleasant. The county has, however, adopted as a policy the practice of closing the pool for 30 minutes whenever thunder is heard. Other indoor pools use the “flash-bang” method—counting off seconds between visible lightning and the first sound of thunder to determine distance from the lightning assuming sound travels 1100 feet per second. Some indoor pools ignore thunderstorms altogether.

Given that no evidence exists that a swimmer has ever been affected by lightning while using an indoor pool, how should we calculate this risk? This example provides an introduction to the use of probability distributions. Here, we will consider

the Poisson distribution, a collection of integer values that expresses the number of events occurring in a fixed interval given that the events occur independent of time. The Poisson distribution is defined by single parameter, the rate, or  $\lambda$ . The best-known historical application of the Poisson distribution is the estimate of the number of Prussian cavalry officers killed accidentally by horse kicks. These officers were uniformly superb horsemen, and accidental death by horse kick was a very rare event.

The historical estimate of the number of people injured or killed by lightning while swimming in an indoor pool is zero, based on the statement from the National Association of Parks and Recreation. Unfortunately, the Poisson distribution is undefined at a rate parameter of zero. One can, however, use the chi-squared distribution as a surrogate for the Poisson distribution. A reasonable value for the upper bound of a Poisson distribution with a rate parameter of zero is 3. An exploration of this calculation is provided as an exercise at the end of this chapter.

In the US, 15% of adults and 36% of children aged 7–17 go for a swim in an indoor at least six times a year. The US population in 2019 is estimated at 328,035,332.<sup>9</sup> The number of children aged 5–17 is 53,716,518.<sup>10</sup> Thus, the number of adult and child swimmers in the US is estimated at 60,485,769, and 3/60,485,769 equals about 5E-08, or 5 in 100,000,000. Considering the 2017 estimate for the population in Douglas County, Georgia, or 143,882,<sup>11</sup> the number of lightning strikes causing injury or death at the aquatic center would be 7 in 1000. About 140 years would elapse between such events!

This calculated risk is almost 20 times lower than the risk of lightning in the USA. Given this difference in risks, why would Boundary Waters Aquatic Center maintain such a seemingly unreasonable policy? A possible answer will be given when this example is revisited later in the book.

The point of this discussion has been to use the risk from a familiar event to illustrate just how one can characterize risk. All of the estimates of the risk of being struck by lightning are incorrect, but they do illustrate the types of risk estimates and the difficulty of having sufficient confidence in a risk estimate to undertake a risk management action, even one as minor as closing a pool for 30 minutes.

## **2.2 DESIGNING RISK ASSESSMENTS: PLANNING AND SCOPING VERSUS PROBLEM FORMULATION**

Risk management decisions necessarily proceed from the initial steps of (1) planning and scoping activities and (2) problem formulation. There will be practical implications stemming from the results of both steps about which adverse outcomes to investigate, which data are most relevant to the problem, and which risk management options should be considered. Stakeholders will likely have different goals and likely a range of divergent perspectives on the problem. These divergent perspectives will necessarily lead to different problem formulations, and thus different decisions.

For example, a response to concern about the risk of being struck by lightning when visiting SeaWorld would be to shut down this popular attraction—the same risk management decision as at some indoor swimming pools. Stakeholders in this

decision would, of course, be the owners and patrons of the facility as well as patrons fearful of lightning. Obviously, the owners would be opposed to closure—as would those children who had been looking forward to their SeaWorld visit.

In these initial risk assessment activities, the wishes of all parties need to be considered. Inclusion of a range of stakeholders in planning and scoping is important, both to be fair and to avoid missing aspects of the problem of which a more limited group of stakeholders might not be cognizant.

Early in the development of ecological risk assessment guidance, the US Environmental Protection Agency (EPA) separated the initial steps of risk assessment into (1) planning and scoping and (2) problem formulation.<sup>12–15</sup>

Planning and scoping involve discussions between risk managers and stakeholders, with risk assessors playing a supporting role. The result of planning and scoping activities is ideally a broad conceptual statement of the problem, options for its solution, and any tradeoffs that need to be considered.

Problem formulation involves discussions between risk managers and risk assessors to develop the detailed design for the assessment, including technical and scientific considerations. The result of problem formulation would ideally reflect that broad conceptual statement developed in planning and scoping.

The National Environmental Policy Act (NEPA) did not discuss problem formulation *per se*; however, NEPA outlines a scoping process for environmental impact statements that includes elements of problem formulation.<sup>16</sup>

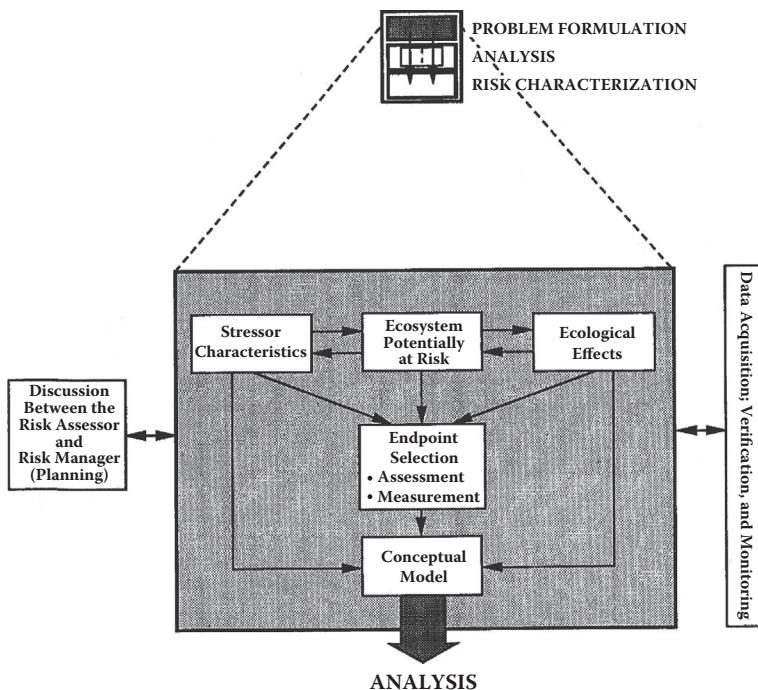
## 2.2.1 History of Problem Formulation

The first use of the term “problem formulation” and first discussion regarding environmental risk assessment were presented in EPA’s 1992 *Framework for Ecological Risk Assessment*.<sup>12</sup> Although the definition presented was limited to ecological risk assessment, it was applicable to any type of risk assessment:

Problem formulation is the first phase of ... and establishes the goals, breadth, and focus of the assessment. It is a systematic planning step that identifies the major factors to be considered in a particular assessment, and it is linked to the regulatory and policy context of the assessment.<sup>12</sup>

The centerpiece of problem formulation is a conceptual model. This model contains a set of working hypotheses of how stressors might affect human health or aspects of the natural environment. Hence, problem formulation would determine the nature and extent of data collection efforts to support the risk assessment. Figure 2.1 shows EPA’s diagrammatic representation of problem formulation in ecological risk assessment.<sup>12</sup>

In the 1996 report *Understanding Risk: Informing Decisions in a Democratic Society* from the National Academies of Sciences (NAS), problem formulation is the first step in the analytic-deliberative process that results in a risk characterization.<sup>17</sup> This was the first document related to human health risk assessment that recognized the importance of careful up-front planning and the need to formalize problem formulation as part of risk assessment.



**Figure 2.1** Problem formulation in ecological risk assessment (from EPA's *Framework for Ecological Risk Assessment*).

## 2.2.2 The Need for Problem Formulation Is Not Limited to Ecological Risk Assessment

The 1997 Federal Commission Report indicated that problem definition and context should be the first step in a risk assessment.<sup>18</sup> In human health risk assessment, the general activity of planning seems to have been given short shrift by EPA until well past the year 2000. The discussion of “scoping” provided by EPA in *Risk Assessment Guidance for Superfund* (RAGS) is, at best, a placeholder, brief and overly general.<sup>19</sup> As noted, in ecological risk assessment, planning and scoping is distinguished from problem formulation, and the latter is defined very specifically. Problem formulation is a process for generating and evaluating preliminary hypotheses about why ecological effects may occur or have occurred. The process includes plans for developing a conceptual model, collecting and analyzing data, and characterizing risk.<sup>14,20</sup>

Other organizations and disciplines also use the process of problem formulation. It is the focus of activities in operations research, and problem formulation as a formal defined activity is used in evaluation of medical treatments, public health interventions, and military planning.<sup>21-25</sup>

For example, problem formulation is an inherent part of the North Atlantic Treaty Organisation (NATO) *Code of Best Practice for Command and Control Assessment* (COBP).<sup>26</sup> The principles and methods described by NATO for the assessment for

risk associated with war and operations other than war also apply to environmental risk assessment. A multi-disciplinary and eloquent description of problem formulation is provided in the COBP:

Explicit problem formulation must precede construction of concepts for analysis or method selection. This is not a trivial exercise ...

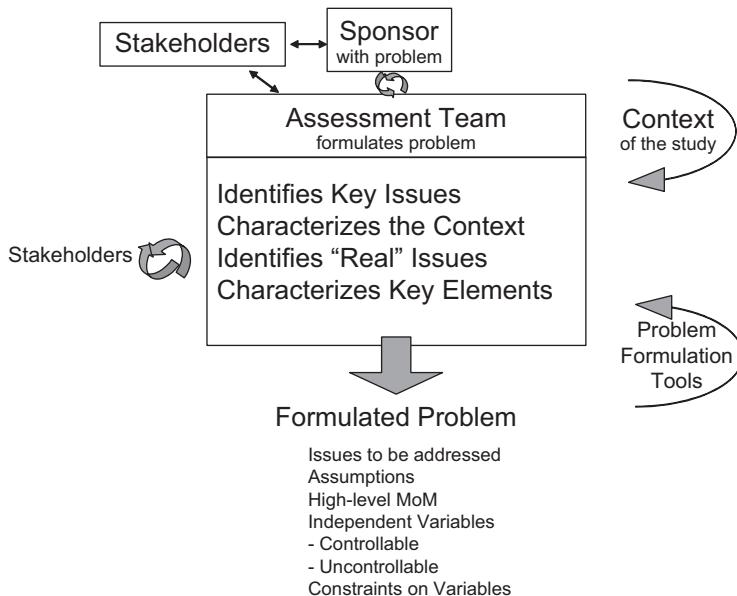
Problem formulation must not only provide problem segments amenable to analysis, but also a clear and valid mechanism for meaningful synthesis to provide coherent knowledge about the original, larger problem. The formulated problem is thus an abstraction of the real problem ... that can be interpreted in terms of decisions and actions.

Problem formulation must be broad and iterative in nature, accepting the minimum of a priori constraints and using methods to encourage creative and multi-disciplinary thinking, such as proposing a number of hypotheses for the expression of the problem.

Practical constraints such as data availability, study resources (including time), and limitations of tools should be treated as modifiers of the problem formulation rather than initial drivers. Such constraint may, in the end, drive the feasible solutions, but it is important to recognize this as a compromise rather than an ideal. *Proper problem formulation takes substantial time and effort!*

It is important that problem formulation address risk from multiple perspectives. In addition to sensitivity analysis of the dependent variables, risk analysis techniques should be used to directly explore options to mitigate risk.<sup>26</sup>

The iterative nature of problem formulation becomes clear from the diagram of the problem formulation process used by NATO (Figure 2.2). Essentially, the NATO guidance described problem formulation as a “voyage of discovery.”



**Figure 2.2** NATO overall study plan for problem formulation. MoM stands for “measures of merit” for command and control options and the likely outcome of these options in terms of effectiveness or performance.

### 2.2.3 The Importance of Problem Formulation for All Risk Assessments

Although several EPA guidance documents have indicated that problem formulation as well as planning and scoping should become a part of human health risk assessment, in practice, this does not always happen.<sup>12–14,27</sup>

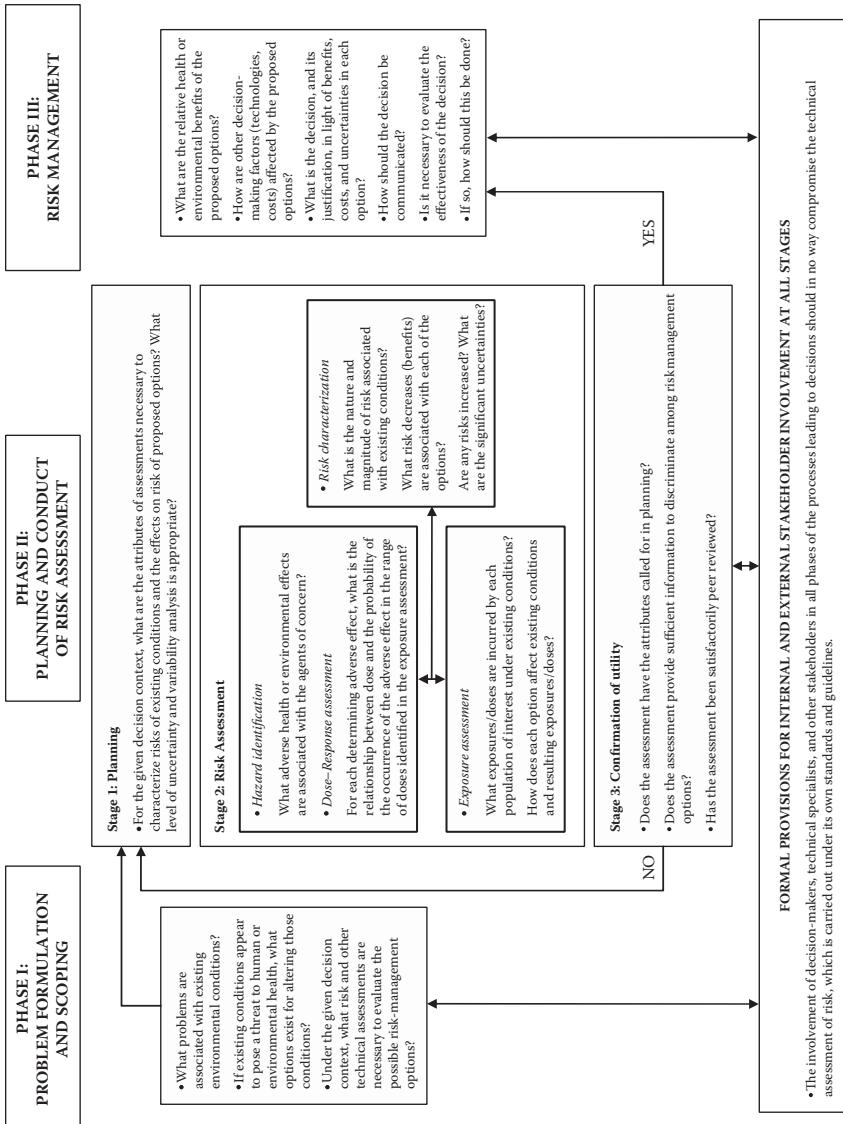
In 2009, the National Research Council released a report titled *Science and Decisions: Advancing Risk Assessment*.<sup>28</sup> This report is known as the “Silver Book” because of the color of its cover. Its purpose was to provide the EPA with a plan for improving the risk assessment/risk management process in the short term of two to five years and the long term of 20 years. The report recommended a three-phase approach to risk assessment—Phase I would be problem formulation (Figure 2.3). The report made several recommendations to EPA, and indicated that implementing these recommendations would constitute a significant transformation of the culture of risk assessment and decision-making within EPA.

Risk assessment is both a process and a product, in that the process creates the product. As such, a major challenge in risk assessment is to design a process that includes considerations of technical quality to create a product that is useful to a community of consumers and decision-makers who may have disparate and, at times, conflicting concerns. The “Silver Book” uses the term “design” to imply the adoption of a viewpoint of user-friendliness to develop both a transparent and science-based assessment process and decision-support tool useful to all stakeholders. Problem formulation is a design activity that occurs, or should occur, early in the risk assessment process and involves understanding and weighing the risk management objectives, the recognition for statutory and state-of-knowledge constraints, and explicit acknowledgement of the need for tradeoffs.<sup>28</sup>

The 1983 “Red Book” discussed in Chapter 1 was strongly supportive of the need for a conceptual distinction between risk assessment and risk management so that the scientific/technical process of risk assessment was free from political or economic influence.<sup>29</sup> Recognition of this conceptual distinction by both risk assessors and risk managers is critical during problem formulation.

The product of a problem formulation likely the most useful to the largest number of stakeholders is the conceptual model. Figure 2.4 shows a conceptual model for an air pollution risk assessment. The major elements of a conceptual model that provide information for the risk assessment process about what data to obtain and how to interpret and analyze these data are:

- sources;
- stressors or pollutants;
- exposure pathways and/or exposure media;
- routes of exposure;
- exposed populations;
- endpoints/outcomes of concern;
- metrics used for decision-support.



**Figure 2.3** The role of problem formulation in the overall process defined by the “Silver Book.”

• The involvement of decision-makers, technical specialists, and other stakeholders in all phases of the process leading to decisions should in no way compromise the technical assessment of risk, which is carried out under its own standards and guidelines.

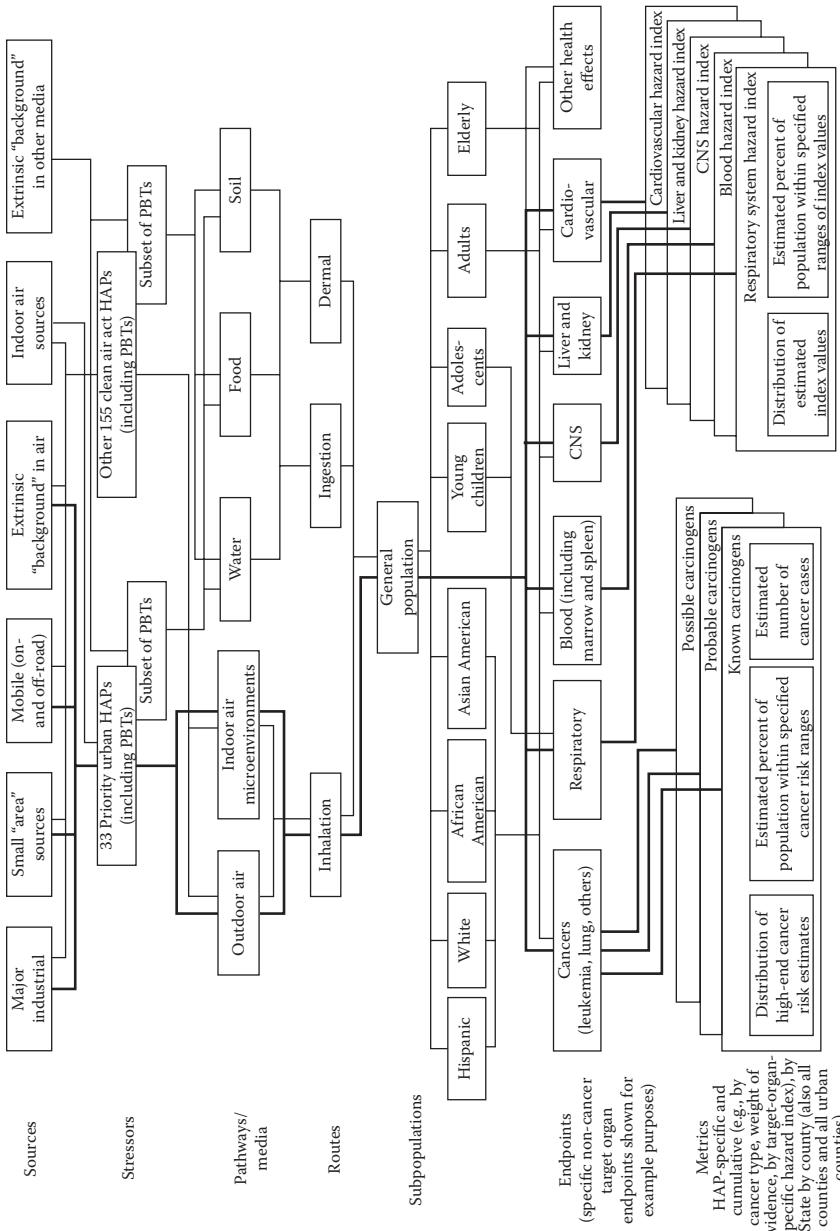


Figure 2.4 Example of a conceptual model for air pollution risk assessment (from the "Silver Book").

The usefulness of conceptual models and problem formulation led the National Research Council (NRC) to recommend that EPA formalize these as part of the human health risk assessment process.<sup>28</sup>

EPA faces significant challenges in the implementation of problem formulation and other “Silver Book” recommendations.<sup>30</sup> One of the NRC committee members even suggested, quite eloquently, scrapping the divide between risk assessment and risk management because it interferes with effective problem formulation.<sup>31</sup>

The basic dogma holds that risk assessment must precede risk management. But there is an opposite and perhaps better way: the opening question should not be “How bad is the problem?” but “How good are the solutions we might apply to the problem?”<sup>31</sup>

In 2012, EPA initiated a multi-agency collaborative effort called the NextGen program—presumably to address these challenges. The agencies involved include the National Institute of Environmental Health Sciences, the National Center for Advancing Translational Sciences, the Centers for Disease Control, the National Center for Toxicological Research of the Food and Drug Administration, the Department of Defense, and one state agency, California’s Environmental Protection Agency.

A 2012 publication by EPA staffers on NextGen references the “Silver Book,” but no specific details of how recommendations therein, including those related to either planning and scoping or problem formulation, will be implemented or addressed.<sup>32</sup> Hence, the future role of problem formulation remains to be determined.

One area in which problem formulation became codified and formulaic was the approach of Integrated Risk Information System (IRIS), part of EPA’s National Center for Environmental Assessment. In EPA’s 2010 formaldehyde IRIS assessment, the concentration in air at a cancer risk level of 1 in 10,000 equaled 1.2 parts per billion (ppb).<sup>33</sup> Just to put this risk-specific dose in context, formaldehyde is produced naturally in the body, and formaldehyde concentrations occurring in normal human breath may be up to 50 ppb. Higher levels may occur as the result of disease and are being explored for use as a clinical biomarker.<sup>34-37</sup> Using heavy isotope labeling, endogenous and exogenous formaldehyde could be distinguished; when data on exogenous adducts were used as the basis of the risk assessment, the risks were up to 20,000 times lower than estimated by EPA.<sup>38,39</sup> EPA did not consider natural endogenous levels of formaldehyde in the body; a good faith problem formulation might have alleviated this knowledge gap.

Congress requested that the National Academies of Sciences review the formaldehyde IRIS assessment, and the ensuing report was highly critical of the IRIS program. One of the responses to the NAS review was to develop a preamble to IRIS assessments—essentially a codification of the necessary problem formulation.

At its heart, problem formulation is a set of hypotheses and a plan for interpreting the available information to rank the likelihood of these hypotheses. Problem formulation is applicable to all phases of risk assessment, including the characterization of both exposure and hazard. Conducting a credible problem formulation requires a systematic approach to identify all the factors critical to the goal of the particular phase

of the assessment, including the depth and scope of analysis, available resources, and possible outcomes.<sup>40,41</sup> In short, the NATO description of problem formulation as a voyage of discovery was spot on!<sup>126</sup>

## 2.3 HAZARD VERSUS RISK

At the beginning of this chapter, we considered the risk of being struck by lightning. The point of that discussion was to use the risk from a familiar event to illustrate ways one can characterize risk. The quantitative estimates of the risk of being struck by lightning presented earlier were wrong—nonetheless, they illustrate the types of risk estimates.

How might one determine in which risk estimate one has more confidence? One way is to examine the weight of the scientific evidence supporting each estimate.

Relating these lightning risks to hazard identification, all this information could serve as the basis of identifying lightning as a hazard—and, of course, not just in Orlando. The single incident of the lightning strike and the resulting injuries at SeaWorld are sufficient to identify lightning as a hazard even if the risk cannot be accurately predicted. This is the essence of the difference between hazard identification and risk characterization. The management at Boundary Waters Aquatic Center chose to use an identified hazard as a surrogate for risk.

The task of hazard identification is complete when one can say: “We know it’s bad, but we don’t know how bad.” Conversely, hazard characterization requires one to provide an estimate of just how bad it is.

Life is never risk-free—there is no such thing as zero risk in any situation. Hence, the task of hazard identification is based to a large degree on ascertaining when conditions have the potential for unreasonable risk. Chapter 1 dealt extensively with the definition of unreasonable risk, and “unreasonable” is most always defined by societal consensus, most often in the form of judgment by elected government officials or their appointees.

Obviously, there has to be some information upon which to base the claim of hazard. Weight of evidence (WOE, discussed in depth below) is an important consideration.

For example, high doses of the artificial sweetener saccharin have been shown to be carcinogenic in rats, evidenced by a dose-related increase in urinary bladder tumors. High doses of the sweetener aspartame produced an increase in brain tumors in rats.<sup>42</sup> As a society, shouldn’t we be concerned about these two carcinogenic chemicals that are used ubiquitously as sweeteners and consumed every day by millions of people? Why are these substances approved for human consumption? Shouldn’t they be banned? Such a ban would certainly be in the spirit of the Delaney Clause.

Additional studies on both substances suggest that the mechanism by which saccharin causes cancer in rats is not relevant to humans, and that the experimentally observed carcinogenicity of aspartame could not be confirmed in later experiments.<sup>43–45</sup>

The point is that hazard identification and risk characterization are not the same. In passing the Delaney Clause banning all suspected carcinogens from food packaging, the US Congress confused hazard identification with risk characterization—just as the woman in the “story of stuff” video did in the exercise at the end of Chapter 1.

### 2.3.1 What Is Hazard Identification?

Likely the first attempt at developing information on the hazard of various diseases was that of John Graunt, a London merchant who was born in 1620. In 1603, the city of London began keeping records of births and deaths. There were several reasons—that year, one of the worst outbreaks of plague occurred, and information about the population of London was needed for tax revenues. In 1663, Graunt published the frequency of various causes of death experienced by Londoners in *Natural and Political Observations Made upon the Bills of Mortality*, quoted at the start of this chapter.<sup>46</sup>

Hazard identification, as defined by the “Red Book” is the procedure for determining whether exposure to a chemical can increase the incidence of an adverse health outcome. Hazard identification characterizes the nature and weight of the evidence, and thus involves consideration of causation. Hence, there is almost never a simple yes/no answer supported by definitive data. The evidence for hazard identification may depend on epidemiologic or other human studies, results from laboratory animal testing, *in vitro* studies of cells of both human and animal origin, quantitative structure–activity estimates, and other *in silico* predictive methods.

By itself, hazard identification can provide the conclusion that a chemical poses little or no risk to human health or the environment, and thus would not be of regulatory concern. However, should a chemical be identified as potentially hazardous, then the other three steps of the risk assessment process—exposure assessment, dose–response assessment, and risk characterization—would need to be undertaken. The distinction between hazard identification and hazard characterization is an important one; dose–response assessment might be more appropriately named hazard characterization.

Following the “Red Book” in 1986, a consortium of US government agencies essentially codified the use of the term “hazard” as separate from “risk.”<sup>47</sup> Figure 1.1 showed the four parts of risk assessment detailed in the “Red Book” and elsewhere, and for risk to occur, there must be both a hazard and sufficient exposure to this hazard.<sup>29</sup>

The “Red Book” pointed out that the regulatory actions stemming from the Delaney Clause were based on hazard identification only, not on a complete risk assessment. In fact, the Delaney Clause precluded the performance of a risk assessment for known or suspected carcinogens.<sup>29</sup> To be perfectly clear, the Delaney Clause, inappropriate or not, was an exercise of the Precautionary Principle.

The “Blue Book” defines hazard identification as:

the identification of the contaminants that are suspected to pose health hazards, quantification of the concentrations at which they are present in the environment, a description of the specific forms of toxicity (neurotoxicity, carcinogenicity, etc.) that

can be caused by the contaminants of concern, and an evaluation of the conditions under which these forms of toxicity might be expressed in exposed humans.<sup>48</sup>

Data for hazard identification are typically obtained from environmental monitoring data as well as epidemiologic and animal studies. Like the “Red Book”, the “Blue Book” was also careful to distinguish hazard identification from both dose-response assessment and risk characterization.<sup>48</sup>

The 1997 *Presidential/Congressional Commission Report on Risk Assessment and Risk Management* mentioned but did not discuss hazard identification.<sup>18</sup> This report was focused on the interface between risk assessment and risk management. The report notes that hazard is an intrinsic property of a substance or a situation, and gives some useful examples. The report indicates benzene does not cause lung cancer, but can cause leukemia. A garter snake bite may be harmless, but a rattlesnake bite can kill if untreated. Hence, an unidentified snake should be considered a potential but uncharacterized hazard.

In the framework for regulatory decision-making in the report, four data sources for hazard identification of potential carcinogens were identified—epidemiology, lifetime rodent bioassays, high-throughput *in vitro* tests and structure-activity considerations. The ability of high-throughput data to inform risk assessment is an area of intense research, spearheaded by the multi-agency Tox21 program that includes EPA, the Food and Drug Administration (FDA), and the National Institutes of Health. Translating the results of high-throughput assays into risk-based decisions necessitates establishment of scientific confidence in the assay results and the associated prediction models. To be useful, hazard characterizations from high-throughput screening (HTS) assays must provide as much or more confidence in the results as do traditional sources such as animal testing or epidemiology.<sup>49–52</sup>

The various data sources are discussed below, and the situation today is similar to that in 1997 except that much more is known about the strengths and limitations of these data sources.

### 2.3.2 Uncertainty Classifications Used in Hazard Identification

In 1977, the International Agency for Research on Cancer (IARC) produced guidelines giving five classifications of evidence that a chemical might be carcinogenic in humans. IARC pointed out that “for practical purposes” and because of the lack of scientific evidence of a correlation between animal and human carcinogenicity, the pragmatic position was to assume that animal carcinogens could also be human carcinogens.<sup>53</sup> The five classes of evidence defined by IARC were:

- *sufficient evidence of carcinogenicity*—increased incidence of malignant tumors: (a) in multiple species or strains, or (b) in multiple experiments (preferably with different routes of administration or using different dose levels), or (c) to an unusual degree with regard to incidence, type of tumor, or tumor site or age at onset;
- *limited evidence of carcinogenicity*—data suggesting a carcinogenic effect, but limited because: (a) the studies involve a single species, strain, or experiment, or

- (b) the studies use inadequate dosage levels, inadequate duration of exposure, inadequate follow-up or survival, low statistical power because of methods or number of animal, or (c) the neoplasms were likely spontaneously occurring or difficult to classify as malignant;
- *inadequate evidence of carcinogenicity*—inability to interpret the evidence as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations;
- *negative evidence of carcinogenicity*—within the limits of the tests;
- *no data on carcinogenicity*.

In 2006, IARC published a preamble to its monographs. The preamble presented groups related to the weight of evidence of human carcinogenicity:<sup>54</sup>

- Group 1—carcinogenic to humans;
- Group 2A—probably carcinogenic to humans;
- Group 2B—possibly carcinogenic to humans;
- Group 3—not classifiable as to its human carcinogenicity;
- Group 4—probably not carcinogenic to humans.

EPA's 1986 *Guidelines for Carcinogen Risk Assessment* indicated that six types of information should be included when considering hazard identification for potential carcinogens:<sup>55</sup>

- physical-chemical properties and routes and patterns of exposure;
- structure-activity relationships;
- metabolic and pharmacokinetic properties;
- toxicologic effects;
- short-term tests, including *in vitro* tests;
- long-term animal studies;
- human studies.

EPA indicated that the weight of evidence for human carcinogenicity was expressed in a letter grouping. These groups were:

- Group A—carcinogenic to humans;
- Group B—probably carcinogenic to humans;
- Group C—possibly carcinogenic to humans;
- Group D—not classifiable as to human carcinogenicity;
- Group E—evidence of non-carcinogenicity in humans.

A number of state agencies and other groups inappropriately adopted these weight of evidence summary criteria as hard-and-fast guidelines. These groupings were the result of attempting to provide an overall picture of nuanced and often contradictory evidence, hence their inappropriate use as “bright” lines. In 2005, these groups were updated with the revision to the Cancer Guidelines as follows:

- carcinogenic to humans;
- likely to be carcinogenic to humans;

- suggestive evidence of carcinogenic potential;
- inadequate information to assess carcinogenic potential;
- not likely to be carcinogenic to humans.<sup>56</sup>

The National Research Council published *Science and Decisions: Advancing Risk Assessment* in 2009. This report does not break any new ground in hazard identification, but points out that any quantitative analysis of uncertainty in hazard identification would require sophisticated methods to synthesize information from multiple scientific domains and multiple scales of information.<sup>57</sup> One important insight provided here was the recognition that uncertainty associated with hazard identification was related to lack of information about critical cause–effect relationships. This uncertainty cannot easily be quantified in a way that would yield a confidence interval or statement of probability. Hence, to some extent, hazard identification ends up being as much an exercise in cognitive science, understanding of bias and heuristics, and epistemology as it is an analysis based in toxicology or risk assessment.<sup>58–61</sup>

In 2015, an attempt was made to identify the key characteristics of carcinogens (KCCs) to be able to use HTS results in hazard identification.<sup>62</sup> IARC assigned various high-throughput assays in the Tox21 program to seven of the ten KCCs and used these to determine cancer hazard classifications. These assignments were done in a broad-brush and uncritical fashion and drew considerable criticism. The short answer was that the IARC determinations of cancer hazard based on HTS data were no better than chance.<sup>63</sup>

### 2.3.3 Weight of Evidence

Although this term was used in the “Red Book,” no specific definition was provided. Despite this, the “Red Book” advanced a long list of questions regarding how risk assessors should weigh various types of evidence, especially when considering carcinogenicity. Weight of evidence plays a central role in risk assessment, and a specific definition, while not yet available, is being shaped.<sup>64–71</sup>

Uncertainty is the unwelcome but constant handmaiden of science. The decision process for hazard identification to which the term “weight of evidence” is applied has so far been an unstructured combination of scientific evidence, interpretation of that evidence and so-called expert judgment—vulnerable to the biases of those involved.

The term “weight of evidence” may possess three meanings:

- *metaphorical*—where WOE refers to a collection of studies and an unspecified approach to examining these studies in the aggregate;
- *methodological*—where WOE refers to interpretive methodologies used in meta-analysis, systematic review, or application of considerations of causation;
- *theoretical*—where WOE has a specific meaning for pattern recognition in cognitive psychology, and still another theoretical meaning in the legal system.<sup>72</sup>

Psychologically, humans tend to “weigh” evidence incorrectly, and heuristic evaluations of evidence lead to over- or underconfidence in the conclusions (see Box 2.1).

### BOX 2.1 WEIGHT OF EVIDENCE VERSUS STRENGTH OF EVIDENCE

In assessing the confidence or degree of belief in a given hypothesis, it is vital to distinguish between the weight of the evidence—its predictive validity—and the strength of the evidence—its level of extremeness. Human nature tends to make one overconfident when strength is high and weight is low, and underconfident when strength is low even if the weight is high. In other words, humans tend to rely on anecdotal evidence. Scientists, being human, must exercise discipline to conduct an appropriate weight of evidence analysis that a particular chemical is linked to cancer or some other adverse effect.

Because of human nature, the formation of a belief that a particular chemical causes a particular effect may depend on a single study in which the effect was easily observed or a large proportion were affected. This belief may persist even though the predictive validity of the study was weak. Predictive validity depends on study design, sample size, background rates, and other factors. Hence, even experienced scientists may tend to use heuristics when a “wow” factor is present.<sup>73,74</sup>

Hypothesis-based weight of evidence evaluation is an increasingly used tool to understand and put into context the growing body of data on the effects of chemicals.<sup>73</sup> One particularly difficult issue is the distinction between effects that are adaptive and effects that are adverse.<sup>75</sup> Two factors have given new urgency to the task of understanding just which effects are adverse and which are not—first, the ever-increasing ability of chemists to measure lower and lower levels of chemicals in human tissues as well as other biomarkers, and second, the extreme sensitivity of many *in vitro* assays that use biologically engineered systems with unknown relevance to humans. Weight of evidence evaluations in toxicology are now based on some understanding of the mode of action, as discussed in Chapter 1. Weight of evidence frameworks are expected to be a way to avoid bias when interpreting the plethora of available toxicological data.<sup>75,76</sup>

Physicians have been most obviously guilty of such errors in judgment. To address this issue in the practice of medicine, where decisions based on scientific evidence are routine, in 1971, Dr. Archie Cochrane, a student of Sir Austin Bradford Hill, published a monograph titled *Effectiveness and Efficiency* that was strongly critical of subjective decision-making processes of most physicians because of the inherent biases and inconsistencies. Cochrane was a strong and vocal champion of randomized clinical trials as the best evidence for medical decisions.<sup>77</sup>

Decisions based on so-called expert judgment have been called “authority-based” rather than evidence-based.<sup>78</sup> The Cochrane collaboration develops systematic reviews of medical and scientific evidence for health care interventions.<sup>79</sup> This collaboration was developed precisely because physicians tended to base their health care decisions on heuristics, with the associated biases and overconfidence. The Cochrane collaboration is the foundation of evidence-based medicine and provides

systematic reviews of health care interventions so that providers can use evidence to inform their medical decisions.

Recently, the Evidence Based Toxicology Consortium, part of the Center for Alternatives to Animal Testing at Johns Hopkins University, is attempting to adapt the methods of evidence-based medicine to toxicology to determine the best use of human, animal, and *in vitro* data to inform regulatory decisions.<sup>80-83</sup>

One motivation for using *in vitro* testing is a concern for animal welfare and the growing realization that high-dose experiments in animals are unlikely to yield high-quality information about low-dose effects in humans.<sup>84</sup>

High-throughput *in vitro* testing is used routinely in the pharmaceutical industry to identify potential drug candidates. EPA and others are attempting to use these same methods and assays to determine the risks of the many untested chemicals in commerce today. To date, it appears that high-throughput *in vitro* testing can identify certain positive assay results as no more than qualitative risk factors.<sup>85</sup> What this means is that the results of *in vitro* testing cannot, at present, be used for quantitative predictions of risk, but may possibly be a useful tool for hazard identification.

## 2.4 EPIDEMIOLOGIC STUDIES FOR HAZARD IDENTIFICATION

From a scientific point of view, well-conducted epidemiologic studies provide the most convincing evidence for identifying chemicals or other agents as hazardous to humans. Although a well-conducted epidemiologic study provides evidence of the greatest weight linking a chemical to an adverse effect in humans, such studies are few. In most epidemiologic studies, the statistical power is low, the latency between exposure and disease occurrence is long, and there will always be confounders such as exposure to multiple chemicals, genetic variation in susceptibility, and others.

The most uncertain aspect of observational epidemiology is generally the exposure characterization. Exposure in epidemiologic studies is a time-varying complex quantity for which a summary must be developed before any relationship to health outcomes can be determined. This summary of exposure is most often cumulative over time—e.g., pack-years for cigarette smoking.

The two general types of exposure measures that can be used in epidemiologic studies are: biomonitoring and historical reconstruction. These three are discussed below in relation to hazard identification.

### 2.4.1 Biomonitoring and the Use of Biomarkers

For some chemicals, there may exist biomonitoring data or biomarkers, and these can greatly increase the accuracy of exposure characterization. Biomarkers may represent exposure or effect. Biomarkers of exposure are not viewed in the same way as biomarkers of effect. These are discussed in more detail below with an example.

In the United States, the Centers for Disease Control (CDC) conducts the National Health and Nutrition Examination Survey (NHANES) with the National Center for Health Statistics (NCHS). NHANES data are available at the CDC's website, and include results from questionnaires, physical measurements such as height and

weight, and measurements of hematological parameters and levels of various chemicals in blood. NHANES uses statistical sampling methods to ensure that the data are representative of the entire US population.<sup>86</sup> For example, NHANES includes measurements of more than 200 environmental chemicals, including mercury in hair and blood, lead in blood, as well as dioxin-like chemicals, perfluorinated compounds, and volatile organic compounds in blood.

Thus, for many chemicals, specific biomarkers exist. When such a biomarker is used to verify exposure, epidemiologic studies become much more usable because much of the uncertainty associated with exposure is eliminated.

A variety of human tissues or fluids have been used as sources of biomonitoring or biomarker data. These tissues or fluids include: whole blood or serum, urine, adipose tissue, hair, breast milk, saliva or sputum, semen, and exhaled air. The increasing ability of analytical chemists to measure extremely low concentrations of a variety of chemicals in human tissues requires that these data be presented in the proper context.<sup>87</sup> The presence of a chemical in the body is only indicative of the need for understanding what this finding means—as such, the finding of chemicals present in the body constitutes hazard identification only.

Drs. Harvey Clewell, Melvin Andersen, and Jerry Campbell of the former Hamner Institute are pioneers of the use of physiologically based toxicokinetic (PBTK) modeling (Box 2.4) in risk assessment. These musician/scientists formed a band called the Belladonna Blues Band. Dr. Clewell had written a funny song called “Bad Blood Blues” that the band performed at the 2007 Society of Toxicology meeting, available on YouTube at [www.youtube.com/watch?v=5b7HsDRWPkE](http://www.youtube.com/watch?v=5b7HsDRWPkE). This song humorously illustrates the need for context when interpreting biomonitoring data.

#### **2.4.2 Biomarkers of Exposure and Biomarkers of Effect**

A number of endogenous and exogenous chemical react with DNA to form adducts. The use of DNA adducts as biomarkers of exposure is problematic because a huge amount of DNA damage occurs due to endogenous substances and oxidative stress.<sup>88,89</sup> Endogenous DNA damage is often indistinguishable from that due to chemical exposure, and this greatly complicates the assessment of DNA adducts as biomarkers of exposure. The mere presence of adducts cannot be indicative of a potential deleterious effect of a chemical.

There remains confusion within the risk assessment community regarding the difference between genotoxicity and mutagenicity. A mutation is a heritable change in the DNA sequence that leads to a phenotypic effect, whereas DNA damage reflects genotoxicity only. DNA damage can be repaired, and even if this damage is not repaired, biological regulatory mechanisms will likely cause the cell to undergo apoptosis, or programmed cell death.<sup>88,90–95</sup>

Mutations in certain genes are associated with cancer. A number of acquired characteristics or “hallmarks” constitute the phenotypic changes associated with metastatic transformation.<sup>96,97</sup> The presence of DNA adducts, as a potential source of mutations occurring via faulty DNA repair, is associated with cancer, but without identification of the source of these adducts or consideration of adducts within the overall cancer process, their use for hazard identification cannot be supported.<sup>94,98,99</sup>

One may also measure biomarkers of effect. The most widespread use of this type of biomarker measurement is the level of liver enzymes. Pharmaceutical companies routinely use this sort of testing (see Box 2.2). However, there may be opportunities and motivation to discover chemical-specific biomarkers. For example, 1,3-butadiene, used in rubber manufacture, is metabolized to a highly reactive di-epoxide that reacts with both DNA and proteins; hemoglobin adducts have been shown to be a reliable biomarker of butadiene exposure.<sup>100–103</sup> Chromosomal aberrations and the occurrence of mutations in specific genes in lymphocytes have been used as biomarkers of effect for 1,3-butadiene (see Box 2.2).<sup>89,100,104</sup>

## BOX 2.2 MEASURING BIOMARKERS OF EFFECT IN HUMANS

Cytochrome P450 proteins (CYPs) comprise an enzyme superfamily present in virtually all organisms. The enzymes are also called the mixed-function oxidases, and are located in the endoplasmic reticulum of hepatocytes (liver cells). CYPs biotransform many substances in food and drugs as part of phase I metabolism.<sup>105</sup> CYPs are classified according to their substrates—CYP2E1 metabolizes alcohol and trichloroethylene; CYP1A2 metabolizes caffeine, and phenacetin.

Induction of CYPs can occur via activation of nuclear receptors (NRs). NRs are a family of highly evolutionarily conserved transcription factors that bind a variety of ligands and then bind to DNA to alter gene expression. NRs regulate a constellation of biological processes, including development, hematopoiesis, and metabolism.<sup>106</sup> Classical NRs include the estrogen receptor, androgen receptor, and thyroid hormone receptor. Other NRs, such as the constitutive androstane receptor (CAR), the pregnane-X-receptor (PXR) and the aryl hydrocarbon receptor (AHR), bind ligands generally occurring in food or drugs and can alter metabolism by increasing CYP gene expression.<sup>107</sup>

A number of *in vivo* measurements of the activity of drug metabolizing enzymes in humans are commonly used to assess liver function.<sup>108</sup> All these methods use a common drug that is metabolized by one or more of the CYPs. The most commonly used drug is caffeine, which is metabolized by CYP1A2, and metabolites of caffeine occurring in urine or blood may be used to assess CYP1A2 activity. The most accurate measure is obtained when using caffeine labeled with <sup>13</sup>C on the 3-position and then measuring <sup>13</sup>CO<sub>2</sub> in exhaled breath.

Smoking, consumption of meat, consumption of brassica vegetables (broccoli), and exposure to dioxin-like chemicals all induce CYP1A2 and result in an increase in caffeine metabolism that can be measured *in vivo*.<sup>109,110,111,112</sup>

The occurrence of mutations may also serve as a biomarker of effect. The activity of X-linked gene for hypoxanthine-guanine phosphoribosyl transferase (HPRT) can be used to select thioguanine-resistant mutants in peripheral human lymphocytes and mutant clones can be expanded with the use of a mitogen.<sup>113</sup> The PIG-A gene codes a enzyme subunit involved in the biosynthesis of glycosylphosphatidylinositol. This molecule serves to tether a number of proteins to the surface of the red blood cell. Hence, erythrocytes deficient in PIG-A can easily be measured with flow cytometry.<sup>114</sup>

### 2.4.3 Historical Reconstruction of Exposure

A number of methods are available to epidemiologists for exposure reconstruction. These include:

- self-reported occupational histories and exposures;
- occupational histories based on employer records;
- job-exposure and task-exposure matrices;
- expert assessment and the use of occupational/industrial hygiene measures.

These various types of measurements have strengths and weaknesses and should be assessed on a case-by-case basis. For example, an individual may indicate that he/she was employed as a pipefitter for ten years and then may also note that after six years, the company used a different plastic solvent for pipes. This sort of information may not be included in the employer records.<sup>115</sup>

A job-exposure matrix (JEM) is often used as measure of exposure.<sup>116</sup> Exposure misclassification is a significant problem with JEMs due to variability of exposure within job titles. If exposure differences can be determined for specific tasks, a task-exposure matrix may be used instead.<sup>117</sup>

Expert assessment of occupational exposures is very similar to the exposure assessment in environmental risk assessment in that measurements of concentrations in abiotic media such as dust, soil, or air are combined with estimates of the worker contact rate with these media. There may be between-worker and within-worker variability in exposure, and these variations may differ depending on the exposure medium.<sup>118</sup>

The goal of epidemiological exposure reconstruction is to assign group average exposure levels that can be used to compute individual cumulative exposures. A sufficient quantity of individual exposure data is required. Often, these data are lacking or sparse. Ways around this data gap include:

- project results back in time from current exposure data;
- recreate the actual physical processes that were assumed to result in exposure and take measurements;
- use worker recall of exposures;
- mathematical or statistical modeling for process reconstruction and exposure analysis.

#### 2.4.3.1 False Positives in Epidemiologic Studies

A number of epidemiologists lament the search for and reporting of weak associations in observational epidemiology, and a major problem with the use of epidemiologic studies for hazard identification, and for other aspects of risk assessment as well, is the frequent occurrence of false positive results.

For example, in 1993, a case-control study in New York city reported a link between breast cancer risk and serum levels of DDE, the major metabolite of the insecticide DDT.<sup>119</sup> However, seven studies that followed and a cumulative meta-analysis failed to confirm the original findings.<sup>120</sup>

A larger analysis of studies reporting a positive association found that the main determinants of false positive findings were the absence of a specific a priori hypothesis, small magnitude of association, failure to adjust for smoking, and the absence of a dose–response relationship.<sup>121</sup>

Another example is the relationship of pancreatic cancer to coffee consumption. In 1981, a small but significant positive association was noted.<sup>122</sup> By the end of the 1980s, subsequent studies failed to confirm this association, and in 2011, a pooled analysis that included over 850,000 individuals failed to show an association.<sup>123</sup>

In 2012, a study of over 229,000 men and over 173,000 women demonstrated that when adjusted for smoking, inverse associations were observed for deaths due to heart disease, respiratory disease, stroke, injuries and accidents, diabetes, and infections, but not for deaths due to cancer. The association between coffee consumption and reduced total mortality showed a significant trend, an observation about which many coffee drinkers were no doubt ecstatic. Nonetheless, these authors were careful to state that the constellation of evidence was insufficient to view the association as causal.<sup>124</sup>

#### **2.4.3.2 Quantiles and Statistical Power**

It is tempting in many epidemiological studies that employ continuous variables to split the entire cohort into groups based on quantiles of the continuous variable. Most often, tertiles (three groups), quartiles (four groups) or quintiles (five groups) are used. Quantiles can be thought of as potentially low, medium and high-risk groups, and thus are intuitively appealing. In addition, quantiles afford the possibility of using generalized linear models to search for trends in the data.

There are a number of problems associated with the use of quantiles. Obviously, risk will vary between individuals within a given quantile to an unknown degree. On top of this is the ever-present potential for exposure misclassification. What happens in many cases is that the number of individuals in each quantile becomes so low that the study loses sufficient statistical power to justify its conclusions. The last problem with quantiles is that the cut points selected are most often based on the continuous variable and chosen for statistical convenience as opposed to biological relevance. Implicitly, individuals within a single quantile are assumed to be homogeneous and the choice of cut points has the potential to produce both false positives and false negatives.<sup>125</sup>

In Chapter 1, a discussion of counterfactual evidence was provided. The same sort of thinking is needed for examination of epidemiologic studies that use quantiles. Often, each quantile is separately tested against the control group. Such multiple comparisons increase the chance of a false positive. Box 2.3 provides a discussion of type 1 or false positive error rate and appropriate p-value corrections for multiple comparisons.

### BOX 2.3 MULTIPLE COMPARISONS AND THE FALSE POSITIVE ERROR RATE

When multiple comparisons are made between several treatment groups and a control group, the multiple comparisons can greatly elevate the chance of a type 1 error—i.e., concluding that a difference exists when in fact it does not, and incorrectly rejecting the null hypothesis of no difference.

If the p-value of the overall error rate, known as a familywise type 1 error rate, is not adjusted, this p-value will be too high, with increased likelihood of a type 1 error. The familywise type 1 error rate is calculated as:

$$\alpha_{\text{FWE}} = 1 - (1 - \alpha)^k \quad [2.8]$$

where:

$\alpha_{\text{FWE}}$  is the familywise error probability

$\alpha$  is the pre-specified significance level for the individual comparisons

$k$  is the number of comparisons

For three comparisons, as would occur with three dose groups/quantiles and a control group, the commonly selected value  $\alpha = 0.05$ , the familywise error rate would be 0.1426. Thus, in order not to commit a type 1 error, the pre-specified value of  $\alpha$  for individual comparisons must be lowered.

There is a consensus that adjustment for multiple comparisons is a necessary procedure because of the likelihood of an inflated type 1 error rate without adjustment.<sup>126,127,128</sup>

There are a number of correction methods for adjusting the type 1 error rate. The best-known of these is the Bonferroni method. The Bonferroni correction partitions the nominal level of significance in the equal components,  $\alpha_B$ . For the case of three comparisons,  $\alpha_B$  would be  $0.05/3$ , or 0.0167, and  $\alpha_{\text{FWE}}$  (Equation 2.8) would be 0.04917, very close to 0.05.

#### 2.4.3.3 Reverse Causation

Biomarker-based studies may be difficult to interpret, and care in interpretation is warranted. For a long time, measurements of many persistent organic pollutants in human serum have been normalized to serum lipid concentrations. Hence, these lipid-adjusted measurements would be reported on as “pg/g lipid” or similar. Blood lipid concentrations may be measured gravimetrically or estimated with various formulae, with considerable variation between these methods.<sup>129,130</sup> The issue of reverse causation may also confound any observed associations with adverse health effects.

Recently, the association of type 2 diabetes with a biomarker of exposure, dioxin in serum lipid, was investigated and shown to be the result of so-called “reverse

causation.” For a number of years and in a number of studies, a positive association has been observed between lipid-adjusted measurements of serum dioxin and the occurrence of type 2 diabetes. This association was notable in the Ranch Hand cohort—herbicide workers in the US military during the Vietnam War; however, it was not observed in mortality studies of populations with occupational or environmental exposure. Recently, this association was examined among members of the Ranch Hand cohort and the increases in serum dioxin concentrations were shown to be associated as well with hyperlipidemia, obesity, and poor diabetes control. In other words, the increases in serum lipids associated with diabetes also increased the levels of the lipid-soluble dioxins in serum, rather than dioxin producing diabetes. The only reason this demonstration of reverse causation was possible was the existence of 20 years of longitudinal data on the Ranch Hand cohort.<sup>131</sup>

Per- and polyfluoroalkyl compounds have been associated with a large number of adverse effects in animals. The two most notable are perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). A huge stumbling block in developing credible toxicity factors for perfluorinated chemicals (PFCs) is the lack of specific concordance between effects observed in humans and animals. Humans are, of course, exposed to many different PFCs, whereas test animals are exposed to a single substance only. This fact complicates the understanding of the observed human health effects. In addition, achieving an understanding of the possible modes of action of PFCs in producing observed effects in both humans and animals has been given short shrift by all regulatory entities. The loose concordance between the developmental effects in humans and those in animals led to the choice of developmental endpoints for the RfDs for both PFOA and PFOS.<sup>132,133</sup>

Two specific endpoints—low birth weight and age of menopause—appear to be due to reverse causation. Regarding low birth weight, both birth weight and concentrations of PFCs in blood depend on glomerular filtration rate (GFR)—how rapidly blood is filtered by the kidneys: PFCs are increased by lower GFR, and birth weight is reduced by lower GFR. Hence, the natural variation in GFR appears as an association between birth weight and PFCs.<sup>134,135</sup> Regarding age of menopause, PFCs are removed from blood by menstrual flows, and this process explains much of the association with increased PFCs in blood of post-menopausal women.<sup>136</sup>

The factors underlying reverse causation for PFCs are related to pharmacokinetics and were discovered through the careful application of pharmacokinetic models. These models, the available software, and the interpretation and use of model results will be discussed in detail in Chapters 3 and 5.

#### **2.4.4 Example of Hazard Identification from Epidemiology**

Indoor dampness and exposure to mold has been known or suspected of causing health problems since the beginning of humankind. Chapter 13 in the Book of Leviticus in the Bible provides instructions on detecting and remediating dampness, mold, and mildew within dwellings—even back then, mold was considered the cause of a number of diseases, including leprosy.

Much more recently, in 2004, the Institute of Medicine (IOM) of the National Academies of Sciences reviewed the evidence on health effects related to dampness and, in contrast to the Bible, found no causal associations. From the 45 studies reviewed, the IOM did find sufficient evidence of association between both indoor dampness and the presence of mold and coughing, wheezing, upper respiratory tract symptoms, and exacerbation of asthma symptoms.

An additional 354 studies published before 2009 and not included in the IOM review were the subject of a review in 2011. Evidence from epidemiologic studies and meta-analyses showed indoor dampness or mold to be associated consistently with increased asthma development and exacerbation, diagnosis of asthma, dyspnea, wheeze, cough, respiratory infections, bronchitis, allergic rhinitis, eczema, and upper respiratory tract symptoms. Associations were found in both allergic and non-allergic individuals. Evidence strongly suggested causation of asthma exacerbation in children. The evidence for causation was both the strong and consistent association of dampness and mold with worse asthma symptoms, and the complementary finding that remediation of mold and dampness led to dramatic reductions in asthma exacerbation.<sup>137</sup> The removal of a specific factor associated with a reduction in the effect or response provides a powerful counterfactual demonstration of the likelihood that the factor is causal to the effect.

The evidence for causation that could not be observed was any trend between quantitative measures of either dampness or the presence of mold—hence, there was no biological gradient or dose response. No doubt with an eye on problem formulation, the authors conclude, appropriately or not, with consideration of risk management, pointing out that targeting of resources towards reduction of indoor dampness would likely be more effective in lowering the global burden of respiratory disease than would research to determine safe levels of dampness.<sup>137</sup>

What is instructive and possibly unique about this study is that the sole conclusion that could be drawn did not go beyond hazard identification. Nonetheless, in the case of indoor dampness, nothing more than hazard identification was needed to inform risk management. It seems this study confirmed what was written in the Bible, and that Leviticus indeed had the first and last word on the assessment and management of risk from indoor dampness.

## 2.5 ANIMAL BIOASSAYS AS THE BASIS FOR HAZARD IDENTIFICATION

In 1775, Percivall Pott, a surgeon at St. Bartholomew's Hospital in London, recognized the relationship between cancer and occupation, observing that scrotal cancer was highly prevalent in chimney sweeps. In 1915, malignant tumors were produced by applying coal tar to the ears of rabbits. The same set of chemicals, polycyclic aromatic hydrocarbons (PAHs), is present in both soot and coal tar, and they were thus shown to be the potential causative agent.<sup>138</sup>

Often, the results from animal bioassays confirm prior epidemiological observations; however, predictions of human carcinogenicity from animal results are

not as reliable.<sup>139</sup> Notwithstanding, animal bioassays have been used for both hazard identification and human dose–response assessment for over 40 years. In the United States, the Environmental Protection Agency (EPA), the Food and Drug Administration, the National Cancer Institute and the National Toxicology Program have supported the use of animal bioassays. A two-year bioassay in rats requires a minimum of 50 animals per dose group—more if interim sacrifices are required—and may cost about \$3 million. Fifty animals per dose group per gender are needed to provide sufficient statistical power to observe a 10% risk of cancer.<sup>140</sup>

In addition to the uncertainty of qualitative species extrapolation—simply assuming that animal carcinogens are also human carcinogens—additional uncertainty is inherent when the dose at the 10% point of departure is extrapolated down to a 1 in 1,000,000 risk for compliance with target regulatory risk levels.

When the predictive ability of rat bioassays to predict mouse carcinogens, and vice versa, was examined, there was a sufficient lack of overlap to raise serious concerns about the predictive ability of a single rodent bioassay to predict human carcinogenicity.<sup>141</sup> Out of 392 tested chemicals, 76% of rat carcinogens also caused cancer in mice and 70% of mouse carcinogens were positive in rat bioassays.<sup>142</sup>

The International Agency for Research on Cancer was a pioneer of hazard identification of human carcinogens and pointed out that both long-term animal bioassays and short-term *in vitro* tests could be used to identify possible human carcinogens. Both of these claims have, however, subsequently been proved false.<sup>2,63,143</sup> Nonetheless, IARC, before losing its way, developed one of the first weight of evidence schemes with the goal of standardizing the evaluation of carcinogenic activity from human and animal studies. Sufficient evidence of carcinogenicity is provided by positive results in two species or in two or more independent studies in the same test species. Limited evidence of carcinogenicity is used when positive results are observed in a single bioassay only.<sup>144,145</sup>

Later studies indicated that any observed correlations tended to be highly dependent on study design. In fact, a mismatch was observed between chemicals predicted to be carcinogenic by IARC and those predicted by the National Toxicology Program.<sup>146</sup>

The demonstration that a chemical is carcinogenic in both humans and animals with concordance of tumor site and tumor type constitutes a conclusive identification of hazard. Vinyl chloride used to manufacture PVC pipes and siding for houses causes liver hemangiosarcoma in both humans and rodents.<sup>147</sup> However, this concordance of effects in humans and animals is hardly the norm. By far, animal experimentation without additional evidence has identified more chemicals as having the potential to produce adverse effects in humans than has any other source of information. This specific source of uncertainty consumes both time and resources in unnecessary regulatory efforts.

## 2.6 *IN VITRO* TESTING AND INFORMATICS AS THE BASIS FOR HAZARD IDENTIFICATION

The “Blue Book” stated explicitly that laboratory animals were not human beings, and that this obvious fact was a clear disadvantage of animal studies. Another

disadvantage was the relatively high cost of animal studies containing enough animals to detect an effect of interest. In addition, extrapolation of effects observed in animal studies requires both interspecies extrapolation and extrapolation from high bioassay test doses to lower environmental doses. Even in the early 1990s, the scientific community was well aware of the uncertainties inherent in animal testing.<sup>48,148</sup>

The vision and framework articulated in NRC's 2007 report, *Toxicity Testing in the 21st Century: A Vision and a Strategy*, is that toxic effects result from the departure from homeostasis due to dysregulation of multiple biological pathways or systems.<sup>149</sup> This vision stems from recent advances in toxicogenomics, bioinformatics, systems biology, and computational toxicology, and shows considerable promise in changing the manner in which toxicity evaluations are performed. The aspiration in this "vision" is to transform hazard evaluation and risk assessment from a system that uses high-dose whole-animal bioassays to one based primarily on computational profiling linked to *in vitro* methods that evaluate changes in biologic processes using cells, cell lines, or cellular components, preferably of human origin. The "strategy" refers to the path forward for increasing use of *in vitro* high-throughput assays in lieu of animal bioassays for risk assessment, and when animal testing is necessary, to conduct only those tests that are absolutely needed.

The first motivation for this effort is the growing recognition that high-dose animal experiments are unlikely to provide useful information about low-dose effects in humans. The second is the consideration of animal welfare and the desire to reduce the use of animals in regulatory toxicity testing. The third is that conducting traditional animal toxicity testing for the thousands of untested chemicals in commerce would be prohibitively expensive and would take longer, by decades, than the regulatory need for this information.

The methods discussed below are collectively referred to as new approach methodologies, or NAMs.

### **2.6.1 Toxicity Pathways, Adverse Outcome Pathways, and Mode of Action (MOA)**

Toxicity pathways are cellular response pathways that when sufficiently perturbed are expected to result in adverse health effects. Low exposures could cause small perturbations that do not lead to any alterations in normal biological functions. Higher exposures could lead to adaptive responses as the organism responds to maintain homeostasis. These adaptive responses do not necessarily compromise cellular or organ functions. When exposures are sufficiently large, then the magnitude of the perturbations in the response pathway would cause significant cell injuries and adverse effects.

The scope of toxicity pathways to define the broader construct of adverse outcome pathway (AOP) as representing "existing knowledge concerning the linkage between the molecular initiating event (MIE) and an adverse outcome at the individual or population level." By definition, an AOP spans multiple levels of biological organization. The MIE is defined as the initial point of chemical–biological interaction within an organism, and an AOP links a MIE to an adverse outcome.<sup>150–153</sup>

Hence, the difference between a toxicity pathway and an AOP is that toxicity pathways are identical to cellular response pathways and the level or type of activity in these pathways is what constitutes toxicity. On the other hand, an AOP represents a plausible set of connections leading from the MIE to the adverse effect, thus activity in the AOP is obligatorily connected to an adverse outcome. The connection between the initial event and the adverse outcome may not be obligatory, and the suggestion has been made to change the term MIE to initial molecular event, or IME.<sup>154</sup>

### **2.6.2 Implementing Toxicity Testing in the 21st Century (TT21C)**

The ToxCast™ program of the US Environmental Protection Agency is an effort to incorporate the use of *in vitro* assays into risk assessment. ToxCast™ consists of a battery of both commercial and publically developed *in vitro* assays. One distinct and obvious advantage is that these assays can be robotically automated to generate data very quickly. For example, the robotic assay at the National Chemical Genomics Center can develop concentration–response information on about 10,000 chemicals in a single day.

Many of the assays used in ToxCast™ and other Tox21 efforts have been taken directly from the pharmaceutical field. For pharmaceutical purposes, the screening of chemicals with potent biological activities is a routine aspect of the drug candidate development process. In contrast, commodity chemicals are selected and designed because of their physicochemical properties with the goal of improving the performance of a specific product, and such chemicals typically possess orders of magnitude less biological activity than pharmaceutical agents.

This difference between commodity chemicals and drug candidates begs the question of whether the new *in vitro* testing paradigm is capable of delivering meaningful information to inform risk-based decision-making. For these assays to be useful, it is necessary to anchor each assay in terms of its biological context within a toxicity pathway as well as what the *in vitro* results mean in terms of real-world exposures.

In 2003, the EU's 7th Amendment to the Cosmetics Directive banned the use of animal testing for acute toxicity.<sup>155</sup> This ban was followed in 2009 by another on *in vivo* genotoxicity testing in animals, and animal testing for cosmetics was banned entirely in 2013. This ban has significant ramifications that continue to ripple throughout the European chemical industry.<sup>156,157</sup>

In response, risk assessment approaches are being developed that use data from *in vitro* testing and prediction models with the goal of interpreting the predictions in terms of realistic exposure levels obtained from biomonitoring.<sup>158</sup> Three key components of this approach are envisioned—the development of exposure-driven risk assessment approaches, new targeted *in vitro* methods and predictive models, and understanding the applicability of new technologies to risk assessment.<sup>159</sup>

### **2.6.3 Can *In Vitro* Assays Cover All Toxicity Pathways?**

Whether the suite of ToxCast™ assays or those being developed in Europe cover the entire range of toxicity pathways in humans remains to be seen. How many toxicity pathways are there? How many assays are needed for adequate coverage of each pathway?

When asked about the number of toxicity pathways, Dr. Melvin E. Andersen, Senior Program Advisor at Scitovation LLC, answers, tongue in cheek, “132,” and then qualifies his answer by adding, “as a toxicologist, I am used to working with false accuracy.” Thomas Hartung, director of the Center for Alternatives to Animal Testing at Johns Hopkins University, opines:

as the number of cellular targets and metabolic pathways is finite, the number of PoT (Toxicity Pathways) should be, too. Evolution cannot have left too many Achilles heels given the number of chemicals surrounding us and the astonishingly large number of healthy years we enjoy on average.<sup>83</sup>

Although there are evolutionary and energetic constraints on the complexity of human biology,<sup>160</sup> the question of coverage of the entire domain of toxicity pathways remains unknown and the question of whether a sufficient number of pathways are represented remains unanswered.

Having a “Taxonomy of Adverse Effects” is one means of addressing the question of the domain of applicability of the various assays and what constitutes reasonable and relevant integration and use of the assay results.<sup>161</sup> In response, the American Society for Cellular and Computational Toxicology and the International QSAR Foundation have developed an “Effectopedia” to attempt to catalog the current list of AOPs (<https://sourceforge.net/projects/effectopedia/>).

#### **2.6.4 *In Vitro* Assays May in Time Be Useful for Hazard Characterization**

In order to interpret the results of *in vitro* assays, a prediction model is needed to determine how the concentrations used in the assay correspond to human exposures. Hence, confidence in the accuracy of this prediction model is necessary to be able to use *in vitro* assays in risk assessment. Recently, the difficulties in the interpretation of *in vitro* toxicity evaluations were demonstrated in an analysis of the predictive performance of more than 600 *in vitro* assays across 60 *in vivo* endpoints using 84 different statistical classification methods. In addition, the predictive power of these models based on *in vitro* results was compared with that of QSAR and other *in silico* models (see below) and was not a significant improvement. Hence, the assays are currently seen as a survey of MIEs, and the responses of some assays or combinations of assays appear to be positive or negative “risk” factors for toxicity. From this study,<sup>85</sup> a few instances make clear the possibility of using *in vitro* testing for hazard identification—but not for all substances as yet.

#### **2.6.5 What Do *In Vitro* Assays Actually Measure, and How Should They Be Used?**

Understanding and interpreting the results of *in vitro* assays is not easy, and in 2019, is still a work in progress. For example, many chemicals tested in the suite of ToxCast™ assays showed activation of a large number of assays over a narrow

concentration range at which cytotoxicity is also observed. Essentially, cytotoxicity is a non-specific response indicating general disruption of cellular processes, whereas the specific responses often occurred at lower concentrations and observed responses were due to alterations in specific cellular targets. Hence, scientists at EPA's National Center for Computational Toxicology explored this issue in detail and developed computational tools to distinguish specific from non-specific responses.<sup>162</sup>

Presentation of case studies at a series of workshops are used to evaluate the new assessment methods as an alternative to animal testing. The case studies are focused on data-poor chemicals.<sup>50</sup> The adoption of NAMs is especially challenging for developmental/reproductive endpoints and neurotoxicity. Chemical-specific integrated approaches to testing and assessment (IATAs) have become part of the landscape of 21st-century toxicity testing.<sup>163</sup>

## 2.6.6 High-Throughput Exposure for Selecting Chemicals

A triage process using sophisticated high-throughput exposure estimates of production volume, consumer use, and chemical properties is being rapidly developed.<sup>164–169</sup>

The relationship between structure and toxicity was explored with a large database of over 600 substances and a range of endpoints. This approach is known as the threshold of toxicological concern (TTC). The resulting database contained 2941 no effect levels (NOELs) for a total of 613 organic substances. The substances were then assigned to one of three structural classes.<sup>170,171</sup> The 5th percentile NOEL for each structural class and was converted to a human exposure threshold using a safety factor of 100. The TTC values established were 1800 µg/person/day for Cramer Class I, 540 µg/person/day for Cramer Class II, and 90 µg/person/day for Cramer Class III substances.

This work is still being advanced today because the TTC provides a relatively fast, albeit potentially inaccurate, means of hazard characterization as a prioritization strategy. The TTC approach has been adopted in Europe for cosmetics and household products because of the 2013 ban on animal testing.<sup>172–174</sup> One immediate goal is to obtain internal TTC, in other words, statistical threshold values based on internal exposures such as blood or plasma concentrations that could be compared to biomonitoring data.<sup>175</sup>

## 2.7 *IN SILICO* PREDICTION MODELS AS THE BASIS FOR HAZARD IDENTIFICATION

A structure–activity relationship relates features of chemical structure to a property, effect, or biological activity associated with that chemical. This can be done in either a qualitative or quantitative fashion. The underlying idea is that the structure of a chemical determines its physical and chemical properties and reactivities, which in turn specify biological/toxicological properties.

In 1869, Alexander Crum Brown, a graduate of the University of Edinburgh medical school and the University of London, was the first to explore structure–activity

relationships with his demonstration that discovered the first structure–activity link by showing that a number of alkaloids, including the convulsant strychnine, could be converted into muscle relaxants by converting them to quaternary amines.<sup>176</sup> The reason was finally understood over 50 years later with the work of Henry Dale and Otto Loewi, who identified acetylcholine, another quaternary amine, as the transmitter substance at several different types of synapses, including the neuromuscular junction.<sup>177</sup> The work of Arthur Cushny early in the 20th century demonstrated that usually only a single member of a pair of optical enantiomers possessed biological activity.<sup>178</sup> Around 1900, Meyer and Overton independently advanced the theory that anesthetic potency was related to lipophilicity and developed a quantitative relationship between the solubility of a drug in olive oil versus that in water.<sup>179</sup> All these early discoveries led to the recognition that the biological activity of a chemical could be predicted from its chemical structure and associated physical-chemical properties.

### 2.7.1 Quantitative Structure–Activity Relationship (QSAR)

Some of the chemical features used in QSAR include the octanol–water partition coefficient as a measure of lipophilicity, molecular weight or molar refractivity as a measure of size, and polarity as a measure of reactivity. Initially, QSAR methods were used for prediction of aquatic toxicity in ecological risk assessment.<sup>180</sup> QSAR is used for human health risk assessment as well, and is often combined with physiologically based toxicokinetic modeling. Hence, QSAR is used to estimate the toxicodynamic properties of a chemical, and PBTK is used to estimate the toxicokinetic properties (Box 2.4).<sup>181</sup>

#### BOX 2.4 TOXICOKINETICS AND TOXICODYNAMICS

Toxicokinetics refers to the distribution of chemicals in the body. Processes considered in toxicokinetics are absorption, distribution, metabolism, and excretion (ADME). Often, quantitative descriptions of these processes are incorporated into a mathematical model called a physiologically based toxicokinetic model. These are also known as physiologically based pharmacokinetic models.

Toxicodynamics refers to the processes by which chemicals produce effects in the body. For example, in rodents, phenobarbital binds to a nuclear receptor, the constitutive androstane receptor (CAR), and alters gene expression. This binding leads to induction of enzymes, increased cell proliferation, and liver tumors. In humans, although phenobarbital binds to CAR, the hyperplastic effects are absent. Mathematical models of toxicodynamic effects may also be developed.

When a PBTK model and a toxicodynamic model are combined, the resulting model is known as a biologically based dose–response model.

In Chapter 4 on dose–response assessment, it will become abundantly clear just how consideration of both toxicokinetics and toxicodynamics plays an important role in risk assessment.

Of necessity, QSAR requires a prediction model for the biological activity. Often, this is a statistical regression of the predicted value versus the predictor value.<sup>182</sup> One of the early uses of QSAR was EPA's attempt to predict dermal permeability of chemicals from water. Measurements of the dermal permeability coefficient  $K_p$  were available for 90 chemicals, and EPA used a regression model to estimate  $K_p$  for other chemicals. The independent variables were the octanol-water partition coefficient and the molecular weight. Unfortunately, this regression method did not work for high molecular weight highly lipophilic chemicals, and an effective prediction domain was established inside which the regression was applicable.<sup>183</sup>

### **2.7.2 Read-Across: Using What Is Already Known**

Read-across is a technique that uses toxicity data from chemicals with structures similar to the one under consideration.<sup>184</sup> These structurally similar chemicals are then used to restrict the domain of application of QSAR results.<sup>185</sup> An associated area of interest is the grouping of chemicals and the identification of analogs. Analog identification may be based on presence within a congeneric series, similar functional groups, overall chemical similarity, mechanism of action, or 3-D structure.<sup>186-189</sup> Graphic and statistical methods for displaying chemical similarity via network mapping are being used to communicate the correspondence (or lack thereof) between the shared structure of chemicals and biological activity.<sup>190-194</sup>

Read-across enables the filling of data gaps based on chemical analogs or mechanistic chemical categories. Similarity in chemical structure such as a similarity metric can provide a starting point to define categories. Within a category or set of analogs, toxicity data from tested chemicals is used to determine the toxicity of untested chemicals.<sup>195</sup>

Categories can be determined on structural similarity or on the basis of biological mechanism. Obviously, uncertainty exists whether a chemical is correctly assigned to a category or whether tested analogs can actually represent the toxicity of the untested chemical. Addressing this uncertainty appears to be an ongoing challenge for regulatory acceptance of read-across.<sup>196</sup>

### **2.7.3 Integrated Testing and Assessment**

An IATA is essentially a problem formulation that considers how to use data from all the NAMs discussed above to achieve a specific information goal. Adverse outcome pathways provide the biological underpinnings and the frameworks for development of IATAs.<sup>197</sup>

As with any problem formulation, the development of an IATA should be viewed as an iterative process to reach an effective regulatory decision in the most efficient manner. The first step in an IATA is to consider relevant existing information to derive an initial conclusion. The data gaps are identified based on the regulatory need, and guide a hypothesis-driven approach to collection of

additional data. The overall purpose of each iteration is to reduce the uncertainty that obstructs a credible risk management decision. An IATA can use extant animal testing results, computational approaches such as QSAR and/or read-across, and *in vitro* testing.<sup>197</sup>

AOPs represent accumulated biological knowledge that provides the rationale for additional steps in an IATA. As such, AOPs are not intended to be actual systems biology models; rather, they represent the minimal mapping of toxicity pathway sufficient to identify knowledge gaps and so guide further testing.<sup>151</sup>

## 2.8 CONCLUSIONS

Ideally, the collection of NAMs and their contextualization with AOP-driven IATAs will enable a better understanding of the surfeit of human biomonitoring data. As yet, confidence around the predictions from *in vitro* data such as ToxCast™ has not yet been achieved.<sup>85,198</sup> This lack of confidence has not prevented some from using these data, often uncritically, in an attempt to drive regulation.<sup>63,199–202</sup> Recently, the uncritical use of HTS results by IARC is exemplified by the controversy over the herbicide glyphosate.<sup>203–205</sup>

Human biomonitoring data has become the focus of attention in both Europe and North America. Understanding these data with an appropriate screening tool could provide another method of hazard identification.<sup>182,206,207</sup>

IATAs and other frameworks are being developed for integrating information from a variety of sources into hazard identification and screening.<sup>208</sup> Hybrid modeling, in which biological results and chemical structural properties are pooled, has begun to show improvement in the accuracy of prediction over *in silico* models alone.<sup>209–211</sup>

The early part of the 21st century is truly an exciting time to be studying the science of risk analysis. The application of this science to environmental problems is an obvious need for humanity. The ongoing revamping of toxicity testing was born from the recognition that techniques and methods used routinely in the pharmaceutical industry could revolutionize toxicology. But then came the challenge of implementing these techniques. Confidence in the predictive power of these methods has yet to be achieved. Hence, the extent to which these non-animal testing methods are considered in planning and scoping, in problem formulation, and in hazard identification have yet to be determined.

## 2.9 EXERCISES FOR THOUGHT AND DISCUSSION

### 2.9.1 Understanding Statistical Power

With a small or highly variable effect, a relatively large sample size is needed to make inferences with confidence, especially when effects are of small magnitude or highly variable. Statistical power is the likelihood that a study is able to detect the

presence of an effect when the effect is indeed present. Statistical power is affected by the size of the effect and the sample size of the study.

Considerable variation in semen quality parameters exists in humans. This variation is due to both between- and within-person variability. The 2010 World Health Organization (WHO) *Laboratory Manual for the Examination and Processing of Human Semen*, 5th edition, flatly states that it is impossible to characterize semen quality from evaluation of a single sample.<sup>212</sup> Length of abstinence is a major determinant of this variation.<sup>213</sup> A commonly measured semen quality parameter is sperm concentration, the number of spermatozoa, usually in millions, in a milliliter of semen. Sperm concentration is related to time to pregnancy and is a predictor of conception.<sup>214</sup> Sperm concentration is measured by counting individual sperm using a haemocytometer grid.<sup>215</sup>

Using a relatively simple power calculation, we will examine a recent report of the effect of chemical exposure on sperm concentration.<sup>216</sup> The paper is available without charge at [www.ncbi.nlm.nih.gov/pmc/articles/PMC2199303/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2199303/).

In this paper, two groups of young men, one group exposed to 2,3,7,8-tetrachlorodibenzodioxin (TCDD) as boys and the other not exposed, were examined for reproductive parameters, including sperm concentration. It is important to note that the WHO manual provides the normal range of sperm concentration as 15,000,000–213,000,000 per ml. The group of 71 exposed individuals had a geometric mean (GM) value of 53,600,000 and the control group of 82 individuals had a geometric mean of 72,500,000. The geometric standard deviations (GSDs) were 2.46 and 2.29 respectively. Please note that both samples were in the normal range. Statistical analysis of semen concentrations is most often conducted in logarithmic space, which is why the GM and GSD values are provided.

You can download an Excel file called “power.xls” from [www.crcpress.com/9780367250973](http://www.crcpress.com/9780367250973). Alternatively, those of you proficient in Excel can set this up on your own.

The spreadsheet works by having random numbers coded with the formula =RAND() in the hidden columns A and B. Column C has 71 values that represent the exposed group, and Column D has 82 values that represent the control group.

The value you will be looking at is in cell G9, labeled “p-value.” What you will do is obtain ten different alternate realizations of these two datasets and perform a Student’s t-test on the differences. The proportion of the times the p-value is less than  $\alpha = 0.05$  is a measure of the ability to demonstrate that these two samples are indeed different.

Enter a value in cell J1. This will be a dummy value just to get the random number generator in Excel to turn over. Note whether the p-value is less than 0.05. Repeat nine more times. If the p-value was less than 0.05 on two out of ten trials, the power of the statistical test is 20%. Generally, one wants a power of 80% to show that the number of samples was adequate.

Based on your simple investigation of power, discuss what this means for your confidence in the results presented in the paper.

### 2.9.2 Discussion of the Differences in Problem Formulation between NATO and the “Silver Book”

Figures 2.2 and 2.3 show these two problem formulation diagrams. The NATO diagram was developed essentially by individuals trained in operations research, whereas the “Silver Book” diagram was developed by statisticians, toxicologists, and epidemiologists. How are these similar? How are they different?

### 2.9.3 Exploring QSAR, Part 1

The Flynn dataset of dermal permeability values can be downloaded as an Excel file from [www.crcpress.com/9780367250973](http://www.crcpress.com/9780367250973). Read Appendix A of EPA’s *Supplemental Guidance for Dermal Risk Assessment* and try to develop a predictive regression for the dermal permeability coefficient. You should be able to explore this method using the LINEST function in Excel.

### 2.9.4 Exploring QSAR, Part 2

There exist a number of public domain tools for *in silico* prediction of toxicity. The links are shown below. Download as many of these as you care to and give them a spin. Try them with chemicals of known toxicity to see if they can predict effects observed in humans. To obtain data on human health effects, use EPA’s IRIS database at [www.epa.gov/iris/index.html](http://www.epa.gov/iris/index.html).

The links are:

- OECD QSAR Toolbox: <https://qsartoolbox.org>
- OECD QSAR Project: [www.oecd.org/env/existingchemicals/qsar](http://www.oecd.org/env/existingchemicals/qsar)
- OCHEM: [www.ochem.eu](http://www.ochem.eu)
- ChemBench: <https://chembench.mml.unc.edu>

### 2.9.5 Small World/Large World

This exercise is based on the discussion of the risk from a lightning strike while swimming in an indoor pool. An additional reason for this exercise is introduce the statistical computing program called R, if you’re not already aware of it.

R provides a variety of mathematical and statistical calculations using packages that can be downloaded. The best aspect of R is that all of it is absolutely free for a single user. You can learn more about R at [www.r-project.org/](http://www.r-project.org/). R is easiest to use with an integrated development environment available at [www.rstudio.com/](http://www.rstudio.com/). In addition, many resources are available for learning R. Using R to perform the necessary calculations for analyzing risk will be considered in more detail in Chapter 3.

The upper limit of a Poisson distribution with rate parameter  $\lambda$  is the same as that obtained from a chi-squared distribution with degrees of freedom equal  $2*\lambda + 2$ . Halving the value from a chi-squared distribution can be shown to be identical to the Poisson distribution and is easy to calculate in R.<sup>217,218</sup>

For the risk of lightning in an indoor swimming pool, we want the upper 95% confidence limit on the Poisson rate of zero. In R, the function `qchisq()` provides quantiles of the chi-squared distribution. We can calculate the 95% upper bound of a Poisson distribution with a rate equal to zero by entering the following into R:

$$0.5 * \text{qchisq}(0.95, 2)$$

The result comes back 2.995732, or ~3, used as the numerator in the risk calculations shown earlier in the chapter. Any math nerds reading this may wish to investigate the relationship between the Poisson and chi-squared distributions themselves.

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# CHAPTER 3

## A Risk Analyst's Toolbox

... the practice of statistics is no closer to mathematics than cooking is to chemistry.

**Terry Speed**

Everything should be made as simple as possible, but not simpler.

**Albert Einstein**

All models are wrong; some are useful.

**George E. P. Box**

Identifying hazards cannot provide sufficient insight to compare and contrast the risks associated with various management decisions. For example, between 1968 and 1982, the Sherman Mine near Leadville, Colorado produced over 10,000,000 ounces of silver found alongside lead and zinc. The area affected by the mine was over 10 square miles. Digging up and trucking away that much lead-contaminated material would likely entrain sufficient dust, also laden with lead, that not just the air, but also the areas inside homes and businesses would likely be contaminated. The risk of leaving this material in place and using *in situ* techniques such as revegetation to address lead exposure at the site could be compared to the risk from lead in airborne dust from active removal. Such a comparison would not be meaningful without quantitative estimates of risk.

Hence, in this chapter, an introduction to the mathematical aspects of the science of risk analysis will be presented. These aspects include statistics and probability, quantification of uncertainty, value of information, and a discussion of the computational tools available in the 21st century.

### 3.1 PROOF VERSUS INFERENCE: HOW MUCH IS ENOUGH?

A cause–effect relationship between a chemical and an adverse effect can never be unequivocally proven because causality itself cannot be proven—only inferred with a degree of certainty based on the strength and weight of the evidence.<sup>1–3</sup>

The ideal risk analysis would document sufficient evidence of a causal association between exposure and disease in the hazard identification; further, the exposure assessment would include sufficient characterization of uncertainty that quantitative estimates of exposure, even at percentiles approaching 100%, would be acceptable; even further, the dose–response assessment would address not just the general population, but would specifically address susceptible sub-groups, with quantitative estimates of toxicity in those sub-groups. Well, good luck with all that!

The purview and purpose of environmental regulation is explicitly not meant to protect those choosing maladaptive behaviors from the consequences of their choices; rather, the goal is protection of all citizens from involuntary risks beyond the control of individual citizens. For multifactorial diseases such as cancer, it is impossible to know the contribution of environmental determinants of health versus lifestyle choices versus the fact some of us are just unlucky. This particular uncertainty will likely never be resolved.

Regarding luck, in 2015, a paper in the journal *Science* reported a strong correlation ( $\rho > 0.80$ ) between the number of stem cell divisions of stem cells normally occurring in a tissue versus the lifetime risk for each of the 31 types of cancer considered. Randomly occurring mutations in stem cells that occur during normal replication appeared to explain about two-thirds of the variation in cancer risk, a greater fraction than was accounted for by hereditary or environmental factors. The authors indicated that the majority of cancer risk was due to “bad luck.”<sup>4</sup>

Significant push-back to this “bad luck” hypothesis was observed in letters to the editor and in papers examining age-adjusted incidence of various types of cancer. These papers concluded that only about 10–30% of cancers could be attributed to random mutations during normal stem cell replication.<sup>5–7</sup>

A re-analysis of these data in 2017 concluded that neither of these statistical analyses of cancer risk considered aspects of the fundamental biology of cancer, including which genes are mutated in the dividing stem cells, differences in the rates of cell division, programmed cell death or immune surveillance, and exposure to environmental agents that might interact with these processes.<sup>8</sup>

Exactly what proportion of the burden of cancer in a population is due to bad luck versus hereditary or environmental factors will never be known. The notion that cancer is due to bad luck, however, is singularly unsatisfying—especially to a risk analyst. Perhaps the message of this ongoing controversy is to know the limitations of science and its capabilities to offer meaningful analysis. This chapter provides an introduction to techniques and tools for analyzing risk. The additional message for risk analysts is to use these tools with the appropriate degree of humility and good faith and be able to explain what has been done with simplicity and clarity.

### **3.2 UNDERSTANDING AND COMMUNICATING UNCERTAINTY**

Risk may be considered as an event inherent in a situation in which an item of value to humans is at stake and its continued existence is uncertain. Risk may also be considered as a consequence inherent in the uncertain outcome of something valued by humans.<sup>9</sup>

Here, uncertainty will be considered as arising from the same distinct sources as considered for risk in Chapter 2, and methods for accounting for these uncertainties will be presented in this chapter:

- aleatory uncertainty, stemming from the risk analyst's inability to specify how known variability in the outcome or factors on which the outcome is based will manifest;
- epistemic uncertainty, stemming from the lack of knowledge of the factors that contribute to the outcome;
- ontological uncertainty, stemming from inappropriate beliefs or misconceptions regarding the causal factors for the outcome.

Probabilistic modeling can be used to address aleatory uncertainty when the factors contributing to an outcome are well understood and can be represented by probability distributions. Categorical representation of different sets of assumptions representing various states of knowledge can be used to address epistemic uncertainty; Bayesian methods may be useful in such an exercise.

Targeted data collection, if possible, can be used to address epistemic uncertainty. During problem formulation, significant data gaps in the knowledge base of the planned risk assessment would have been identified, with specific investigations to fill these gaps.

Ontological uncertainty is much more difficult to address because the underlying lack of knowledge is not recognized or understood. Ontological uncertainty represents the gap between the risk analyst's perception of reality and the true reality. The first efforts in a new area of technology bear considerable ontological uncertainty. The difficulties with self-driving cars and facial recognition software are examples of ontological uncertainty. Because these technologies are untested, the designers can do no more than presume what might happen in untested scenarios. For example, if both human-operated and self-driving cars share the roadway, how will the self-driving cars adjust to the behavioral changes of drivers who may have a variety of feelings toward self-driving cars?<sup>10</sup> Humans tend to focus on what is immediately obvious and neglect other factors.<sup>11</sup> The idea of the “unknown unknowns” was made popular in a 2002 speech by US Secretary of Defense Donald Rumsfeld.<sup>12</sup> The understanding of any problem by risk analysts will always be incomplete, and ontological uncertainty will always be present.

### 3.3 A BAYESIAN PERSPECTIVE

From a scientific point of view, statistics is hardly an end in itself; rather, statistics provides a set of tools for making inferences from data. These inferences naturally lead to predictions. Bayesian methods involve leveraging what one knows already along with some data collected regarding a question or problem to make inferences about the cause of the problem. This situation is exactly the one found in risk analysis. Bayesian methods allow one to model the problem with a range of assumptions and different datasets and form inferences from this collection of models with differing inputs and assumptions.<sup>13</sup>

### 3.3.1 P-Values versus Larger World Inferences

The National Academies of Sciences published a document in 2019 titled *Reproducibility and Replicability in Science*.<sup>14</sup> Reproducibility was defined as computational reproducibility—obtaining consistent computational results using the same input data, computational steps, methods, and code, and conditions of analysis; replicability was defined as meaning the ability to obtain consistent results across studies aimed at answering the same scientific question, each of which is supported by its own data.

In that document, generalizability was defined as the extent to which the results of a study could be applied in other contexts or populations that differ from those used in the study. The Bayesian perspective goes hand in hand with the idea of generalizability.

In scientific investigations, the ability to generalize from the results obtained from the sample in hand to the larger world—predictive power—is the underlying premise of the science of risk analysis. In the 20th and early 21st century, statistical research has tended to focus on null hypothesis methods using p-values. This trend was viewed as unfortunate by the American Statistical Association (ASA) due to the belief by ASA's board of directors that the focus on p-values contributed to the reproducibility crisis in science.<sup>15</sup> This focus on p-values may have led in part to p-hacking, including the exhaustive modeling of datasets to find a method that yields a p-value less than 0.05, transformation of variables and accompanying loss of information, and even exclusion of some data for a variety of reasons.<sup>16</sup>

### 3.3.2 Systematic Review and Data Quality

Systematic review is a means of attempting to synthesize data from a variety of sources. In the 1970s, Archie Cochrane, a British physician and student of Sir Austin Bradford Hill, pioneered the use of evidence-based medicine and randomized clinical trials.<sup>17,18</sup> In the 1990s, Iain Chalmers, another British physician, spearheaded the establishment of the Cochrane Collaboration that developed and published systematic reviews of medical interventions.<sup>19</sup>

The ideas behind the Cochrane reviews led to the application of systematic review in toxicology. The challenges unique to toxicology include multiple evidence streams, multiple animal endpoints, and, often, lack of human data.<sup>20</sup> The guiding principle of a systematic review is to minimize bias. Bias here refers not to individual opinions, but rather issues with study design or data collection that may bias the results of a particular study.

Systematic review represents a data-driven path to provide a comprehensive assessment of data quality before these data can be used for decision-making. Basically, the result of a systematic review addresses whether the data can be used and how reliable these data might be. Conducting a systematic review is hardly a trivial exercise, and the motivation may be to provide a summary of information on an issue in toxicology in order to resolve controversies or uncertainties by exploring the reasons for observed inconsistencies, and to identify relevant data gaps.

Systematic reviews often address specific questions, and the importance of framing that question *a priori* to guide the review cannot be understated.<sup>21</sup>

### **3.4 VALUE OF INFORMATION: JUST HOW MUCH EFFORT DOES THE PROBLEM FORMULATION SUPPORT?**

While knowing *a priori* just how much the gathering of specific data will help inform the risk assessment, techniques for estimating the value of this information can be used for this decision. The value of gathering additional evidence depends on just how much these data can reduce the uncertainty in the ultimate decision.<sup>22</sup>

At many hazardous waste facilities, contaminant concentrations in soil become the driver for soil treatment or removal—both costly remedial alternatives. Many environmental risk analysts wished to have additional data on inadvertent soil ingestion by children. Children aged less than 6 years were generally assumed to ingest 200 mg of soil and dust per day and spend part of each and every day outside. How true this assumption is for children in states with long, cold winters such as Michigan and Minnesota, where the soil is covered with snow for almost four months and the frigid weather means children venture outside infrequently; this observation has led researchers to wonder whether it might be worth obtaining more data on this exposure factor. If one of the proposed remedial alternatives for contaminated soil is removal to a hazardous waste landfill, a comparative risk assessment can be used to assess the potential risks from dust generation from increased truck traffic against other possible alternatives.<sup>23</sup> Newer studies of children suggest they spend much less time outdoors than in the 1980s when these exposure assumptions for soil ingestion and time outdoors were determined.<sup>24,25</sup> Would incorporation of this new information change the results of the risk assessment? Would the associated expense be worth it in terms of the overall decision?

Multi-criteria decision-making uses value of information methods to attempt to find the best alternative in terms of both risk and benefit that is acceptable to all the stakeholders in the decision.<sup>23</sup>

#### **3.4.1 Expert Elicitation and Structured Peer Review**

For issues that bear considerable aleatory and epistemic uncertainty that extend across multiple disciplines, expert elicitation may provide a means to find greater understanding. Expert elicitation is one of the umbrella terms under which a variety of methods for involving experts in knowledge assessment can be found. Expert elicitation is a structured approach that seeks to make explicit the knowledge and wisdom of experts. Such an elicitation is a path to synthesizing the available knowledge in situations where dispositive scientific evidence is lacking.<sup>26</sup>

If a risk analyst has sufficient data, expert elicitation would not be considered. For “wicked” problems with limited scientific knowledge, great uncertainty, conflicting values, and high stakes, these structured “guesses” of experts may be the only path forward.<sup>27,28</sup>

SciPinion LLC is a small company with its headquarters in Bozeman, Montana that has become a leader in the use of structured peer review. In a structured peer review, experts are selected based on expertise metrics, i.e., education level, number of publications, years of experience, reputation, etc. The initial selection is scored by an independent third party. SciPinion personnel then refine the panel selection to improve diversity based on demographic factors such as age, geographic location, and employment sector. The sponsor provides initial charge questions that are reviewed by an independent editor to ensure they are not leading. The responses of the panel experts to each of the questions can be tracked according to demographic factors to reveal any inherent biases.<sup>29</sup>

The Delphi method, which includes interactions between peer reviewers, may be helpful in some instances. Anonymity of the reviewers may encourage greater participation. Currently, this structured peer review is being used to assess the feasibility of quantitative scoring of mode of action with the inclusion of meetings and discussion among panel members.<sup>30</sup>

### **3.5 COMPUTATIONAL TOOLS FOR A RISK ANALYST**

In the 21st century, a number of computational and quantitative tools are available to the risk analyst. This section will briefly describe these tools and their uses.

#### **3.5.1 The R Statistical Computing Language**

R is a programming language for statistical computing that is available at no cost. The language was created by two scientists at the University of Auckland based on the S statistical language developed earlier at Bell Labs by John Chambers and colleagues.<sup>31</sup> An integrated development environment called RStudio is available.<sup>32</sup> These can be downloaded at [www.r-project.org/](http://www.r-project.org/) and [www.rstudio.com/](http://www.rstudio.com/).

Several years ago, well after publication of the first edition of this book, a colleague said to me that learning R was necessary with “since I have at least 15 years left in my career.” This advice motivated me to learn R, and I’ve had no regrets.

In Chapter 6, two of the risk evaluations use R. The code and data are provided as part of the figures to enable readers who don’t yet know R to get started with it.

#### **3.5.2 Python**

Python is an open-source programming language that provides a more general approach to data science than R, with less focus on statistics and more on data manipulation. Python is more useful for web applications than R. Several integrated development environments are available for Python.

#### **3.5.3 Microsoft Excel and Add-Ins**

The statistical modeling facility in Excel is somewhat limited and has engendered the development of a number of packages to perform Monte Carlo simulation.

In Chapter 4, a method of fitting several types of distributions to data in Excel is demonstrated.

In the 1990s, a small company called Decisioneering developed a Monte Carlo add-in for Excel named Crystal Ball®. The company was eventually sold to Oracle, and the price increased almost tenfold. A number of free Excel add-ins exist for conducting Monte Carlo simulation in Excel. One of these, YASAI, was developed at Rutgers University and is available on the internet.

### **3.5.4 Epa's Benchmark Dose Software**

EPA's Benchmark Dose Software (BMDS) runs only in Microsoft Windows. In the 1990s, EPA scientists decided to use the benchmark dose method, and have since invested much time and energy in maintaining and updating this software. BMDS provides data management tools and an Excel interface.

For a number of years, BMDS was maintained by Dr. R. Woodrow Setzer. After his retirement in 2018, the software continues to be maintained by Drs. Jeff Gift and Allen Davis. The newest version (3.1) of BMDS includes Bayesian versions of dichotomous models and Bayesian model averaging.

BMDS software and information on its history and use can be found at [www.epa.gov/bmds](http://www.epa.gov/bmds).

### **3.5.5 PROAST—a BMDS Alternative**

PROAST is an R language package developed by the Dutch National Institute for Public Health and the Environment and used by them and the European Food Safety Agency.<sup>33</sup> PROAST performs the same tasks as BMDS without requiring the use of Excel. Web versions of PROAST are available as well. You can learn more about PROAST at [www.rivm.nl/en/proast](http://www.rivm.nl/en/proast).

Discussion of additional tools for dose–response modeling will be provided in Chapter 5.

### **3.5.6 Physiologically Based Pharmacokinetic (PBPK) Modeling**

Pharmacokinetics is the study of the quantitative relationships between the absorption distribution, metabolism, and elimination (ADME) of chemicals in biological systems. This study is also called toxicokinetics when applied to toxic chemicals. Pharmacokinetic models were first used in the early 20th century to describe the absorption and elimination of alcohol and ether from the blood.<sup>34</sup> PBPK models are mathematical representations of biological tissues, organs, and physiological processes occurring in the body and affecting the absorption, distribution, metabolism and excretion of chemicals.

#### **3.5.6.1 History of PBPK Modeling**

The first use of PBPK modeling was a study of ether in 1924.<sup>35</sup> At that time, the methods for numerical solution of nonlinear ordinary differential equations

(ODEs) were essentially undeveloped; some workers built electric circuits consisting of resistors and capacitors to simulate kinetics, understanding that the mathematics governing current flow in an electrical circuit was identical to that governing distribution of chemicals within the body.<sup>36,37</sup> Numerical methods for solving ODEs were impractical until the advent of computing in the second half of the 20th century.<sup>38</sup>

In the 1980s, PBPK models were used to predict the distribution of volatile organic chemicals in the body from inhalation exposure. A number of these models were used in risk assessments.<sup>39-41</sup>

Mathematical models of ADME of a large number of chemicals have been developed for use in environmental risk assessment and in the pharmaceutical industry. Early models concentrated on the estimation of vapors from volatile organic chemicals.<sup>42-44</sup> These models range in complexity, and are referred to as either physiologically based pharmacokinetic (PBPK) models or physiologically based toxicokinetic (PBTK) models.

One of the first non-pharmaceutical substances to be investigated with probabilistic techniques was trichloroethylene (THC).<sup>45-48</sup> Bayesian methods have been applied to pharmacokinetic modeling, but this application has focused to a greater extent on pharmaceutical development rather than environmental or chemical risk assessment.<sup>49</sup> In the 1990s, Frederic Bois of the Lawrence Berkeley Labs applied Bayesian methods, specifically Markov Chain Monte Carlo methods, to estimate parameter distributions in PBPK models.<sup>50</sup>

### **3.5.6.2 Software for PBPK Modeling**

Today, many PBPK models are implemented with proprietary modeling platforms. Some of these are hugely expensive and available only to large institutions. A dedicated PBPK modeling platform such as SIMCYP, developed for use in the pharmaceutical industry and with data underlying many physiological processes as part of the software, is one of the more expensive alternatives.<sup>51-53</sup>

The Advanced Continuous Simulation Language (ACSL) was first introduced by the Simulation Council in 1967 with a view toward defense application. The FORTRAN-based software was obtained by Mitchell & Gautier of Concord, Massachusetts in the 1980s; the price was out of reach for anyone but institutions. This company broke up, and the program ended up as the property of Aegis Technologies of Huntsville, Alabama; Aegis re-branded the software as ACSL/X and reduced the price to \$500. In 2015, Aegis discontinued ACSL/X. Conrad Housand, the highly skilled modeler and computer scientist who maintained ACSL/X, has provided software called Magnolia that runs as a stand-alone or as an R package. Magnolia is currently available as a free download at [www.magnoliasci.com/](http://www.magnoliasci.com/).

General-purpose mathematical programs such as MATLAB or Mathematica can be programmed to solve the model equations, but these programs are usually quite costly. Berkeley Madonna (<https://berkeley-madonna.myshopify.com/>) is an easy-to-use package that has an intuitive language and interface on both OSX and Windows; the software is available at the student price of \$99.

The use of such specific software, especially costly proprietary modeling platforms, hinders transparency. The R package DeSolve for solving ordinary differential equations can be used if one is experienced with R programming. Using R or Python for free may be the most cost-effective alternative, albeit with the overhead of learning a new computer language.

Scitovation LLC in Research Triangle Park, North Carolina developed the R package plethem in collaboration with EPA's National Center for Computational Toxicology. Plethem is an abbreviation for Population Life Course Exposure to Health Effects Modeling. The package is freely available; however, in contrast to most R packages, the documentation is extremely sparse and the package is difficult and frustrating to use, even for someone experienced with R.<sup>54</sup>

PK-Sim® is an open source software package from Bayer that runs under Microsoft Windows and has interface for data export to both R and MATLAB. The software appears to be very powerful, and can even incorporate variability in gene expression. Downloads, documentation, and tutorials are available at <http://www.open-systems-pharmacology.org/>.<sup>55</sup>

## 3.6 SPECIFIC METHODS AND ALGORITHMS

Probabilistic simulation, also known as Monte Carlo, is a uniquely valuable tool for risk calculation. In most instances in environmental risk assessment, the equations for calculating risk are sufficiently complex that analytic solutions for propagating variance are technically impossible.

Computer power continues to increase over time. Hence, the process of probabilistic simulation has become the method of choice for most complex risk assessments. In probabilistic simulation, a large number of iterations are performed, and with each iteration, a random selection from the distributions of the input variables is used in the calculation. The outcome of probabilistic simulation is a set of outcomes that can be summarized with simple statistics such as the mean or upper percentile values.<sup>56-58</sup>

Probabilistic simulation is becoming common for decision support in a number of areas in which risk assessment is used, including environmental cleanups as well as civil and criminal litigation.<sup>59</sup> The purpose of this section is not to make you an expert in Monte Carlo methods, but to enable you to “dip a toe in the water.” Excel is now taught in many high schools and is used almost universally. The methods and formulae are presented for use in Excel. For those conversant with R or other computational languages, adapting these formulae will be easy.

### 3.6.1 Working with Probability Distributions

In Chapter 4, fitting distributions to data on body mass will be presented. As a risk analyst, you will likely be expected to be able to generate random variates. Here, the Excel formulae for doing so for several distributions will be provided. Many more types of distributions exist, both continuous distributions with examples and Excel code below, and discrete or integer distributions.

### 3.6.1.1 The Uniform Distribution

The uniform or rectangular distribution is characterized by minimum and maximum values with equal probability of any value within this range. The standard uniform distribution with limits of 0 and 1, denoted as  $U(0,1)$ , is available in Excel as the RAND function with the code:

$$= \text{RAND()} \quad [3.1]$$

### 3.6.1.2 The Standard Normal Distribution

The standard normal distribution is the well-known “bell curve” with a mean of 0 and a standard deviation of 1. Percentile values from the standard normal distribution are often referred to as Z-scores. The standard normal distribution can be modeled from two standard uniform distributions to give two standard normal variates.<sup>60</sup> The Excel code is:

$$= \text{SQRT}(-2 * \text{LN}(\text{RAND}())) * \text{SIN}(2 * \text{PI()} * \text{RAND}()) \quad [3.2]$$

Putting this code in a single cell in a worksheet will generate a single normal random variate. The code can be easily copied down a column to produce as many values as one wishes.

### 3.6.1.3 The Normal Distribution

The normal distribution is characterized by two parameters,  $M$ , the mean, and  $S$ , the standard deviation. Any normal distribution can be modeled from the variates or Z-scores generated from a probabilistic simulation of the standard normal distribution. The standard deviation is multiplied by the standard normal variate or Z-score calculated from Equation 3.2 and the result added to the mean. The Excel code for a normal variate with mean  $M$  and standard deviation  $S$  is:

$$= M + S * \text{SQRT}(-2 * \text{LN}(\text{RAND}())) * \text{SIN}(2 * \text{PI()} * \text{RAND}()) \quad [3.3]$$

### 3.6.1.4 The Lognormal Distribution

The lognormal distribution is simply a normal distribution of the logarithms of the values in the distribution. The bounds of the distribution are 0 and positive infinity. As discussed further in the next chapter, lognormal distributions are characterized by a long upper tail and occur frequently in natural phenomena. The distribution of incomes in the US, for example, is often characterized as lognormal.

The lognormal distribution is characterized by two parameters,  $\mu$ , the mean of the natural logarithms of the values, and  $\sigma$ , the standard deviation of the natural

logarithms of the values. The Excel code for a lognormal variate with log mean  $\mu$  and log standard deviation  $\sigma$  is:

$$= \text{EXP}(\mu + \sigma * \text{SQRT}(-2 * \text{LN}(\text{RAND}()) * \text{SIN}(2 * \text{PI}() * \text{RAND}()))) \quad [3.4]$$

### 3.6.1.5 The Weibull Distribution

The Weibull distribution is used to model particle size distributions and for survival analysis. The Weibull distribution has bounds of 0 and positive infinity, with a more flexible shape than the lognormal distribution.

The Weibull distribution is characterized by two parameters, *scale* and *shape*. The Excel code for a Weibull distribution is:

$$= \text{scale} * (-\ln(1 - \text{RAND}))^{(1/\text{shape})} \quad [3.5]$$

### 3.6.1.6 Correlations and Dependencies

In many probabilistic simulations, dependencies between input variables may not be known. This lack of knowledge is a significant uncertainty. When these dependencies are known, they can easily be simulated. The simplest way to model a known dependency between two variables is to use correlated standard normal distributions. This process requires generation of two sets of standard normal variates and a correlation coefficient to calculate a third set. We will call these  $Z_1$ ,  $Z_2$ , and  $Z_3$ . These can be thought of as three columns in an Excel worksheet. The code in the first two columns that represent  $Z_1$  and  $Z_2$  is shown in Equation 3.2. The code in the third column, representing  $Z_3$ , which is correlated with  $Z_1$  with correlation coefficient  $\rho$ , is:

$$= \sigma * Z_1 + \text{SQRT}(1 - \rho^2) * Z_2 \quad [3.6]$$

## 3.6.2 Graphics

No question that graphics is difficult! Compelling graphics is an inescapably huge factor in presenting the results of a risk analysis in a convincing and credible fashion. Graphic tools capable of the flexibility needed to present the results of a risk analysis are difficult to learn and require much trial and error. The description of all of these is beyond the scope of this book. The best graphic presentations represent an integration of evidence—pictures, words, and numbers—to make a point, and do so without extraneous information.

One of the best thinkers on achieving excellence in graphic presentations is Edward R. Tufte, an American statistician, professor emeritus of political science, statistics, and computer science at Yale University, and a renowned sculptor. A

book of his is listed as further reading at the end of the chapter. Tufte continues to present his ideas on graphic communication in one-day courses held in many US cities.

## **3.7 TRANSPARENCY AND COMMUNICATION OF MODELING RESULTS**

It is important to remember that a risk analyst is likely not personally responsible for the risk under study. The outcome of the analysis should be as unbiased as possible. The one allegiance an analyst has is to the strength and quality of the analysis and how well the data and methods support the conclusions.

### **3.7.1 Exploration of a Range of Approaches**

A familiar example of the use of different approaches is fitting to a range of dose-response models as done in EPA's Benchmark Dose software. Model averaging approaches should be considered as well that find a middle ground for the results of different modeling methods.<sup>13,61</sup>

An attempt to understand where aleatory and epistemic uncertainties occur in environmental risk assessments was made by using expert elicitation.<sup>62</sup> The study found that the risk characterization step bore the greatest combined uncertainty. The results of the elicitation were then compared to case study risk evaluations of the effects of genetically modified plants, atmospheric particles, and pesticides in surface water. The apportionment of the various calculated uncertainties generally agreed with the results of the elicitation.<sup>63</sup>

### **3.7.2 Clarity and Transparency about Methods, Assumptions, and Data**

Most scientific journals encourage the inclusion of supplemental materials with accepted publications. Providing a supplement or set of appendices as part of a risk assessment report accomplishes the same goal, allowing others to use the same assumptions, tools, data, and methods to replicate the results. This transparency will only strengthen the analysis.

### **3.7.3 Taking Responsibility for the Choices Made**

Many times, the analyst will need to rely on professional judgment, essentially a more or less educated guess, for some of the assumptions made. As much information as possible about the assumptions, the source of data, and any other decisions made in the course of the assessment is part of the transparency needed for credibility.

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## CHAPTER 4

# Exposure Assessment

A better understanding of exposures will exonerate the majority of chemicals people are afraid of.

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International Society of Exposure Science*

There are two basic aspects to consider in an exposure assessment—the first is what happens to chemicals in the environment, and the second is what behaviors of the receptors produce contact with potentially contaminated environmental media. Thus, exposure assessment for human health risk assessment requires consideration of both physical-chemical aspects of contamination—how chemicals occur in environmental media—as well as human behavior—how people come in contact with these media. These two aspects will be referred to as the environmental and behavioral realms. Aspects of exposure in ecological risk assessment will be considered in Chapter 6. The need to obtain data that address questions in both these realms and the resulting use of a number of assumptions introduces uncertainty into exposure assessment—evident in numerous examples in this chapter.

In order for a risk to occur, there must be exposure to environmental media, i.e., soil, air, water, or sediment, and the medium must contain hazardous materials. The “Red Book” defines exposure assessment as the “process of measuring or estimating the intensity, frequency, and duration of human exposures to an agent currently present in the environment or of estimating hypothetical exposures that might arise from the release of new chemicals into the environment.”<sup>1</sup>

### 4.1 SCENARIOS AND RECEPTORS

Within the behavioral realm of exposure assessment in human health risk assessment, a receptor is a participant in an exposure scenario. All exposure scenarios require that one or more environmental media contain chemicals believed hazardous, but also cover the ways in which populations or individuals might contact these media. These populations and individuals are considered receptors.<sup>2,3</sup>

Scenario evaluation is the most common means of exposure assessment. Estimates of factors in the behavioral realm that bring a receptor into contact with a contaminated medium are used, along with measurements of the chemical concentration in that medium, to estimate external dose. One of the most controversial and uncertain exposure factors used in scenario evaluation is children's soil and dust ingestion. The assumption underlying this factor is that children will contact outdoor soil, and then any soil remaining on their hands after contact will be ingested by incidental hand-to-mouth contact; indoor dust may be partially comprised of outdoor soil, and thus provides a similar exposure pathway indoors.

Generally, risk assessments conducted by EPA involving media other than air use a set of standard exposure scenarios. These scenarios include residential property use, commercial or industrial use, and recreational use. The receptors in these scenarios include adults, children, and workers. EPA produced supplemental guidance to RAGS in 1991, the *Standard Default Exposure Factors*, that essentially codified four distinct exposure/land use scenarios as:

- residential;
- commercial/industrial;
- agricultural;
- recreational.<sup>4</sup>

To comply with the recommendation in the "Red Book" to produce standard inference guidelines, EPA prescribed a set of default exposure factors for these scenarios (Table 4.1). This document was produced following internal EPA discussions occurring in 1990 and 1991.

**Table 4.1 EPA's Standard Default Exposure Factors<sup>4</sup>**

	Residential		Commercial/ Industrial		Agricultural		Recreational	
	Adult	Child	Adult	Adult	Child	Adult	Adult	Child
Water Ingestion (L/d)	2	NA	1	2	NA	NA	NA	NA
Soil Ingestion (mg/d)	100	200	50	200	100	NA	NA	NA
Total Inhalation rate (m <sup>3</sup> /d)	20	NA	20	20	NA	NA	NA	NA
Indoor Inhalation rate (m <sup>3</sup> /d)	15	NA	NA	15	NA	NA	NA	NA
Exposure Frequency (d/y)	350		250	350		350	NA	
Exposure Duration (y)	24	6	25	24	6	30	NA	NA
Body Weight (kg)	70	15	70	70	15	70	NA	NA
Consumption of home-grown produce (g/d)					42 (fruit) 80 (veg.)	NA		
Consumption of locally caught fish (g/d)					NA	54		

This guidance is an initial attempt to provide values to use in the standard intake equation:

$$\text{Intake} = (C \times IR \times EF \times ED) / (BW \times AT) \quad (4.1)$$

where C = chemical concentration in a medium

IR = intake/contact rate

EF = exposure frequency

ED = exposure duration

BW = body weight

AT = averaging time

These variables are known as exposure factors. From 1990 to 1997, EPA released a series of drafts of the 1997 *Exposure Factors Handbook*.<sup>5</sup> This final document is extremely comprehensive and provides a very complete description of the data upon which the values of the various exposure factors were based. This report and its updates were the work of Jacqueline Moya of EPA's National Center for Environmental Assessment. The various releases of the *Exposure Factors Handbook* are similarly comprehensive and detailed enough that they have become the *de facto* standard reference for information on exposure factors. In 2008, also under Ms. Moya's direction, EPA released the *Child-Specific Exposure Factors Handbook* and, three years later, the updated *Exposure Factors Handbook, 2011 Edition*.<sup>6,7</sup>

EPA continues to update the *Exposure Factors Handbook*. In 2017, an update to its Chapter 5 on soil and dust ingestion was released and in 2018, four chapter updates were released: Chapter 9 on fruit and vegetable intake, Chapter 11 on intake of meats, dairy products and fats, Chapter 12 on intake of grains, and Chapter 19 on building characteristics.<sup>8-13</sup>

In a later section of this chapter, a detailed description of the various exposure factors is provided; this description is based on the extensive and very useful information in these EPA publications.

## 4.2 INDIVIDUAL AND POPULATION EXPOSURE

As part of the response to the “Red Book”, EPA released a draft version of the *Guidelines for Exposure Assessment* in 1986. This version is no longer available on EPA's website. In 1988, EPA produced the *Superfund Exposure Assessment Manual*.<sup>14</sup> This manual dealt almost exclusively with the environmental realm, models of environmental fate, and transport of chemicals. In 1992, EPA updated and finalized the *Guidelines for Exposure Assessment*.<sup>3</sup>

In contrast to previous work in epidemiology and industrial hygiene, which focused on external doses only, these guidelines defined two steps occurring in exposure—contact with a chemical, followed by entry or absorption into the body to produce an internal dose. Specifically, internal dose was used to refer to the amount of chemical absorbed across an exchange boundary such as the

gastrointestinal tract, lungs, or skin. The distinction between internal and external dose was a giant leap forward because it allowed risk assessors to distinguish between systemic effects—produced at locations in the body other than the point at which entry occurs—and portal-of-entry effects that occur at the point of contact. This distinction paved the way for the use of physiologically based pharmacokinetic (PBPK) models as part of the toxicity assessment. Perhaps even more important, this distinction encouraged a focus on biomonitoring, such as the National Health and Nutrition Examination Survey conducted by the Centers for Disease Control and the identification and quantitation of internal dose as part of the exposome.<sup>15,16</sup>

#### **4.2.1 The Concept of Reasonable Maximum Exposure (RME)**

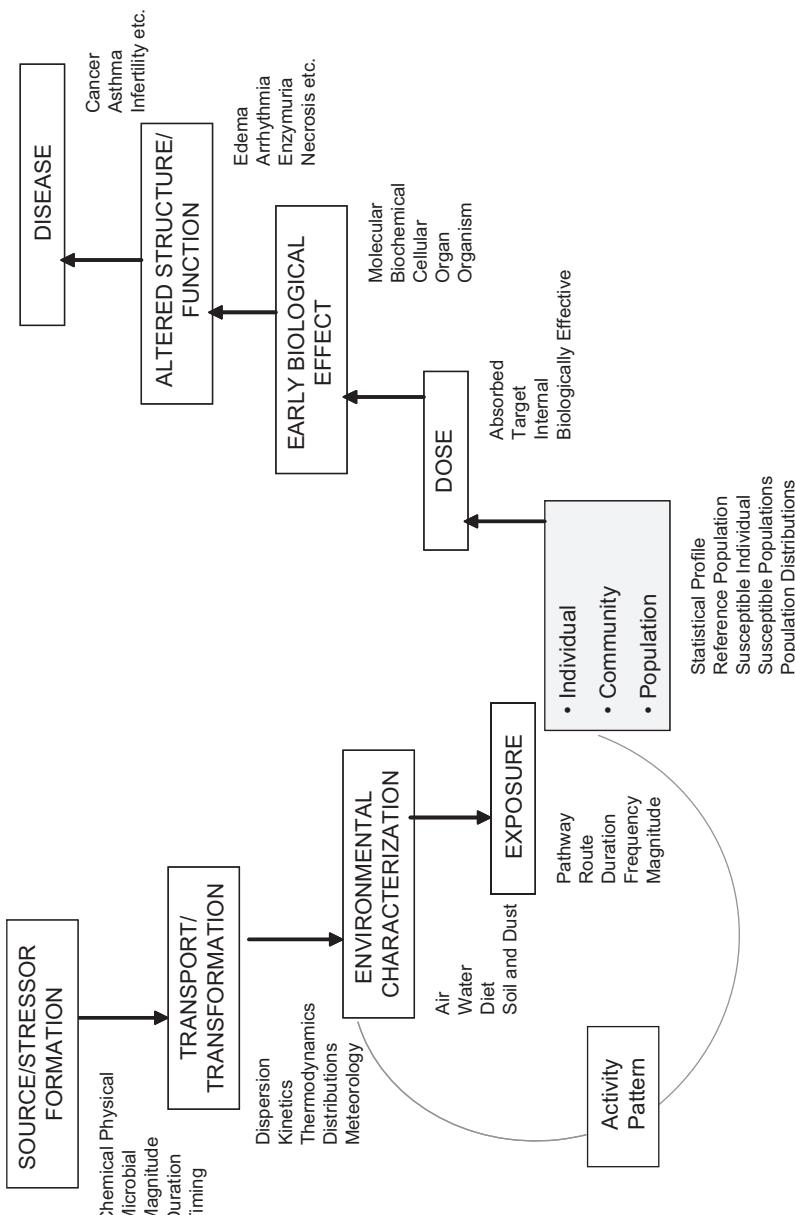
For the majority of exposure assessments in environmental risk assessment, exposures will be modeled using equations similar to Equation 4.1. In such cases, these individuals will be hypothetical—assumed to represent specific percentiles of exposure within the target population.

When point estimates of the various exposure factors are used in Equation 4.1, the percentiles of the resulting estimates of exposure and risk remain unknown. For example, in Superfund-type risk assessments, the risk estimate used to determine whether a cleanup is warranted is determined for the hypothetical individual at the point of reasonable maximum exposure.<sup>2,17</sup>

The RME concept was also presented in the 1992 *Final Guidelines for Exposure Assessment*. The Guidelines state that the upper end of the distribution of risk should be characterized, and high-end estimates of individual risk, such as the hypothetical RME individual, and the high-end estimate should fall at the 90th percentile or above. Additionally, the Guidelines provide a detailed and cogent discussion of uncertainty assessment that concludes:

It is fundamental to exposure assessment that assessors have a clear distinction between the variability of exposures received by individuals in a population, and the uncertainty of the data and physical parameters used in calculating exposure.<sup>3</sup>

Within EPA, the Risk Assessment Forum (RAF), part of the Office of the Science Advisor, produced these guidelines. The RAF does not become involved in regulation. Instead, this group was established to promote consensus on difficult and controversial risk assessment issues within EPA. As such, the recommendations of the RAF are not necessarily for immediate regulatory application, but rather represent long-term policy recommendations. Regarding the statement from the *Final Guidelines for Exposure Assessment*, the RAF understood that, in many cases, risk assessment practitioners might not be able to estimate variability and uncertainty in a quantitative fashion, but wanted to ensure that the goal of doing so was maintained and the qualitative distinction between variability and uncertainty kept in mind.



**Figure 4.1** Exposure–effect continuum from the 2011 *Exposure Factors Handbook*.

The distinction between various types of doses and exposures is discussed clearly in Chapter 1 of the *Exposure Factors Handbook 2011 Edition*.<sup>7</sup> Exposure does not necessarily produce a dose, but a dose cannot occur without exposure. EPA presents a continuum from exposure to effects; the continuum considers both individuals and populations. This continuum is essentially the same as that described as an adverse outcome pathway.<sup>18–20</sup> The exposure–effect continuum is shown in Figure 4.1.\*

In EPA's Food Quality Protection Act, the Office of Pesticide Programs (OPP) determined in 1999 to choose the 99.9th percentile of exposure as the regulatory target for single-day acute dietary exposure to pesticides.<sup>21</sup> This was an interim choice because OPP recognized that individuals might be exposed to more than one pesticide with a common mechanism of action. For example, chlorpyrifos and methamidophos are both organophosphate pesticides that act by inhibition of an enzyme called cholinesterase that has important functions in regulating neuromuscular transmission and brain activity in mammals.<sup>22,23</sup> In 2006, OPP withdrew the guidance that stipulated use of the 99.9th percentile in favor of a cumulative risk assessment approach.<sup>24,25</sup>

#### 4.2.2 Matching Exposure Duration to the Adverse Effect

Exposure may occur over an acute or chronic time scale. Toxicity also has a time scale, and it is important that these time scales match. For example, exposure to chlorine gas at 1000 parts per million is fatal within minutes. However, chronic exposure to other substances at low level for many years may or may not produce chronic effects, often depending on individual factors including diet and lifestyle. Generally, most environmental risk assessments deal with chronic exposures. Previously, EPA defined three distinct time scales for both exposure and toxicity—chronic as greater than seven years, subchronic between 14 days and seven years, and acute less than 14 days.<sup>2</sup> The Agency for Toxic Substances and Disease Registry (ATSDR) in its derivation of minimum risk levels considers a chronic time period to be one year or greater, an intermediate time period to be 14–365 days, and an acute time scale to be 1–14 days.<sup>26</sup> In more recent toxicity assessments in EPA's Integrated Risk Information System, four different time periods were specified—acute, meaning less than 24 hours; short-term, 1–30 days; subchronic, 30 days to seven years; and chronic, longer than seven years.<sup>27</sup>

If contact with a chemical occurs over a chronic time scale, the external dose is usually averaged or integrated over time to obtain an average daily dose. In most risk assessments, the exposure assessment provides measures of average daily dose, usually in units of mg of chemical per kilogram of body weight per day, or mg/kg/d. In many cases, only a portion of the chemical is absorbed or moves across the exchange boundary. In such a case, the chemical is considered less than 100% bioavailable. While bioavailability may be considered an aspect of the toxicity assessment, EPA's *Final Guidelines for Exposure Assessment* made it clear that it could also be considered as part of the exposure assessment—especially when using internal dose as a measure of exposure.

\* The concept of the exposure–effect continuum, while not incorrect, does not tell the whole story. The idea of the exposure–effect discontinuum and its relation to dysregulation of homeostasis and thresholds will be discussed in Chapter 5.

### 4.2.3 Point-of-Contact Exposure

Point-of-contact exposure assessment measures the chemical or stressor concentration at the interface between the body and the environment. The value of this method is that exposure is directly measured rather than estimated, with the proviso that the measurements are accurate. The most familiar example of such a measurement is a radiation dosimeter, the small film badge worn by X-ray technicians and others exposed routinely to radiation. All point-of-contact measurements suffer from two difficulties: most often, they produce short-term measurements, and they are not specific to any source of the stressor or chemical being measured. Hence, means of source discrimination and extrapolation of the short-term measures to the generally longer time scale of the risk assessment are needed.

### 4.2.4 Modeling Internal Exposure

Knowing the organ or tissue at which the most sensitive response of a receptor occurs enables one, in some instances, to create a model of internal dose. In the 1980s, ongoing work on the toxicity of volatile solvents spurred a group of scientists at Wright-Patterson Air Force Base in Ohio and the Dow Chemical Company in Midland, Michigan to develop PBPK models that could predict the concentration of these solvents in specific target tissues. The sophistication and complexity of PBPK have increased considerably since that time.<sup>28,29</sup> These models are also known as physiologically based toxicokinetic (PBTK) models.

Many risk analysts consider PBTK models to be part of the toxicity or dose-response considerations. Exactly where these models fit in the overall scheme of risk assessment is in the eye of the beholder. PBTK models are used to predict the concentration of a xenobiotic substance in a tissue of interest—as such, the model results can be considered a measure of internal exposure. Conversely, the use of physiologic data such as blood flow and inhalation make them seem part of the toxicity assessment.

Much more detail of the execution and use of PBTK models will be presented in Chapter 5.

### 4.2.5 Biomonitoring and Biomarkers

Modeling tissue concentrations of potentially toxic substances can be a powerful tool and a highly engaging intellectual exercise. In general, measurements are preferable to model results.

Biomonitoring or measuring internal dose provides a third means of performing an exposure estimate. Biomonitoring data can be used along with knowledge of the toxicokinetics of the chemical to estimate historical doses.<sup>30–33</sup>

Since 1999, the Centers for Disease Control and Prevention (CDC) has conducted the National Health and Nutrition Examination Survey (NHANES). This effort collects data on the US civilian population through confidential and voluntary participation. Biometric measures such as height and weight, demographic data including

age, gender and ethnicity, and the concentrations of a large number of environmental chemicals in blood and urine are collected. NHANES data provides population-specific ranges of chemicals representing background exposure for comparison with data on specific target populations. For each chemical measured in NHANES, the data represent cumulative exposure without regard to source, thus additional work is needed to identify the source and exposure route.<sup>15</sup>

Summit Toxicology is a very small consulting company in the US with an international set of clients. Dr. Sean M. Hays, the president and founder of Summit Toxicology, has pioneered the development and use of biomonitoring equivalents (BEs) that represent a urine or blood concentration that would occur with exposure at exposure guidance values or toxicity reference value. The notion of BEs as monitored blood or urine concentrations consistent with existing exposure guidance values is a screening method based on integrating toxicokinetics data with extant chemical risk assessments to provide a convenient screening tool.<sup>34</sup> Underlying each BE value is a quantitative understanding of the relationship between biomonitoring levels in humans and the observed toxicological response.<sup>34-36</sup>

Likely the best-known biomonitoring-derived standard similar in concept and application to BEs is the CDC level of concern for blood lead in children, with a value of 5 µg/dL.<sup>37</sup>

In cases in which exposure information or percentiles are obtained from biomonitoring data, individual data values may represent actual people—their identities will, of course, not be revealed because of ethical considerations. Assuming the population from which the biomonitoring results were obtained is representative of the target population, the percentiles within the biomonitoring data will thus represent percentiles of exposure within the target population.

#### **4.2.6 Natural Variation in Internal Exposure: The Problem of Reverse Causation**

Around 2000, the term “reverse causation” sprouted in studies of body weight and mortality. Generally, reverse causation is the situation in which the outcome is actually causal to the effect. For example, some claim that an active lifestyle protects cognitive function in old age; those older adults with high cognitive function may, however, choose a more active lifestyle. Which one is the cause, and which is the effect?

A 1992 study of over 3000 Dutch children observed that respiratory allergy and asthma symptoms were lower among current pet owners than those who owned no pets. However, the lowest prevalence of symptoms occurred in children whose families had never owned pets, and the highest prevalence occurred in children whose families owned pets in the past. In a significant number of instances, the pets were removed from the home following the occurrence of symptoms in the children.<sup>38</sup>

Dioxin is a contaminant found in the herbicide Agent Orange used in the Vietnam war. Operation Ranch Hand conducted aerial spraying of herbicides during that conflict. A dose-response association between dioxin exposure measured with a blood biomarker and type 2 diabetes was later observed in Vietnam veterans exposed to Agent Orange.<sup>39,40</sup>

The disease progression of diabetes can produce lipolysis of fat stores and the release of free fatty acids into the blood concomitant with increased insulin resistance.<sup>41</sup> Rapid loss of body fat can cause mobilization of chemicals stored in fat such as organochlorine insecticides, tetrahydrocannabinol in cannabis users, and dioxin.<sup>42</sup>

After the 1970s, the worldwide human body burden of dioxin began to decrease.<sup>43,44</sup> In a number of Ranch Hand veterans who handled Agent Orange during the Vietnam War, increases in dioxin blood levels were observed, followed by significant weight loss, with reductions in body mass index of between 3.5 and 6.6. In addition, the diagnoses of diabetes in these individuals preceded both the weight loss and dioxin measurements.<sup>45</sup> Hence, the pathological lipogenic weight loss associated with diabetes produced the increase in dioxin concentrations in blood.

In other instances of biomarker use as a measure of exposure, normal variation of a biological process may affect both an outcome and the biomarker value. Kidney function is generally measured as glomerular filtration rate (GFR), and maternal GFR is positively related to birth weight.<sup>46,47</sup> Perfluorooctanoic acid (PFOA) can be measured in blood, and its concentration is strongly related to birth weight.<sup>48</sup> A recent meta-analysis that separated studies where blood was sampled early in pregnancy or before conception showed no association of birth weight with PFOA, whereas in studies where sampling occurred late in pregnancy, high PFOA concentrations were associated with lower birth weight. The variation in pregnancy-related changes in GFR affected both the serum PFOA concentrations and birth weight—another example of reverse causation.

### **4.3 PROBABILISTIC EXPOSURE ASSESSMENT: FREQUENCY DISTRIBUTIONS FOR EXPOSURE ASSESSMENT**

The work of David Burmaster in the 1990s regarding compounding conservatism and realism likely led to EPA's publication of *RAGS, Volume III: Process for Conducting Probabilistic Risk Assessment*.<sup>49</sup> Probabilistic risk assessment is viewed as one way to improve risk assessment—both by regulators and those within the regulated community. Probabilistic methods provide tractable means for propagating estimates of uncertainty and variability through an equation or model. Analytical solutions for the propagation of variance exist, but these are often difficult to implement. In contrast to the analytical methods, Monte Carlo analysis (MCA) is a specific probabilistic method that uses computer simulation to combine multiple probability distributions in an equation. MCA is relatively simple to implement with commonly available software. In one of the exercises at the end of the chapter, readers will be able to perform a relatively simple Monte Carlo exercise implementing the bootstrap method for calculating the 95% upper confidence limit on the arithmetic mean as the concentration term.<sup>50,51</sup>

One area of probabilistic risk assessment that continues to provide difficulties is the specification of distributions. This problem has been around ever since the French mathematician Pierre-Simon Laplace used the uniform probability distribution for

ease of analysis rather than for any metaphysical reason.<sup>52</sup> His lack of preference for a particular value in a range became known as the “principle of indifference.” Why the uniform distribution? Because in the absence of any information, all values are equally probable.

The use of uniform probability distribution is generally problematic in risk assessment because almost always, one can determine additional information to specify a more informed distribution.<sup>53-55</sup>

There are a host of techniques to be used to develop appropriate distributions, and the field of probabilistic exposure assessment continues to evolving.<sup>56</sup> One method of performing a probabilistic risk assessment (PRA) deserves mention—microevent exposure analysis.<sup>57</sup> This method was developed by Paul Price, a proponent of common sense in risk assessment. In the microevent exposure approach, an individual’s chronic dose rate is modeled as the sum of doses received from separate exposure events. Because this approach tracks individuals through time, values of exposure factors appropriate to the life stage can be used. Probabilistic aspects of specific exposure events can be selected from the appropriate distributions, e.g., the size of a meal of fish or the number of fish meals per month. Various frequency distributions used in exposure modeling will be discussed in this section.

Just how should one choose a specific probability distribution to represent a specific exposure factor from the plethora of distributional forms available? Ideally, the phenomenology of the data-generating process and known limits will be used to inform the choice of distribution. Results of goodness-of-fit tests are not usually helpful in selecting a distribution; in most cases, demonstrating coverage and similarity comparing a histogram of the data to the modeled probability density function of the selected distribution is sufficient. In 2016, the American Statistical Association released a statement de-emphasizing the importance of p-values and significance testing in favor of overall scientific reasoning. If a distribution is concordant to the data represented and is fit for the purpose of the risk analysis, no statistical testing need occur; the corollary is that the risk analyst must present the reasoning behind his/her work in a clear and transparent fashion.

A brief description of several useful distributions is presented below. This description will tend toward the utility of these distributions rather than their mathematical basis.

### 4.3.1 The Lognormal Distribution

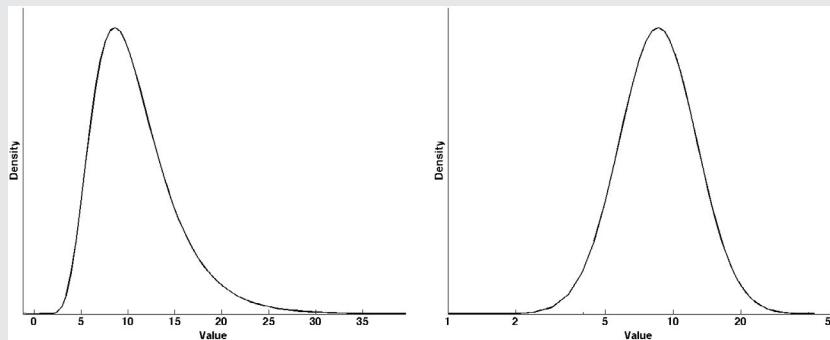
Most exposure factors have right-skewed distributions, with most of the values near the median and a few high values. Income in the US follows this pattern—most citizens earn near the median and a very few earn over \$1,000,000. These high earnings of these few raise the average or arithmetic mean income in the US to a value quite a bit higher than the median. The other real advantage of the lognormal distribution is that it provides a mathematically tractable and therefore useful distribution with which to represent most exposure factors.

The lognormal distribution is most often used for the concentration term. Box 4.1 provides more information and some useful formulae for the lognormal distribution.

### BOX 4.1 THE LOGNORMAL DISTRIBUTION

This probability distribution is widely used in environmental applications. The lower bound is zero, and it has no upper bound. One can think of this distribution as a normal or Gaussian distribution of the logarithms of the data. The normal distribution is the familiar “bell curve.”<sup>59</sup>

The two plots below show the probability density functions of an sample lognormal distribution on a both linear (left) and logarithmic (right) x-axes.



The lognormal distribution can be fully characterized by two parameters—but there are three ways these parameters can be expressed. The most basic parameters are  $\mu$  and  $\sigma$ , which are the mean and standard deviation of the underlying normal distribution (right plot). The geometric mean (GM) and geometric standard deviation (GSD) are the exponentiation of  $\mu$  and  $\sigma$  respectively. The GM occurs at the median or 50th percentile of the distribution:

$$GM = \exp(\mu); \mu = \ln(GM) \quad (4.2)$$

$$GSD = \exp(\sigma); \sigma = \ln(GSD) \quad (4.3)$$

The formulae for the arithmetic mean and arithmetic standard deviation are slightly more complicated. Recall the example of the distribution of incomes—the average or arithmetic mean income was higher than the median income. These formulae are:

$$\text{Arithmetic mean (AM)} = \exp(\mu + 0.5\sigma^2) \quad (4.4)$$

$$\text{Arithmetic standard deviation (ASD)} = \text{SQRT}[\exp(2\mu + \sigma^2) * (\exp(\sigma^2) - 1)] \quad (4.5)$$

If one knows the AM and ASD, the GM and GSD can be calculated as follows:

$$GM = AM^2 / \text{SQRT}(AM^2 + ASD^2) \quad (4.6)$$

$$GSD = \exp\left(\text{SQRT}\left[\ln\left(1 + ASD^2/AM^2\right)\right]\right) \quad (4.7)$$

The lognormal can be easily fit to summary statistics such as the mean and variance or to percentile data.

The limits of any lognormal distribution are zero and infinity. The lower limit of zero is useful because exposure factors, such as inhalation rate or soil ingestion, are never negative. The upper limit may be troublesome—if one uses a lognormal distribution for human body weight, 800 kg is a possible result in a probabilistic simulation. NHANES is an excellent source of data on exposure factors, and these are often available as summary statistics and percentiles.<sup>58</sup>

#### 4.3.2 Utility of the Johnson SB Distribution

The Johnson SB distribution is a four-parameter lognormal distribution with both upper and lower bounds. The shape of the distribution is very flexible and can be easily fit to data. Box 4.2 shows an example of fitting both the lognormal and Johnson SB distributions to the percentile data for body mass of women 20 and older from NHANES 1999–2002.

#### BOX 4.2 COMPARISON OF DIFFERENT LOGNORMAL CALCULATIONS FOR BODY MASS

Percentiles of Women's Body Mass: Mean = 74.1; SEM = 0.46; N = 4299									
0.05	0.1	0.15	0.25	0.5	0.75	0.85	0.9	0.95	
48.9	53.4	56.0	60.1	70.2	83.7	93.5	100.2	110.2	

The goal in both calculations is to obtain values for  $\mu$  and  $\sigma$ , the natural logarithms of the GM and GSD respectively.

##### Lognormal Calculation from Equations 4.6 and 4.7

As in Box 4.1, AM is the arithmetic mean and ASD is the arithmetic standard deviation.

From the standard error of the mean, the ASD can be derived by multiplying the standard error of the mean (SEM) by the square root of N, or 65.57:

$$ASD = SEM \times \text{SQRT}(N) = 0.46 \times 65.57 = 30.1$$

$$\mu = \log\left(\frac{AM^2}{\sqrt{AM^2 + ASD^2}}\right) = \log\left(\frac{74.1^2}{\sqrt{74.1^2 + 30.2^2}}\right) = 4.229$$

$$\sigma = \sqrt{\log\left(1 + \frac{ASD^2}{AM^2}\right)} = \sqrt{\log\left(1 + \frac{30.2^2}{74.1^2}\right)} = 0.3915$$

#### Lognormal Calculation from Rank Order Statistics (ROS)

Pctl	BW	Z-score	Log BW	LINEST function	
0.05	49.8	-1.645	3.908	0.244	4.281
0.1	53.4	-1.282	3.978	0.006	0.007
0.15	56	-1.036	4.025	0.996	0.021
0.25	60.1	-0.674	4.096	1565.412	7.000
0.5	70.2	0.000	4.251		
0.75	83.7	0.674	4.427		
0.85	93.5	1.036	4.538		
0.9	100.2	1.282	4.607		
0.95	110.2	1.645	4.702		

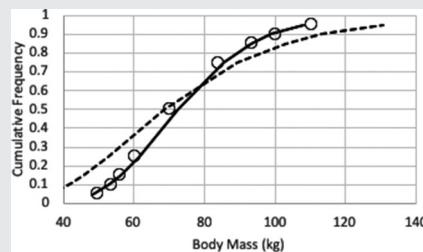
Formulae:

Z-score: “=NORM.S.INV(Pctl)” 2) Log BW: “=LN(BW)

Linest function: Array formula “=LINEST(Log BW, Z-score, 1, 1)”

From the ROS, the values of  $\mu$  and  $\sigma$  are the intercept and slope of the linear regression results from the LINEST function. Hence,  $\mu = 4.281$  and  $\sigma = 0.244$ .

The plot to the right shows the actual body mass percentiles as open circles, the values calculated from Equations 4.6 and 4.7 as the dashed line, and the values obtained with the ROS method as the solid line. Which one fits the data better?



### 4.3.3 Other Useful Probability Distributions

One of the simplest distributions is the uniform distribution with limits of 0 and 1. Any value within this interval occurs with equal probability.

Likely the most familiar distribution is the normal or Gaussian distribution. This is the familiar “bell curve.” The normal distribution is generally not as useful to model exposure factors because the limits are  $-\infty$  and  $+\infty$ . In addition, most quantities in nature vary over a logarithmic scale rather than an arithmetic scale. The other distributions discussed in this section all have long tails and can describe processes occurring on a logarithmic scale more closely than the normal distribution. The standard normal distribution with a mean of 0 and a standard deviation of 1 is very useful for building other distributions. The standard normal distribution will be used in Box 4.3.

Another useful distribution is the beta distribution. This distribution has limits of 0 and 1. The beta distribution is often used to represent a distribution of fractional values or percentages. The distribution can also be scaled to represent an interval of values greater than 1 by setting an upper and lower limit. The shape of the beta distribution is determined by two parameters,  $\alpha$  and  $\beta$ . The beta distribution is often used in Bayesian analysis to describe the proportion of success in a set of trials. In Box 4.3, the fits of the Johnson SB distribution and a scaled Beta distribution to women’s body mass are compared.

#### BOX 4.3 COMPARISON OF THE JOHNSON SB AND SCALED BETA DISTRIBUTIONS FOR REPRESENTING WOMEN’S BODY MASS

The same data as in Box 4.2 will be used. The difference is that the maximum and minimum values can be chosen. The women studied were aged 20 years and older, but the minima and maxima of the 4299 measurements are not provided. Here we will choose 30 kg and 105 kg as these values, equal to 66 pounds and 230 pounds.

##### Johnson SB (JSB) Distribution

The JSB is a four-parameter lognormal distribution. The parameters are  $\gamma$ ,  $\delta$ , minimum, and spread. The minimum and spread may be called  $\xi$  and  $\lambda$

Parameters	pctl	data	% lambda	w	modeled	LSQ
gamma	0.702	0.05	49.8	0.18	-1.7236	51.2
delta	0.8459	0.1	53.4	0.2127	-1.5626	54.26
eta	30	0.15	56	0.2364	-1.4553	56.49
lambda	105	0.25	60.1	0.2736	-1.2974	60.05
		0.5	70.2	0.3655	-0.9467	69.14
		0.75	83.7	0.4882	-0.5194	82.22
		0.85	93.5	0.5773	-0.2142	92.53
		0.9	100.2	0.6382	0.0015	100.05
		0.95	110.2	0.7291	0.3502	112.13
						3.736

respectively. The maximum value is  $\xi + \lambda$ . Having chosen the minimum and spread (or  $\xi$  and  $\lambda$ ), a least squares minimization will be used to obtain  $\gamma$  and  $\delta$ .

### Formulae:

- 1) % lambda: “=(data -eta)/lambda”
- 2) W: “=(NORM.S.INV(% lambda)—gamma)/delta”
- 3) Modeled: “=(eta + (eta + lambda) × exp(W)/(1+exp(W)))”
- 4) LSQ: “= (modeled—data)^2”

The sum of the LSQ column will be minimized to obtain gamma and delta and performed with the Excel Solver.

### Scaled Beta Distribution

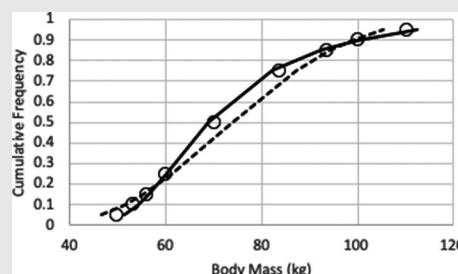
The Beta distribution is bounded at 0 and 1, but can be scaled to model any positive-valued distribution. This fit also uses the Excel Solver to minimize the sum of the LSQ column.

Parameters		pctl	data	Beta inverse	Modeled	LSQ
alpha	3.18	0.05	49.8	0.158	46.623	10.095
beta	4.286	0.1	53.4	0.205	51.55	3.421
min	30	0.15	56	0.241	55.291	0.503
spread	105	0.25	60.1	0.299	61.362	1.593
		0.5	70.2	0.419	73.998	14.424
		0.75	83.7	0.546	87.371	13.475
		0.85	93.5	0.613	94.399	0.807
		0.9	100.2	0.657	98.97	1.513
		0.95	110.2	0.718	105.341	23.607

**Formulae:** (1) Beta inverse: “=beta.inv(pctl,alpha,beta)”;

(2) Modeled: “=min+Beta inverse × spread”

The plot shows the beta fit as the dashed line and the JSB fit as the solid



line. Which do you think is the better fit?

The Weibull distribution has limits of zero and infinity. It has two parameters: shape and scale. The Weibull distribution has been used to model distributions of particle sizes, time to failure of industrial systems, and wind speed.

The gamma distribution also has limits of zero and infinity as well as a scale and a shape parameter. The gamma distribution has been used to model the age distribution of cancer incidence, the inter-spike interval of firing neurons, and the amount of rainfall.

## 4.4 COMMON SENSE THINKING ABOUT EXPOSURE

During the 1990s, the journal *Risk Analysis* and the Society of Risk Analysis maintained a listserver. One of the posts to this listserver was from Paul S. Price, one of the pioneers of probabilistic risk assessment.<sup>57,60–62</sup> Price posted a list of common sense ideas about exposure assessment. This list is presented below:

- Exposures happen people:
  - Model people and how people are exposed.
  - Don’t model exposures and wonder about people.
- People have properties/characteristics that affect their exposures:
  - age, gender, life span, habits, etc.
- Everything is correlated:
  - Exposure events depend on many factors. Engaging in a particular activity will likely produce some exposure but will also preclude exposure from another activity.
- We only know little things:
  - Short-term measurements are easiest to obtain, e.g., activity, food consumption, body weight on a single day.
- Little things add up:
  - For exposure assessment, an extrapolation must be made from short-term measurements to chronic estimates.
- Exposures are real but unknowable—data are knowable but rarely relevant.
- Are the data truly random?
  - True randomness that can be characterized with statistics is easy to account for, but what about randomness characterized by extreme events?
- How does one account for uncertainty?
  - Not all uncertainty is the same.
  - Different types of uncertainty need to be considered in different ways.

### 4.4.1 Common Sense about Variability

The true values of exposure factors change with time—for example, daily soil and dust ingestion rates will be different in a single child at age 2 versus at age 7. Spatial variation in exposure also occurs: for instance, the use of the average concentration of a contaminant in fish in a river might be different in an upstream versus a downstream location. Hence, one might want to know the river location from which consumers obtained fish.

There are, of course, differences in exposure factors between people—inter-individual variability. Measurements of a sample of ten adults selected at random would likely indicate ten different values for body weight or number of daily servings of fruits and vegetables.

One should also not forget to think about variation within a single individual over time—*intra-individual variability*. Body weight may change in a single person depending on age and food consumption. Exposure may also change for that individual depending on alterations in activity patterns.

#### 4.4.2 Common Sense about Uncertainty

Three general types of uncertainty are present in exposure assessment: scenario uncertainty, parameter uncertainty, and model uncertainty.

Scenario uncertainty relates to how closely the qualitative description of exposure represents the true exposure. Does one indeed understand the exposure situation? For example, one might conclude that fish consumption from a small lake can be represented by EPA's default assumption for an individual's daily fish consumption of 54 g/d for 350 days per year would represent a yearly consumption of just under 42 pounds per year.

To see how realistic this value is, EPA's estimates of the total biomass of fish in ponds near the Housatonic River in Massachusetts will be used. These estimates were produced using electrofishing techniques. The value was 8.3 g/m<sup>2</sup> of water surface area.<sup>63</sup>

Assuming this value is representative, a one-acre pond would be about 4100 m<sup>2</sup> in area and would contain 34 kg or about 75 pounds of fish. Two anglers catching and consuming fish at this default consumption rate would decimate the fish population in a year. The fish in the pond are a finite resource. Similarly, a chemical contaminant in groundwater is also present in a limited amount and the exposure concentration may change over time due to degradation of the chemical by microorganisms, groundwater flow, or continued release from an unidentified source. Specific knowledge of how concentrations in environmental media change over time enable one to incorporate this information into a risk assessment.

Parameter uncertainty results from sampling errors and whether the quantitative data used are indeed representative of the target population. A simple example of a sampling error would be the use of average body weight of either National Football League linemen or marathon runners to represent the body weight of the general population. An error of representativeness would result from a mismatch of the sampled population with the target population—such an error could result from assessing soil adherence to skin in children coming from music lessons versus children coming from soccer practice.

Model uncertainty results from the mismatch of the modeled exposure scenario with the real-world exposure situation. Models are simplified representations of reality. In most situations, the dependencies between the various model inputs are unknown. This is especially true in fate-and-transport models, in which various estimated chemical properties may have unknown dependencies that are not included in

the model. Often, models cannot be tested against empirical data and must be judged on heuristics alone.

The classic example of model uncertainty is that of William Thompson, Lord Kelvin's estimate of the age of the earth. Lord Kelvin imagined the earth to have solidified from an originally gaseous or molten state. In 1844, he used Fourier's equations for heat transfer to estimate that the earth was between 20 million and 98 million years old. Modern radiometric dating indicates the earth is 4.5 billion years old.<sup>64</sup>

Kelvin was dismayed by the doctrine of uniformitarianism, popular among geologists of the late 19th century, allowing that the earth was of unlimited age.<sup>65</sup> Kelvin viewed this doctrine as unscientific and inconsistent with thermodynamics. In short, he developed a model based on elegant science and impeccable mathematics that turned out to be spectacularly wrong.<sup>66</sup>

Was Lord Kelvin guilty of hubris to declare as fundamentally flawed any conceptual scheme that allowed for an earth over 1 billion years old? In one sense, Lord Kelvin was more correct than the proponents of uniformitarianism—his estimate was finite. Kelvin's unfounded assumption of the age of the earth was the reason he dismissed Darwin's theory of natural selection on the grounds that there was insufficient time for natural selection to occur.

This is indeed a cautionary tale that model results may be woefully incorrect, but as the quote from the statistician George E. P. Box at the start of the chapter indicates, even incorrect models can be very useful.

#### 4.4.3 Compounding Conservatism

The concept of reasonable maximum exposure was codified in the Exposure Guidelines and RAGS such that intake rate (IR), exposure frequency (EF), and exposure duration (ED) were to be upper percentile values whereas body weight (BW) was chosen as a central value (Equation 4.1). The use of upper percentile values in the numerator and central or lower percentile values in the denominator would tend to increase the estimated exposure. Many risk assessors consider this practice to be “compounding conservatism” that produces unrealistic and exaggerated risk estimates.

Discussion of compounding conservatism was prominent in the scientific literature during the 1990s. David Burmaster of Alceon in Cambridge, Massachusetts was one of the most vocal critics of EPA's risk assessment policies at that time. Sadly, Burmaster was a man ahead of his time and suffered a great deal of frustration when EPA risk assessors turned a deaf ear to his requests that they consider PRA.<sup>67-69</sup>

Mathematically, it can be shown that conservatism compounds dramatically for deterministic point estimates of risk constructed from upper percentiles of input parameters.<sup>70,71</sup>

Burmaster's influence likely resulted in the publication of *Risk Assessment Guidance for Superfund, Volume III: Process for Conducting Probabilistic Risk Assessment* and a number of other EPA guidance documents. Nonetheless, the practice of probabilistic exposure assessment at EPA occurs relatively infrequently, this plethora of guidance notwithstanding.<sup>49,72,73</sup>

## 4.5 THE EXPOSURE CONCENTRATION TERM

The term “C” in Equation 4.1 is the exposure concentration in an environmental medium to which a receptor is exposed. The concentration term in an exposure assessment is the factor in which aspects from the environmental and behavioral realms interact to the greatest extent. Contamination in an environmental medium is never uniform—similarly, human contact with this medium is not uniform. Hence, developing an appropriate value for concentration depends on knowing the spatial and temporal aspects of the occurrence of contamination as well as the spatial and temporal aspects of behavior that bring receptors into contact with the contaminated medium.

Ideally, a risk assessor would observe the behavior of receptors and then design a sampling plan to determine the concentrations in the environmental media with which these receptors come in contact. There are limits, of course—fitting a group of children with Global Positioning System transmitters and following their play might be viewed as intrusive and excessive—although this has been done quite a bit lately, both for environmental exposure assessment and to obtain physical activity data to address childhood obesity.<sup>74,75</sup>

In practice, what generally happens is that environmental sampling plans are designed by environmental scientists or engineers whose main focus is on cleanup. In the case of contaminated soil, a scientist or engineer whose goal is to understand the nature and extent of contamination will tend to oversample the most contaminated areas to support cleanup efforts. Therefore, for risk assessors, the question is: how closely does that sampling to delineate contamination reflect the areas that receptors will contact?

### 4.5.1 Exposure Units

The concept of the exposure unit (EU) is closely associated with the concentration term. If one thinks of the receptor as a sampler of the contaminated medium, the exposure unit represents the extent of that medium contacted by a receptor within a specified period of time.<sup>2,76,77</sup>

The EU concept is easiest to think about with regard to soil. If one assumes that the receptor is a child aged 1–6 years in a residential exposure scenario and this hypothetical child can contact no more than 1000 square feet in a span of a day, then the EU would be 1000 square feet. In the time period of a single day, the child may contact only 1,000 square feet within the 0.5 acre (20,000 square feet) residential EU. If this child lives in a house on a quarter acre lot (approx. 10,000 square feet) and the house occupies 2000 square feet, then there will be eight different exposure units associated with that residence.

Further assuming that the yard has a both a sandbox and a swing set for the child’s use, the area around each of these may be a “preferred” EU. With the sandbox and swing set, a risk assessor might wish to weight the concentrations in these EUs more heavily when determining the concentration term.

In the absence of preferred EUs, the assumption is made that a child will be exposed to the soil in each of the eight EUs within the yard with equal likelihood and the actual concentration contacted by the child will be the true but unknown mean concentration in the entire yard. The long-term average soil concentration contacted by this child will approximate the true but unknown concentration in the yard because of the familiar phenomenon of “regression to the mean.”<sup>78</sup>

The time period that has been considered is a single day. If the time period were increased to a month or a year, it might then be appropriate to consider the entire yard as the EU, exactly because of regression to the mean—but in such a case, the child’s movements constitute the true averaging mechanism. Please note: it is important to understand that aspects from both the environmental and behavioral realms interact over time and to take this interaction into account as much as possible.

#### **4.5.2 Random versus Non-Random Exposure**

Most risk assessments for contaminated land are based on potential future use, and risk assessors are very unlikely to possess information about swing sets or sandboxes. These were mentioned to introduce the concept of random versus non-random exposure within a single EU.

In the list of common sense assumptions from Paul Price presented above, one of these assumptions was that true randomness is easy to characterize with statistics. However, the actual behavior of receptors that brings them into contact with contaminated media is very uncertain, and the assumption of a receptor moving randomly within an EU is an oversimplification and itself a source of uncertainty.

Spatially explicit models of exposure have been developed and refined in the area of ecological risk assessment and have been applied to animal and plant populations.<sup>79-85</sup> Initial attempts have also been made to use spatial techniques in assessing risk to human populations.<sup>86,87</sup>

#### **4.5.3 Temporal and Spatial Variation in Concentration**

A number of environmental factors can produce both spatial and temporal variation in the concentration of a chemical within an exposure medium. Most often, the spatial variability occurs by the mechanism by which the contamination occurred. Application of the exposure unit concept deals with spatial variation based on the behavior of the receptor over a time appropriate for the toxic endpoint. Thinking about how exposure concentrations could vary is an instructive exercise, and is pursued below.

Temporal variability in chemical concentrations needs to be considered. Possible changes in concentration may occur due to wind erosion of soil, leaching of chemicals from soil to groundwater, or bioaccumulation in fish. It is most important that risk assessors consider the time scale of the adverse health effect being considered and make sure that both the derivation of the concentration term and selection of the exposure duration are appropriate to this time scale.

Obviously, there may be considerable variability in short-term exposure within a population of receptors because of spatial and temporal variability within both the environmental and behavioral realms. Such variability may need to be considered for some acute endpoints such as methemoglobinemia in infants caused by nitrates in drinking water.

For risk assessments based on concerns for chronic toxicity with endpoints such as cancer, short-term variability in the concentration a receptor experiences will likely approach the average concentration within the EU because of regression to the mean.

The underlying and possibly incorrect assumption is that the concentrations do not change over time. If concentrations within an EU do in fact change, such as natural attenuation of solvents in groundwater, as noted, these changes may need to be taken into account when calculating the concentration term.

#### **4.5.3.1 Variation of Concentrations in Soil and Sediment**

The spatial variability of soil contamination will generally be due to how that contamination occurred. For example, spills or pesticide application result in a patchy pattern of contamination, whereas stack emissions will form a more even pattern downwind.

In subsurface soil, concentrations of chemicals change mostly due to degradation or leaching to groundwater. Clearly, wind erosion is not a factor.

On the other hand, surface soil is subject to erosion by wind and surface water runoff. Over time, concentrations in surface soil may change, but generally at a slow rate relative to other media.

Like soil, sediment is subject to being physically moved or transported. Ocean currents, river floods, and ship movements may all contribute to sediment transport. Sediment trend analysis may provide information to determine the concentration term to be applied to sediment.<sup>88</sup> One of the most useful tools used in assessment of the Sangamo-Weston site, discussed in Chapter 1, was a sediment transport model.

#### **4.5.3.2 Variation of Concentrations in Groundwater**

Receptors experience exposure to groundwater at a fixed point in space—either a well or a spring. Biodegradation by bacteria, volatilization, and other processes can alter chemical concentrations in groundwater. EPA has long been aware of these processes and has developed many guidance documents on natural attenuation of fuels, chlorinated solvents, inorganic chemicals, and radionuclides. Monitored natural attenuation is considered a viable cleanup option for contaminated groundwater. Relevant guidance documents can be found by searching for “monitored natural attenuation” on EPA’s Environmental Topics page at [www.epa.gov/environmental-topics](http://www.epa.gov/environmental-topics).

As part of the development of the concentration term, consideration of temporal changes in groundwater concentrations occurring by natural attenuation may be appropriate in the risk assessment. In such cases, risk assessors may need to obtain the advice of a hydrogeologist.

#### **4.5.3.3 Variation of Concentrations in Surface Water**

The effects of dilution, evaporation, and mixing constantly alter the chemical concentrations in a flowing stream or lake. Therefore, any surface water sample should be considered a “snapshot” in time. Needless to say, there exists considerable uncertainty in determining the long-term average concentration in surface water from environmental measurements.

#### **4.5.3.4 Variation of Concentrations in Fish**

The availability of food, introduction of a predator species, change in habitat, and intensity of angler harvest all may change the concentration of contaminants within a fish population. The concentrations of chemicals in territorial fish will likely reflect the sediment concentrations in the home range of the individual fish, whereas concentrations in migratory fish will be more unpredictable because the areas the fish frequent change with their migrations.

Recreational anglers may harvest fish from different locations within a lake and consume fish of different sizes and species. It is possible to use site-specific information to determine the exposure point concentration over time in fish. An example is provided as one of the exercises at the end of this chapter.

In 2009, a decision was made at the Sangamo-Weston Superfund site to remove the hydroelectric plants on Twelve Mile Creek and thus facilitate covering the contaminated lake sediments with clean sediments transported from upstream locations. Although sediment concentrations of polychlorinated biphenyls had declined, measurements of fish tissue concentrations in 2008 indicated little change. The reason fish concentrations did not change as did those in the upper layer of sediment was that sediment-burrowing *Hexagenia* mayflies were a major part of the diet of smaller forage fish and some terrestrial species.<sup>89</sup>

#### **4.5.3.5 Variation of Air Concentrations**

With regard to short-term concentration, air is most variable of all exposure media. In addition, single or short-term exposures to chemicals in air may produce very different effects from repeated exposures. Toxicity factors for inhaled chemicals are developed in units of concentration—reference concentrations are generally found in units of mg/m<sup>3</sup>, and inhalation unit risk concentrations are generally found in units of per µg/m<sup>3</sup>, or reciprocal air concentration. In addition, single or short-term exposures to chemicals in air may produce very different effects from repeated exposures. Hence, it is important to understand the time scale of the toxic effect when selecting the exposure duration. In many cases, a receptor will spend time in two or more microenvironments, with different concentrations in each. EPA defines a microenvironment in terms of the chemical concentration therein, but also points out that these microenvironments include homes, schools, vehicles, restaurants, or the outdoors.<sup>90</sup>

When considering variation in air concentrations or the movement of a receptor through multiple microenvironments, the exposure concentration is a time-weighted average of the concentrations in the various microenvironments.<sup>91</sup>

For a number of outdoor air pollutants, standards have been established. National Emission Standards for Hazardous Air Pollutants exist for 188 hazardous chemicals. Compliance with these standards is determined for both stationary sources such as smokestacks and mobile sources such as automobiles. Since 1996, EPA has conducted risk assessments based on modeled air concentrations within census blocks that include stationary and mobile sources as well as background from long-range transport of pollutants in the atmosphere.<sup>92</sup>

Obviously, there is one kind of uncertainty in the estimation of concentrations to which a single individual is exposed within a particular microenvironment and also uncertainty in the estimation of modeled concentrations used in the national-scale assessments.

#### 4.5.4 How to Estimate the Concentration Term

In RAGS, Part A, EPA was vague about how to estimate the concentration term in any medium.<sup>2</sup> This otherwise useful guidance document failed to state exactly what to do to obtain a concentration term that is representative of ongoing exposure.

For soil, it is generally not appropriate to use the highest concentration measured to represent the concentration actually contacted by a receptor that moves. Hence, in 1992, EPA's Superfund Program released a document titled *Supplemental Guidance to RAGS: Calculating the Concentration Term*.<sup>50</sup> In this document, the uncertainty between the measured concentrations at a hazardous waste site and the concentrations actually contacted by receptors was recognized and addressed by the suggestion to use the 95% upper confidence limit (UCL) of the arithmetic mean of the measured concentrations. This value would serve as a health-protective estimate of the true but unknown arithmetic mean.

The document also indicated that in the majority of cases, the distribution of concentration, at least in solid media, soil or sediment, was likely to be lognormal. This claim was based on the theory of successive random dilutions developed by Wayne Ott, an EPA scientist from the agency's inception until the mid-1990s.<sup>93</sup> In this theory, contaminants are diluted by a number of geophysical processes that have a fractional or multiplicative effect on concentrations. Because multiplication is equivalent to addition of logarithms, contamination would occur in a lognormal distribution. In this document, EPA suggested the use of a method for estimating the upper confidence limit of the arithmetic mean developed by Charles Land of the National Cancer Institute.<sup>94</sup>

In many environmental datasets, because the true purpose of data collection was to determine the nature and extent of contamination, there will be a number of non-detect values as well as a number of relatively high values. EPA's policy is to use half the detection limit as a surrogate value for non-detects. When the Land method for calculating the upper confidence limit of the mean is used on such a dataset, the

calculated UCL is often greater than the highest value in the data. In the concentration term guidance, when this occurred, the highest value in the dataset was used in lieu of the calculated UCL. The reason for this policy was to get regulated entities to collect and analyze a greater number of samples.

With increasing experience with this method of calculating the UCL of the mean, the realization came that not all environmental datasets are truly lognormal. Dr. Susan Griffin of EPA's Region 8 office in Denver pioneered the use of bootstrap methods for estimating the upper confidence limit of the mean when the distribution of the dataset could not be determined.<sup>95</sup> The bootstrap method is a useful technique, and a simple example is provided as an exercise at the end of the chapter.

EPA's Site Characterization and Technical Support Center in Las Vegas produced a number of papers on the calculation of exposure point concentrations as well as EPA's ProUCL software to implement these calculations.<sup>59,96–98</sup> ProUCL can be obtained online.<sup>51</sup> The software integrates well with Microsoft Excel and is often useful for working with large datasets.

## 4.6 INCIDENTAL SOIL INGESTION

Incidental ingestion of soil and dust by children has driven the risk at a large number of hazardous waste sites—both in North America and Europe. Because of the deleterious effects of lead on neurodevelopment in children and the accompanying societal and individual costs, scientists came to understand that lead in soil contributed to blood lead levels in children—likely by incidental ingestion.<sup>99–103</sup>

The first attempt at measuring or estimating soil ingestion in children was based on measurements of soil on the hands of 22 children.<sup>104</sup> The mean amount on the hands was 10 mg, and the children were assumed to put their hands in their mouths ten times per day for a daily soil intake of 100 mg. Very health-protective/conservative estimates of soil ingestion by children of between 1 and 10 g per day were used in an early risk assessment for dioxin.<sup>105</sup>

The earliest quantitative method used to measure soil and dust ingestion in children was mass balance using fecal tracer studies. Recently, behavioral analysis using video records of hand-to-mouth contacts and other microactivity have also produced estimates of soil ingestion. Paired blood lead and soil lead measurements can also be used to provide estimates of soil and dust ingestion in children. Values from all three methods are similar (Table 4.2).<sup>106</sup>

**Table 4.2 Comparison of the Most Recent Soil and Dust Ingestion Rates in Children Obtained with Three Different Methods<sup>106</sup>**

Methodology	Mean	Median	95th Percentile
Mass balance of fecal tracers	26	33	79
Behavior Estimates	68	35.7	224
Lead Biokinetics	48	36	128

#### 4.6.1 Mass Balance of Fecal Tracers

Historically, the most common method of estimating soil ingestion in children was fecal tracer studies in which a metal present in soil, such as aluminum, silicon, or titanium, that was considered to be poorly absorbed by the gastrointestinal tract was measured in both feces and soil. With these measurements, soil ingestion rates could be estimated with assumptions about the amount of time spent indoors and outdoors.

Children play on the floor when indoors, on the ground when outside, and frequently put their hands in their mouths—behavior that contributes to the amount of soil and dust ingested. Obviously, this method cannot not distinguish ingestion of outdoor soil from ingestion of indoor dust.<sup>107–126</sup>

The first mass balance studies of soil/dust ingestion in children produced estimates that varied by over ten-fold.<sup>127,128</sup> This variation was due to the tracer metal selected.<sup>107</sup>

Fecal tracer estimates bear considerable uncertainty, and statistical analysis has quantified but not reduced this uncertainty. There are likely biological differences in the handling of these metals in the gut. For example, aluminum may be absorbed or may interfere with the absorption of other chemicals.<sup>129,130</sup> Silicon is absorbed and functions to strengthen bone.<sup>131–133</sup> Titanium is both absorbed and secreted by lymphatic tissue in the gut in a circadian rhythm.<sup>134–136</sup> Examination of the titanium results from fecal tracer studies is consistent with cyclic absorption and release—on some days, fecal titanium is very high, and on other days very low.<sup>5,128,136</sup>

In addition, the poorly soluble aluminosilicate particles in soil may have a mechanical effect on absorption and may enhance or diminish absorption.<sup>137–139</sup>

A meta-analysis of four large soil/dust ingestion studies in children indicated a mean soil ingestion rate of 26 mg/day with a 95th percentile value of 79 mg/d.<sup>118</sup> Details of the mass balance calculation used in soil ingestion studies are provided in Box 4.4.

#### BOX 4.4 MASS BALANCE CALCULATION FOR ESTIMATING SOIL INGESTION FROM FECAL TRACERS IN SOIL

When an individual is in equilibrium with regard to a particular tracer—i.e., when no net gain or loss of the body burden of tracer is occurring—the intake amount from ingestion and inhalation will equal the amount excreted in urine and feces:

$$I_{\text{air}} + I_{\text{food}} + I_{\text{soil}} + I_{\text{water}} = O_{\text{feces}} + O_{\text{urine}} \quad (4.8)$$

where:

$$\begin{aligned} I_{\text{air}} &= \text{intake from air} = \text{air concentration} \times \text{amount of air inhaled} \\ &= C_{\text{air}} \times A_{\text{air}} \end{aligned}$$

$$I_{\text{food}} = \text{intake from food} = \text{food concentration} \times \text{amount consumed}$$

$$= C_{\text{food}} \times A_{\text{food}}$$

$$I_{\text{soil}} = \text{intake from soil} = \text{soil concentration} \times \text{amount of soil ingested}$$

$$= C_{\text{soil}} \times A_{\text{soil}}$$

$$I_{\text{water}} = \text{Intake from water} = \text{water concentration} \times \text{amount of water drunk}$$

$$= C_{\text{water}} \times A_{\text{water}}$$

Generally, the concentrations of tracer metals such as aluminum or silicon in air and water are negligible. However, some tracer metals are present in toothpaste or other personal care items. These can be included in the food term. Hence, the simplified mass balance equation is:

$$A_{\text{soil}} = (O_{\text{feces}} - I_{\text{food}}) / C_{\text{soil}} \quad (4.9)$$

As it turned out, when this equation was applied, soil ingestion estimates based on titanium tended to be ten-fold higher than those based on aluminum or silicon—even when toothpaste is taken into account.<sup>106,126,127</sup> The estimates of soil ingestion were very sensitive to the assumed fecal transit time. The average concentrations of aluminum, silicon and titanium in food, feces, urine, and soil and the dry weights of consumed food and liquid and fecal dry weights are shown below, along with the estimates of soil ingestion. The concentrations in drinking water are assumed to be zero. The numerical calculation is also shown.

	Dry wt. (g/d)	Concentrations (mg/g)		
		Al	Si	Ti
Food	287.2	27	39.5	9.9
Feces	13.6	650	1100	279
Soil		6.16	26.4	0.6
Calculation		$(650 \times 13.6 - 27 \times 287.2) / 6.16$	$(1100 \times 13.6 - 39.5 \times 287.2) / 2$	$(279 \times 13.6 - 9.9 \times 287.2) / 0.6$
Est. Soil Ingestion (g/d)		176	137	1585

#### 4.6.2 Microactivity Studies in Children

Investigation into the role of microactivity in children, concentrating on hand-to-mouth behavior, became a focus of exposure assessment in response to concern about the use of copper chromated arsenic (CCA) to preserve wood used outdoors. This preservative had been used since the 1930s and had been shown to leach from treated decks. A number of states issued warnings that children playing under or around decks might be exposed to unsafe levels of arsenic.<sup>140</sup>

A variety of hand-loading studies of arsenic from contact with decks were performed. The methodologies in these studies were highly variable.<sup>4,141–148</sup> In addition to collecting additional data on the transfer efficiency of arsenic from treated wood to skin, a number of studies on children's hand-to-mouth activity were also conducted. These were put together by EPA in an extensive risk assessment for CCA-treated decks.<sup>149,150</sup> Videotape studies were also undertaken to assess children's exposure to pesticides in or on foods.<sup>151–156</sup>

This behavioral information was obtained using videography, and can be combined with data on the time children spend in various locations to obtain estimates of soil and dust ingestion.<sup>157,158</sup> Young children commonly engage in hand-to-mouth and object-to-mouth behavior, and this assumption underlies this methodology. Surveys about behavior of children obtained from caregivers may provide additional data. One advantage of these studies is that soil ingestion can be separated from dust ingestion, whereas mass balance studies can only provide information on combined soil/dust ingestion. These behavioral data were used to determine soil ingestion rates in children by EPA and published in the open scientific literature.<sup>157–170</sup> Unfortunately, these soil ingestion rate estimates were calculated with a version of the Stochastic Human Exposure and Dose Simulation (SHEDS) model that is no longer available on EPA's website and the publication provides insufficient detail to enable independent checking of the calculations in the paper. Additional resources on the SHEDS model can be found at [www.epa.gov/research/human-health-risk-assessment-research-methods-models-tools-and-databases](http://www.epa.gov/research/human-health-risk-assessment-research-methods-models-tools-and-databases). It requires about 30 minutes of digging through various EPA web pages to learn that SHEDS currently runs under SAS Software, a hugely expensive statistical software package, thus it is beyond the ability of most non-institutional users to verify the results from SHEDS. In contrast, other offices and centers in EPA use the R statistical language and seem to welcome others using their code.

A long-held assumption in risk assessment is that children may receive their entire daily amount of soil ingestion from a single contact with soil. Certainly, a child playing outside will likely have dirty hands and a number of hand-to-mouth contacts may occur before the hands are washed. However, adult volunteers in another soil study noted that as little as 10 mg of soil in the mouth was gritty and unpleasant, and even this little soil would likely be spit out.<sup>171</sup> Children exhibited median indoor hand-to-mouth contact rates of 3.4 to 17 per hour and median outdoor hand-to-mouth contact rates of 0 to 7.1.<sup>172</sup> The hand-to-mouth transfer efficiency of soil was modeled with a beta distribution having a mean of 20%.<sup>157</sup> This value is about the same as observed empirically from palm licking, but higher than observed from either thumb-sucking or finger mouthing.<sup>171</sup> Hence, it would take a lot of hand-to-mouth contacts for a child to ingest 200 mg/day of soil.

#### **4.6.3 Lead Biokinetic Estimates of Soil/Dust Ingestion**

In the 1970s, a positive correlation between child blood lead levels and lead in indoor dust was observed.<sup>101,102,173–178</sup> Ratios of stable lead isotopes have been used to determine lead sources that contribute most to the body burden of lead in children.<sup>179</sup> Biochemically, lead is similar to calcium and there is a reservoir of lead

in bone.<sup>180–182</sup> EPA's *Exposure Factors Handbook 2011 Edition* describes a study showing the decline in blood lead levels following closure of a smelter and remediation of individual yards as providing soil ingestion rates from these data. Similarly, work done at the Bunker Hill smelter site in Coeur d'Alene, Idaho was also cited as an example of biokinetic estimation of soil ingestion rate, but that work actually calculated lead intake and bioavailability from soil and dust rather than soil ingestion.<sup>183,184</sup>

EPA routinely uses and recommends the Integrated Exposure Uptake Biokinetic (IEUBK) model to assess children's exposure to lead.<sup>185</sup> In contrast to the IEUBK model, which is a polynomial approximation of a PBPK model, the Agency for Toxic Substances and Disease Registry uses "slope factors" to estimate blood lead levels in children. In this context, a slope factor is the proportionality constant between lead in a given medium—i.e., food, soil, air, etc—and blood lead. This methodology has been used to calculate a target soil concentration for lead based on an increase in blood lead of 2 µg/dL and has also been used to estimate soil ingestion rates in children, and those estimates were in between those obtained from mass balance of fecal tracers and those from behavioral studies; the estimates from all three methods are similar in value.<sup>106</sup>

#### 4.6.4 Adult Soil Ingestion

For many years, EPA used an estimate of soil ingestion for construction or excavation workers derived from an observational estimate and a few assumptions. The value was 480 mg/d.<sup>4</sup> The assumption was made that all the soil in a 50 µm-thick layer on the thumb and fingers of one hand could be transferred to the mouth during activities such as eating or smoking. Indeed, the slightly spongy and uneven surface of a slice of sandwich bread would be ideal for conveying soil to the mouth for ingestion—assuming the excavation worker failed to wash up before lunch. The median surface area of the hands, front and back is about 0.1 m<sup>2</sup>, or 1000 cm<sup>2</sup>. The palmar surface of the thumb and fingers would be about one-sixteenth of the total, or about 65 cm<sup>2</sup>. The volume of a 50 µm layer over this area would be 0.625 cm<sup>3</sup>. Assuming a dry bulk density of soil of 1.5 g/cm<sup>3</sup>, the mass of soil would be 487 mg, very close to this estimate noted.

Baseline soil ingestion rates were measured in six adult volunteers given a known amount of soil in gelatin capsules.<sup>108</sup> The most valid tracers in this study were aluminum, silicon, yttrium, and zirconium. The same investigators measured soil ingestion rates in ten other adult volunteers given soil in gelatin capsules for part of the study. In both studies, incidental soil ingestion rate was calculated by subtracting the soil dose in the gelatin capsules. The most valid tracers in this study were identified as aluminum, silicon, titanium, yttrium, and zirconium.

Other workers measured soil ingestion in 19 families consisting of 19 children aged 7 years or less, 19 adult women, and 19 adult men.<sup>186</sup> The tracers used were aluminum, silicon, and titanium. The mean soil ingestion rates for adult men were 92, 23, and 359 mg/d based on aluminum, silicon, and titanium respectively. The mean soil ingestion rates for women were 68, 26, and 625 mg/d for the same three tracers.

#### 4.6.5 Pica and Geophagy

EPA currently defines pica as the recurrent ingestion of unusually high amounts of soil, from 1 to 5 grams per day. The EPA defines geophagy as the intentional ingestion of earths associated with cultural practice. In children, pica behavior is not abnormal.<sup>187</sup>

Geophagy occurs mostly with consumption of clays, and was likely common in the rural South during the early 20th century.<sup>188–190</sup> The evolutionary/adaptive purpose is likely protection from toxins, parasites, and other pathogens as well as nutritive, for acquisition of micronutrients.<sup>191–193</sup>

#### 4.6.6 Recent Work by EPA on Soil Ingestion

In 2017, an update to the *Exposure Factors Handbook* on soil ingestion was released and can be found at [www.epa.gov/expobox/exposure-factors-handbook-chapter-5](http://www.epa.gov/expobox/exposure-factors-handbook-chapter-5). Table 5.1 in that document provides the current recommendation for soil ingestion, pica, and geophagy for a range of age groups. To my knowledge, neither pica nor geophagy have been used in a site-specific risk assessment. The upper percentile values for incidental soil ingestion have not changed from those in the 2011 *Exposure Factors Handbook* except for explicit separation of age groups

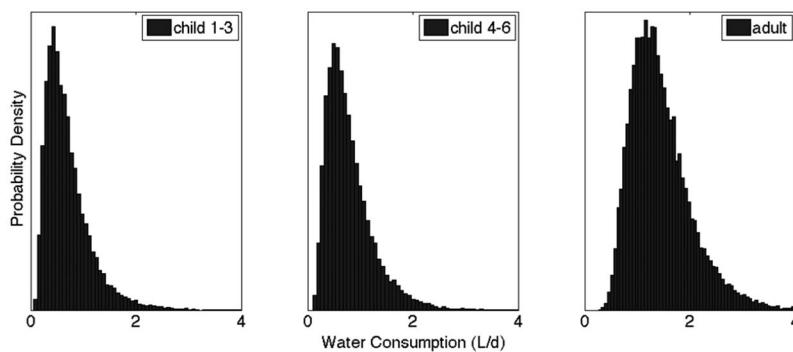
### 4.7 DRINKING WATER CONSUMPTION

Historically, the drinking water consumption values used for risk assessment were 2 L/day for adults and 1 L/d for children under 10 and infants. These amounts include water in beverages as well as tap water. Those living in warm climates or those with a high level of physical activity may consume more water than others, but there is little quantitative information in this regard.

Since 1990 until very recently, water consumption estimates were based on US Department of Agriculture (USDA) 1977–78 Nationwide Food Consumption Survey. The mean and 90th percentile results for adults aged 20 to over 65 were 1.4 L/d and 2.3 L/d. For children aged 1 to 3, these values were 0.65 L/d and 1.4 L/d. For children aged 4 to 6, these values were 0.74 L/d and 1.5 L/d.<sup>7</sup>

Lognormal distributions were fit to these data and adjusted to represent the 1988 US population.<sup>194</sup> These various distributions are shown in Figure 4.2.

The most recent study of water consumption was based on the USDA Continuing Survey of Food Intakes by Individuals using data collected between 1994 and 1998.<sup>195</sup> The data were collected using dietary recall from over 20,000 individuals from all 50 states and the District of Columbia. The water consumed was classified as: direct water—consumed directly as a beverage; indirect water—that added during food or beverage preparation; intrinsic water—that naturally occurring in foods or beverages; and commercial water—that added to processed foods during manufacture. Water source categories were either “community” water obtained from a public water supply, “bottled” water, or “other” water obtained from wells or cisterns.



**Figure 4.2** Lognormal distributions of daily water consumption by adults and two groups of children.

EPA used similar methodology to analyze water consumption from the 2003–2006 National Health and Nutrition Examination Survey. EPA’s *Exposure Factors Handbook 2011* recommends age-specific values for drinking water consumption.<sup>7</sup> EPA’s Regional Screening Level Table (RSLT) (available at <http://rais.ornl.gov>) uses default values from Part B of *Risk Assessment Guidance for Superfund* and the *Standard Default Exposure Factors*, or 2 L/d for adults and 1 L/d for children in a residential exposure scenario.<sup>4,147</sup> The default value for workers in a commercial industrial scenario is 1 L/d.

In February 2019, EPA released an update to Chapter 3 of the 2011 *Exposure Factors Handbook* on ingestion of water.<sup>13</sup> Recommended values representing the mean and 95th percentile in units of mL/day and mL/kg-day are provided for per capita intakes averaged over the population and for water consumers based on a 2-day average reported in NHANES 2005–2010 datasets. For all ages, the mean value is about 1.1 L/day and the 95th percentile about 3 L/day.

## 4.8 DERMAL ABSORPTION OF CHEMICALS

The skin provides a barrier to entry of substances into the body. The outer layer of the skin, or epidermis, is not vascularized. The stratum corneum is the outer layer of the skin and is about 10–40  $\mu\text{m}$  thick. The stratum corneum is composed of keratinized and desiccated epidermal cells. This outer layer is highly hydrophobic because of its high lipid content, and this hydrophobicity contributes to the barrier function of the skin. Cells in the stratum corneum slough off or desquamate and are replaced by growing keratinocytes in the germinal layer of the epidermis below.

The mature and senescent keratinocytes that comprise the stratum corneum are organized into a “brick and mortar” pattern. These cells form a cornified envelope consisting of cross-linked protein and lipid polymers. The lipid polymers are located on the outside and are comprised of specialized and hydrophobic lipids known as ceramides. The formation of these specialized lipids requires specialized

metabolism, and many of these lipids display antimicrobial properties.<sup>196</sup> Healthy skin is a barrier to permeation of chemicals—simple contact with the skin is usually insufficient, and this is why dermally delivered drugs require adhesive patches or hydrophobic gels and relatively long application times.<sup>197</sup> The stratum corneum has different thicknesses on various parts of the body, e.g., the eyelid versus the sole of the foot. These adaptations in the anatomy and physiology of the stratum corneum provide the barrier function of the skin.<sup>198–201</sup>

The inner layer of the skin or dermis is vascular and contains hair follicles and sweat glands. Once a substance has penetrated the epidermis, it will be available to the dermal capillaries for systemic distribution.

#### 4.8.1 Total and Regional Skin Surface Area

In the *Exposure Factors Handbook 2011 Edition*, EPA used data from the 1999–2005 and 2005–2006 NHANES surveys to estimate total body surface area as well as that of the various body areas, e.g., head trunk, arms, and hands. Total surface area is estimated using equations with weight and height as dependent variables.<sup>7</sup> A method that used a simple ratio between body weight and total skin surface area yielded approximately similar results and was used to develop distributions of total skin surface area in three age groups.<sup>202</sup> Distributions were also estimated using the height and body weight equations.<sup>203</sup>

To estimate the area of various body parts in adults, EPA developed regression methods with height and weight as the dependent variables. Body weight and height were obtained from the 2005–2006 and 1996–2005 NHANES data.<sup>7</sup> For children and adolescents, measurement data collected for use in ergonomic and product safety design was used as input to a computer model to estimate the surface area of various body parts in children and adolescents aged 2–18 years.<sup>204</sup>

#### 4.8.2 Fates of Substances on the Skin

Substances applied to the skin may evaporate before penetration or may diffuse through the stratum corneum. Substances that penetrate the stratum corneum may be metabolized in the germinative layer of the epidermis or may continue to the capillaries in the dermis. In addition, some substances may bind irreversibly to lipids or proteins in skin and be sequestered. Sequestered chemicals in the skin may eventually be absorbed or may be lost by desquamation.<sup>205</sup> Hence, studies that measure the amount of material lost from the skin surface may tend to overestimate dermal permeation. Measurements of actual permeation to the blood must also be conducted with care.

#### 4.8.3 Solid Materials Contacting the Skin

Generally, the adherence of soil and sediment to skin is provided in units of mass per unit area, such as mg/cm<sup>2</sup>. Instead, what is needed is some measure of skin coverage such as particle layering. These sorts of data are difficult to obtain or estimate

because soil particles are different shapes and sizes. Even a complete monolayer of soil particles on the skin will not cover the entire area of skin because of the shapes of the soil particles. Volatile chemicals in soil, however, may occur as vapor in the spaces between the soil particles and skin and thus be available for absorption into the stratum corneum over much of the contact area.

Unless the soil is wet, smaller particles tend to adhere preferentially to skin.<sup>206–208</sup> For lipophilic chemicals, sorption to soil is governed by the organic carbon content of soils, and the organic carbon content differs in the various particle size fractions. For example, polycyclic aromatic hydrocarbons tend to be correlated with organic carbon in soil, but metals may or may not be, depending on the particular soil chemistry.<sup>209</sup>

“Aging” of a chemical in soil may occur. This means that the chemical in soil may take months or years to reach an equilibrium state. Partitioning of a chemical from soil to skin may depend on the “aging characteristics. For example, a greater amount of freshly spiked benzo[a]pyrene in soil was absorbed than a sample allowed to “age” for 110 days.<sup>210</sup>

Generally, the movement of a chemical from soil to skin occurs by diffusion, and thus is a dynamic process. Hence, the amount of time soil remains on the skin and the physicochemical characteristics of the substances being considered affect the amount of material absorbed. In 1992, EPA’s Office of Research and Development published *Dermal Exposure Assessment: Principles and Applications*.<sup>211</sup> This publication included a method for estimating dermal exposure by integrating the flux into the skin over time. However, in 2004, when EPA published *Part E: Supplemental Guidance for Dermal Risk Assessment* of RAGS, the flux had been condensed into a single chemical-specific value for dermal absorption fraction.<sup>212</sup>

Much work has been done on the adherence of soil to skin.<sup>165,206,208,213–219</sup> This factor is highly activity-dependent, as one might imagine. This aspect of exposure is quite amenable to empirical investigation, and the experiments can be as simple as pressing the hands into a pan of soil and then collecting and weighing the adherent material. In RAGS, Part E, EPA correctly recommends using the mean or median value of an activity-related adherence factor with an appropriate value for the exposed skin surface area. Children’s activities include playing indoors, playing in dry soil, and playing in mud; adult activities include groundkeeping, pipe laying in both dry and wet soil, and gardening.

#### **4.8.3.1 Uncertainty in the Dermal Exposure to Solid Media**

As part of the re-registration of coal tar creosote for compliance with EPA’s Pesticide Program, a dermal exposure assessment was conducted on workers using “whole-body dosimeters.” These whole-body dosimeters were nothing more than cotton long underwear worn underneath work clothes and protective gear. Each day, the long underwear was sent to the lab for quantitative assessment of polycyclic aromatic hydrocarbons (PAHs) in the adherent particles.

There remains considerable uncertainty regarding the extent of the dermal exposure component for creosote workers. A urinary biomarker of exposure to PAHs is

hydroxypyrene.<sup>220</sup> Several studies could not account for the amount of hydroxypyrene in urine from inhalation exposure alone in creosote workers, and claimed this was due to dermal exposure with no additional evidence.<sup>221,222</sup>

Although the creosote risk assessment was quite controversial, the use of long underwear in this way represents a novel and relatively innovative way to obtain empirical data on dermal exposure to air borne particulate matter.

#### 4.8.4 Dissolved Substances Contacting the Skin

In *RAGS Part E: Supplemental Guidance for Dermal Risk Assessment*, EPA presents a model for estimating the dermally absorbed dose per event for a range of chemicals. For organic chemicals, the dose is dependent both on the duration of the event and chemical-specific parameters such as the permeability coefficient  $K_p$  and the ratio of the permeability through the stratum corneum to that through the living epidermis beneath.<sup>212</sup>

The aqueous pathway is highly uncertain—exposure is estimated using an uncertain prediction model based on data from a small number of chemicals. There remains considerable interest in developing better models for skin permeation because of the potential for transdermal delivery of drugs.  $K_p$ , the dermal permeability coefficient, is defined as the steady state flux through the skin normalized to the concentration gradient. For xenobiotic chemicals, the internal concentration will be assumed to be zero, and  $K_p$  is then the ratio between flux and concentration on the skin.

Anatomically based physicochemical models describing percutaneous absorption were introduced in the early 1970s.<sup>223</sup> Experimental results for the permeation of organic compounds, large and small, polar and non-polar, through human skin were assembled. This is the so-called “Flynn” dataset, named for the scientist who compiled it.<sup>211,212</sup> These data enabled the development of a number of quantitative structure–activity (QSAR) models for skin permeation. These models generally used the octanol–water partition coefficient as a measure of lipophilicity and the molecular weight as a measure of size to predict skin permeability.<sup>224,225</sup>

The difficulty with these models for risk assessment is that they were inaccurate for high-profile lipophilic chemicals—PAHs, PCBs, dioxins, and DDT. A comparison of experimentally measured  $K_p$  values and those predicted with the QSAR models found that the results often varied by up to two orders of magnitude.<sup>226</sup> As one of the exercises at the end of this chapter, estimates of  $K_p$  from dermal application of coal tar in dandruff shampoo and subsequent excretion of PAH metabolites will be compared to a QSAR estimate.

### 4.9 INHALATION EXPOSURE

Defining exposure for inhaled chemicals is more complex than for ingested chemicals. The respiratory system consists of three regions: nasopharyngeal, tracheobronchial, and pulmonary. The upper airway from the nose to the larynx comprises the nasopharyngeal region. The tracheobronchial region consists of the trachea, bronchi,

and bronchioles; it forms the conducting airway between the nasopharynx and the deep lung. The pulmonary region consists of respiratory bronchioles, alveolar ducts and sacs, and alveoli. Exchange of oxygen and carbon dioxide occurs within the alveoli.

Materials are removed from inspired air in all regions of the respiratory system. The hairs in the nose filter out large inhaled particles, and the rest of the nasopharyngeal region moderates the temperature and humidity of inhaled air. The surface of the tracheobronchial region is covered with ciliated mucous-secreting cells. The cilia beat and move mucus upwards as means of removing material from the deep lung regions to the mouth—the so-called mucociliary elevator.

A special case exists for fibers. Fibers can deposit along the wall of an airway by a process known as interception. This occurs when a fiber makes contact with an airway wall. The likelihood of interception increases as the airway diameter diminishes. Fiber shape influences deposition too. Long, thin, straight fibers tend to deposit in the deep region of the lung compared to thick or curved fibers.

*Risk Assessment Guidance for Superfund, Part A* (RAGS) indicated that the following equation (identical to Equation 4.1) should be used for inhalation exposure:<sup>2</sup>

$$\text{Inhalation Intake (mg/kg/d)} = C \times (\text{IR/BW}) \times (\text{ET} \times \text{EF} \times \text{ED}) / \text{AT} \quad (4.10)$$

where:

C = concentration in air (mg/m<sup>3</sup>)

IR = inhalation rate m<sup>3</sup>/hr

ET = exposure time (daily fraction)

EF = exposure frequency (d/yr)

ED = exposure duration (yr)

AT = averaging time (d)

However, as discussed at length in EPA's 1994 *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry*, this method does not account for either species-specific differences in airway anatomy nor physicochemical characteristics of the inhaled contaminant that both result in differences in deposited or delivered doses.<sup>227</sup> Estimation of risk from inhalation of chemicals should use toxicity criteria expressed in terms of air concentrations; such toxicity criteria cannot be used with the standard intake equation (Equation 4.1) that expresses dose in mg/kg/d.

Toxicity criteria expressed in terms of concentration were converted to units of intake (generally divided by 20/70 m<sup>3</sup>/d per kg body mass) to be able to be used with Equation 4.1, with the contact rate being the inhalation rate. This conversion and the method were not correct, and unfortunately this represents an egregious example of the slow rate of change in government: EPA's Superfund Program took 15 years to remedy this problem. Some state environmental agencies, notably the Georgia Environmental Protection Division, have promulgated the use of RAGS, Part B equations and thus have legislated incorrect science. At EPA, this situation was explicitly corrected in Part F of RAGS, *Supplemental Guidance for Inhalation Risk Assessment*.<sup>91</sup>

#### 4.9.1 Gases, Vapors, and Particles

Inhaled materials may be gases, vapors, or particulates. Inhaled gases are considered in three categories, depending on their water solubility and reactivity:

- Category 1—these gases are highly water-soluble and reactive. Generally, they will affect the surface of the proximal respiratory tract and are not absorbed into the systemic circulation. Corrosive materials such as chlorine are category 1 gases.
- Category 2—these gases are water-soluble and possibly reactive, but nonetheless will penetrate to the blood. There is some overlap between category 1 and category 2 gases; however, category 2 gases may cause portal-of-entry effects in the lung as well as systemic effects following absorption into the circulation.
- Category 3—these gases are sparingly soluble in water and generally not reactive. They are absorbed into the systemic circulation and cause effects at sites other than the lung. Styrene is an example of a category 3 gas.

A vapor is the gaseous phase of a substance below the critical temperature of that substance. Generally, vapors exist in contact with liquid or solid. The concentration of a vapor when non-gaseous material is present is determined by the vapor pressure, which, in turn, depends on the ambient temperature. Volatile chemicals dissolved in water may volatilize from the water, resulting in measurable vapor concentrations. Volatilization from either soil or water is determined by the Henry's Law Constant of the substance.

Particulate matter or aerosol droplets will either penetrate to the deep lung or be deposited in the tracheobronchial region, depending on particle size. The site of deposition of particles in the respiratory tract is of profound importance for the potential to produce adverse effects. The size, shape, and density of the particles, either solid or aerosol, all affect which portion of the respiratory system receives the majority of the dose.

Particulate matter and aerosols are characterized by their mass median diameter (MMD). The median value of the diameter of particles or aerosol droplets is the MMD and is generally measured in  $\mu\text{m}$ . For homogenous substances with a uniform density, the MMD of an aerosol provides a measure of the median mass of the individual particles. Particulate matter and aerosols may also be characterized by the mass median aerodynamic diameter (MMAD), a measure that accounts for particle shape as well as size and density. If an aerosol particle of unknown shape has an MMAD of 1  $\mu\text{m}$ , the particle behaves in a similar fashion as a spherical particle 1  $\mu\text{m}$  in diameter.

Inhaled particles may be aqueous with dissolved material or solid insoluble particles. Physical airflow during breathing along with particle size determine where a particle is likely to deposit in the respiratory system. Particles with an MMAD greater than 1  $\mu\text{m}$  and not filtered out in the nasopharynx tend to deposit in the upper respiratory tract at airway branching points. These particles will likely collide with the walls of the airway at branch points in the tracheobronchial tree in a process called impaction. Smaller particles not removed by impaction will likely be

deposited in small bronchi and bronchioles by sedimentation, a process in which they settle out due to lower airstream velocity. Particles less than 0.3  $\mu\text{m}$  move through the air randomly, by Brownian motion. They likely will remain suspended to be exhaled, but also may deposit on the walls of the alveoli or terminal bronchioles.

Hence, the size of the particles, the branching pattern and physical dimensions of the airways, and the velocity of the airflow determine the pattern of deposition of airborne particles in the respiratory tract. Once deposited, particles may be engulfed by pulmonary macrophages and removed by the mucociliary elevator.

In general, particles with an MMD or MMAD of 5 to 30  $\mu\text{m}$  are deposited in the nose and throat. Particles with an MMD or MMAD of 1 to 5  $\mu\text{m}$  are deposited in the trachea and bronchial regions. Particles of 0.3 to 1  $\mu\text{m}$  tend to be deposited in the alveoli. Very small particles of < 0.3  $\mu\text{m}$  are unlikely to be deposited and will be exhaled.<sup>228-230</sup>

#### **4.9.2 Time-Averaging of Exposure Concentrations for Inhalation**

Inhalation toxicity criteria are generally adjusted to represent constant exposure. However, because human receptors live and work in different environments or situations, the exposure details of these various situations need to be combined into a time-weighted average that can be compared appropriately with the toxicity criterion.

The United States Occupational Safety and Health Administration (OSHA) has used this type of time-weighting since the 1970s. OSHA usually provides several regulatory values that are specific to different time periods. The permissible exposure limit is generally compared with an 8-hour time-weighted average to represent a work day. The short-term exposure limit is developed to provide safety for a 15-minute exposure.

Similarly, EPA derives reference concentrations, generally in units of  $\text{mg}/\text{m}^3$ , that can represent chronic, subchronic, or acute time periods. For cancer, the toxicity criterion is the inhalation unit risk value, generally in units of  $1/\mu\text{g}/\text{m}^3$ .

The pattern of exposure may be important to consider. Different toxic effects may occur from a long-duration low-level exposure than from a series of intermittent high exposures. The reasons for this difference include accumulation in the body or formation of a toxic metabolite.

Generally, the exposure concentration for acute exposure can be represented by the measured air concentration. However, for longer exposures, these will need to be averaged to represent a time period appropriate to the toxicity factor. In addition, exposure may occur in multiple environments or situations, and these various exposures must be averaged appropriately.

#### **4.9.3 Outdoor Air Modeling**

The simplest air model is a so-called “box” model. It assumes that air pollutants enter a box from a source within the box or carried on the prevailing winds. Pollutants leave the “box” on the wind or by deposition to the ground. The concentration inside the “box” is the simple average concentration—the amount of pollutant

in the “box” divided by the size of the “box.” The model is a simple input–output model, and is a first step toward obtaining air concentrations for use in exposure assessment.

The Gaussian plume model is also a relatively simple model that is typically applied to point source emitters, such as smoke stacks. The concentration of substances downwind from the source is considered to be spreading outwards in three dimensions from the centerline of the plume following a normal or Gaussian statistical distribution. One of the key assumptions of this model is that over short periods of time (such as a few hours), steady state conditions exist with regard to air emissions and meteorological changes. The model assumes an idealized plume emanating from the top of the stack is representative of the actual pattern of release. Dispersion then occurs in three dimensions. Downwind dispersion is a function of the mean wind speed blowing across the plume. Crosswind or lateral dispersion is dependent on the relative stability of the surrounding air. Dispersion in the vertical direction will depend on the wind speed and density of the emitted substance relative to that of air.

Generally, the models used today are more complex but are also more uncertain than in the past. For example, the Assessment System for Population Exposure Nationwide (ASPEN) is an air quality dispersion model based on a Gaussian plume simulation and a mapping function that produces a concentration specific to each census tract. Census tracts were developed to contain 1500–8000 residents, with an optimum size of 4000. The geographic size of a census tract will vary between urban and rural locations, and the concentration estimates produced by ASPEN are determined by geography and area—not population. Notwithstanding, these estimates are keyed to population, and this potential mismatch is a source of uncertainty.<sup>231</sup>

Some air models include non-point sources such as automobiles; some models consider the effect of terrain or the built environment; both these factors add to model complexity. EPA’s ISC-PRIME (Industrial Source Complex—Plume Rise Model Enhancements) melds a Gaussian plume model with a model of building downwash to include the effects of the built environment.<sup>232</sup>

One of the most challenging areas of air modeling is the modeling of dense gases. Once released, these gases sink to the ground and spread out under their own weight. Both the presence of buildings and the local terrain affect the movement of the ground-level plume. Chlorine is a dense gas and is often transported in railroad tankers. Deaths often occur during railroad accidents from chlorine inhalation.<sup>233</sup> The resulting gas cloud remains at ground level and moves downhill, interrupted by larger ground-level masses such as buildings. Chlorine tanker trucks were used as weapons during the Iraq War.<sup>234</sup>

#### 4.9.4 Indoor Air Modeling

Substances may occur in indoor air from inside sources or may enter the building from the outside. In Chapter 1, the example of how a journalist affected public perception of the risks from hexavalent chromium was described. In the case of indoor air, a similar situation happened when Mark Obmascik of the *Denver Post* criticized

EPA in 2002 for the use of a vapor intrusion model developed by Paul Johnson and Robert Ettinger.<sup>235</sup> This model was used by EPA at the Redfield Rifle Scopes site near Denver as an example of model application. Redfield manufactured rifle scopes and binoculars, and used degreaser solvents such as trichloroethylene that leached from the site into groundwater. Denver Water provided water to residents near the Redfield site, but the model was used to attempt to determine if there might be any risk from migration of solvent vapors from the groundwater into indoor air.

On January 6, 2002, Obmascik wrote an article in the *Denver Post* titled “Toxins in air, regulations fail to protect U.S. residences from gases.”<sup>236</sup> Obmascik was critical of EPA and Colorado state officials because they did not test air within homes. On January 7, 2002, Obmascik wrote: “With that model, you’d get just as good results flipping a coin. Half the times it’s right, and half the time, it’s wrong.”<sup>237</sup> Obmascik was clearly ignorant of the idea that there could be indoor background sources of vapors. For example, trichloroethylene is found in a number of cleaning products used in arts and crafts and household maintenance.

The real advantage of the model is that it provides a way of distinguishing substances occurring in indoor air, and sampling results of indoor air could never distinguish the source. In fact, both EPA and New York State have compiled databases on background indoor air concentrations of volatile organic compounds.<sup>238,239</sup> In his enthusiasm for career-building, Obmascik clearly lost sight of his responsibility as a journalist to inform himself and the public of the true state of the science.

One happy consequence of the public and private sector scrutiny of vapor intrusion is that the strengths and weaknesses of this model are now well known. Basically, the model develops estimates for concentrations of vapors that might exist underneath a house, potentially trapped by a concrete slab with footers. Next, the model develops estimates for the vapors that could penetrate the house through small cracks in the concrete or elsewhere in the foundation. This is the most uncertain part of the model. In fact, the recommendation of both EPA and the Interstate Technology and Regulatory Council is to use the model as a screening tool, and based on the model results, obtain samples of sub-slab soil gas or even indoor air.<sup>240-242</sup>

#### 4.9.5 Inhalation Rates

Early studies on inhalation rates either used spirometry to measure the actual breathing rate or predicted the rate from measurements of pulse. In the 1990s, a method based on energy expenditures was developed.<sup>243</sup> The general equation used in this method is:

$$V_E = E \times H \times VQ \quad (4.11)$$

where:

$V_E$  = ventilation rate in L/min or  $m^3/hr$

$E$  = energy expenditure rate in kilojoules/minute or megajoules/hr

$H$  = volume of oxygen consumed in the production of 1 kJ/min of energy

$VQ$  = ventilatory quotient—the ratio of minute volume to oxygen consumption

In the *Exposure Factors Handbook 2011 Edition*, EPA used three approaches to obtain inhalation rates based on this equation.<sup>7</sup> The first approach was to use food intakes from the USDA 1977–79 Nationwide Food Consumption Survey and adjust these values upward by 20% to account for under-reporting. The values for oxygen uptake of 0.05 L O<sub>2</sub>/kJ and for the ventilatory quotient were obtained from the original study.<sup>243</sup> The second approach was to obtain basal metabolic rate (BMR) data for various age groups from a range of sources and develop a regression between BMR and body weight. The ratio of the daily BMR to energy expenditure was used to convert this value to daily energy expenditure. The third approach involved developing energy expenditure rates associated with different levels of physical activity and using time-activity data from a survey of how people spend their time in these various activities.

More recently, the disappearance from the body of water doubly labeled with isotopes has been used to measure inhalation rates for periods up to three weeks. In this method, water is labeled with the stable isotopes <sup>2</sup>H and <sup>18</sup>O (deuterium and heavy oxygen). These isotopes can be measured in urine, saliva, or blood. The disappearance of <sup>2</sup>H is a measure of water output, and the disappearance of <sup>18</sup>O reflects water output plus CO<sub>2</sub> production. CO<sub>2</sub> production, as a measure of metabolic activity, is then calculated by subtraction. Daily energy expenditures can then be determined from CO<sub>2</sub> production.<sup>7,244–247</sup>

Data from double-labeled water studies have been collected by the Institute of Medicine of the National Academies of Sciences and the Food and Agriculture Organization of the United Nations. These data are diverse, and include subjects with differences in diversity in ethnicity, activity, body type, age and fitness.<sup>248</sup>

To obtain the actual values for inhalation rates, see Chapter 6 of *Exposure Factors Handbook 2011 Edition* (available at <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20563>). Tables at the end of that chapter provide inhalation rate values from a large number of studies.

## 4.10 FISH CONSUMPTION

A number of contaminants tend to bioconcentrate in fish through the food chain. Estimating exposure to contaminants in fish becomes complicated due to the need for knowledge about the fish consumption practices of the target population.

Earlier in the chapter, the concept of an exposure unit was introduced. A common argument among risk assessors dealing with fish consumption is the definition of the appropriate exposure unit—some contend the EU is actually the dinner plate holding the portion of fish to be consumed rather than any water body or part thereof.

More often than not, fish consumption practices are difficult to study. Certainly, avid recreational anglers consume their catch, but how likely is it that individuals support their dietary requirement for protein with self-caught fish—a true subsistence

scenario. Fishing and consumption of self-caught fish are long-standing traditions in rural America.<sup>249–251</sup> These traditions are difficult to maintain in the face of population mobility and the continuing concentration of people in urban and suburban areas.<sup>252</sup>

EPA relies on a relatively small number of surveys on fish consumption and presents these estimates as representative of the general population. For consumption of fresh water fish, the key population study was CDC's 2003–2006 NHANES data. EPA's Office of Pesticide Programs analyzed these data to obtain per capita and consumer-only intake rates for finfish and shellfish. For consumption of salt-water and estuarine fish in coastal regions, EPA has used data from the National Marine Fisheries Service Marine Recreational Fishery Statistics Survey (NMFS/MRFSS).<sup>7,253</sup> However, in 2006, the National Academies of Sciences strongly criticized the MRFSS and suggested that, because of the budgetary and personnel constraints and methodological flaws in data collection and analysis, the data produced by the survey were not reliable.<sup>254</sup>

The “subsistence fish consumer” exposure scenario commonly discussed among risk assessment practitioners is intended to account for those who rely on self-caught fish as a significant proportion of their dietary protein. While this scenario may be valid for Native Americans in remote areas, it is likely not applicable to other populations.<sup>255–257</sup>

Many contaminants in fish are highly toxic. Mercury was used as a catalyst for acetaldehyde production by the Chisso Corporation in Minamata, Japan during the early 20th century. The mercury was discharged into Minamata Bay, formed methylmercury, and accumulated in fish and shellfish with devastating neurological consequences, and often death.<sup>258,259</sup>

Fish consumption, however, confers health benefits, specifically for cardiovascular and brain function, as well as overall health.<sup>260,261</sup> Often, these benefits are not taken into account in risk assessments involving fish consumption.

In an exercise at the end of the chapter, fish consumption rates recommended by EPA will be compared to the recommended daily allowance of protein in order to determine their level of conservatism. In general, fish consumption estimates used in risk assessment are most representative when developed from site-specific data. Although time-consuming and often costly, carefully conducted creel surveys to ascertain actual fish consumption practices are vital to the development to a credible fish consumption risk assessment.

## 4.11 THE EXPOSOME AND BIOMONITORING

During the 20th century, government regulation of chemicals commenced, and exposure science concentrated on specific chemicals and their relationship with disease. The focus in the 20th century was on chemicals in external media—air, water, soil, food, and consumer products. Chemicals with potential toxicity may originate within the body. The concept of the exposome seek to meld these exogenous and endogenous exposures throughout all stages of life.<sup>262,263</sup>

The exposome was conceived to seek out additional causes of disease and new biomarkers for disease processes. Chapter 1 provided an introductory discussion about mode of action. The difficulty with the exposome is that the huge amount of data will hinder the identification of specific causal factors. Almost no progress has been made in using the exposome to understand or target specific diseases.<sup>264,265</sup>

Philosophically, the notion of the exposome flies in the face of the continued evolution of causal analysis<sup>266–274</sup> Even if one believes the exposome can reveal every exposure since conception, the impossibility of discovering any temporal concordance between exposure and disease from the surfeit of biological information revealed by the exposome means this effort would likely be fruitless.

The notion of the exposome also suggests a lack of resilience—are we humans affected by our exposures, our experiences and travails, by life itself? The German philosopher Friedrich Nietzsche wrote in *The Twilight of the Idols*: “What does not kill me, makes me stronger.”<sup>275</sup>

Adverse outcome pathways, discussed in Chapter 2, may in time become a tool for understanding exposome data. One goal of adverse outcome pathway (AOP) efforts is to meld all of the pathways into a systems biology framework. The interactions between various pathways will be elucidated and included in this framework. At this writing, the relative simplicity of most AOPs will be a hindrance to their inclusion in the framework. The links between various pathways of toxicity have yet to be sufficiently understood to incorporate the big data from the exposome.<sup>276–281</sup>

Biomonitoring of specific chemicals in the US population has been going on since 1999 in the National Health and Nutrition Examination Survey. The broad scope of this data collection effort includes information on demographics, anthropometric data, diet, and nutritional status as well as a host of biomarkers in blood and urine.<sup>282</sup> Analytical chemistry has made huge advances during the 20th century, and the result is that minute concentrations of various substances can now be measured; the downside of this analytical improvement is that the actual meaning of these minuscule concentrations and the many sources of underlying variability are only just beginning to be understood.<sup>283–289</sup>

## 4.12 HIGH-THROUGHPUT EXPOSURE ESTIMATION

In 2015, John Wambaugh, a scientist at EPA’s National Center for Computational Toxicology trained in both physics and computer science as well as being a fan of video games, with his co-workers, proposed a framework for conducting high-throughput exposure assessment. The framework was evaluated using QSAR models of chemical properties related to bioaccumulation, consumer usage of personal care products, fragrances, pharmaceuticals, food additives, or general usage, based on 82 chemicals reported in NHANES.<sup>290</sup>

The model was then refined using 106 parent chemical exposures inferred from 68 distinct urine analytes in the NHANES biomonitoring data. Additional heuristics included in the refined model included usage categories and total production volume.

The model was then used to predict the exposure doses in units of mg/kg-day for almost 8000 chemicals.<sup>291</sup>

The ultimate purpose of this model was to support risk assessment and serve as companion tools to the surfeit of high-throughput toxicity data generated by EPA's ToxCast program.<sup>292</sup> The initial motivation for this effort was the 2007 report from the National Research Council, *Toxicity Testing in the 21st Century*.<sup>293</sup>

High-throughput toxicity testing provides data in terms of concentrations that produce biological activity in a test system. These data needed to be converted to exposure doses to compare them with the exposure. This conversion is called quantitative *in vitro*-to-*in vivo* extrapolation (QIVIVE), and required the development of high-throughput assays for hepatic clearance and protein binding. QIVIVE methods deliver external dose values corresponding to activity concentrations in ToxCast assays. For this reverse dosimetry exercise, the activity concentration from the assay is assumed to represent the steady state blood concentration. These daily doses estimated with QIVIVE can then be compared to the high-throughput exposure estimates as a means of selecting chemicals for further study and identifying those chemicals for which the exposure is much lower than a dose that would produce toxicity.<sup>294,295</sup>

This method of triaging has been applied to contextualize the possible estrogenic effects of some pesticides by comparing their exposure/activity ratio to that of genistein, a ubiquitous dietary phytoestrogen with a number of health benefits.<sup>296</sup>

The threshold of toxicological concern (TTC) is a tiered approach that develops human exposure thresholds for several endpoints of different severities. The value of the TTC is estimated as the 5th percentile of the chemical doses that produce a particular toxic effect. The TTC for substances containing structural features indicative of toxicity has a value of 0.0015 mg/kg-day, and that for substances with genotoxic alerts is 2.5E-06 mg/kg-day. Comparing the high-throughput exposure estimates of the almost 8000 chemicals indicated that none of the median exposures was greater than 0.0015 mg/kg-day and that for 79 chemicals, or 4%, was greater than 2.5E-06 mg/kg-day.<sup>297</sup>

The goal of the development of high-throughput exposure modeling continues to be prediction of exposure for use as a screening tool for additional study to understand the toxicity of the chemical being considered. Work in this area is ongoing.<sup>298-300</sup>

## 4.13 EXERCISES FOR THOUGHT AND DISCUSSION

### 4.13.1 Estimating $K_p$ from Experiments with Coal Tar Shampoo

Urinary 1-hydroxypyrene was measured in the urine of volunteers after they shampooed twice in the evening for 30 seconds each time using a total of 20 g of shampoo containing 285 mg/kg of pyrene. Urine was collected for two days thereafter.

The average total excretion of 1-hydroxypyrene was 30.9  $\mu$ mol. The molecular weight of pyrene is 202.25 g/mol and the  $\log K_{ow}$  is 4.88. Now, from EPA's website, download RAGS, Part E on Dermal Risk Assessment from [www.epa.gov/risk/risk-assessment-guidance-superfund-rags-part-e](http://www.epa.gov/risk/risk-assessment-guidance-superfund-rags-part-e).

Use Equation 3.2 on page 3-4 of RAGS, Part E. For this exercise, we will assume that the shampoo has the same density as water.

We will calculate  $K_p$  for pyrene using the Potts and Guy equation shown on the top of page 3-7 in RAGS, Part E. Other physicochemical parameters were obtained from the Hazardous Substances Data Bank at <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB>

The predicted  $K_p$  value from the Potts and Guy equation is 0.194 cm/hr. The values for  $B$  and  $\tau$  are not provided, but those for fluoranthene were used as surrogate values. Fluoranthene has a very similar molecular weight (202.3) and  $\log K_{ow}$  value (4.95) to those for pyrene.

Equation 3.2 in RAGS, Part E predicts the dermally absorbed dose is 0.0168 mg/cm<sup>2</sup>-event for each 30-second shampooing event. Doubling this gives 0.0336 mg/cm<sup>2</sup>-event. Table 7.2 in EPA's *Exposure Factors Handbook 2011 Edition* gives the area of the head as 0.154 m<sup>2</sup> for males and 0.121 m<sup>2</sup> for adult females. Assuming 1/3 of this value represents the scalp, the dermally absorbed dose would be 17 mg for males and 13 mg for females. If all this absorbed dose were metabolized and excreted as hydroxypyrene, then males would excrete 84 µmol and females 65 µmol. Both these values are within a factor of 2 to 3 of the observed value.

Please work through these calculations yourself. There is great value in becoming familiar with the calculation methods and online resources.

#### **4.13.2 Comparison of EPA's Estimates of Fish Consumption Rates with the Recommended Daily Allowance for Protein**

To ascertain the degree of conservatism in these estimates, the daily amount of protein consumed as fish was compared to the estimated average daily protein requirement (EAR) and minimal protein requirements for humans. The narrative and tables below provide the data and a description of what to do in order to enable readers to perform this comparison. The EAR on a daily basis and the recommended daily allowance (RDA) for protein, are both in g/kg/d and taken from *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*, published by the National Academies of Sciences.

Age	EAR(Male and Female)	RDA(Male and Female)
1–3	0.87	1.05
4–8	0.76	0.95
9–13	0.76	0.95
14–18	0.73 M, 0.71 F	0.85
19–30	0.66	0.8
31–50	0.66	0.8
51–70	0.66	0.8
>70	0.66	0.8

You should be able to easily find EPA's *Exposure Factors Handbook 2011 Edition*. It is a sufficiently useful document that it is advisable to keep a copy on your own computer. Please consult EPA's Table 10.1 for recommended consumer-only data on total finfish and shellfish consumption. How do these values compare with the EAR and RDA values in the table above?

#### 4.13.3 Bootstrap Sampling

Please go to [www.crcpress.com/9780367250973](http://www.crcpress.com/9780367250973) and download the Excel spreadsheet "Simon-Chapter4-bootstrap.xls." This file implements a bootstrap in Excel. The data herein are from an actual hazardous waste site. Please note that these data are neither normally nor lognormally distributed. If they were, the log-probability plot would be straight.

On the worksheet named "bootstrap," you will note the value "1" in cell K8. Replace this value with any other integer. The reason is to cycle the random number generator. As you do this, the bootstrap sample in columns H and I will change, as will the arithmetic mean calculated using Equation 3.4 in cell K2 and the arithmetic mean of the bootstrap sample in cell K3. Also examine the formulae in the various cells to understand how the bootstrap was implemented.

For those of you who know R or Python, implementing a bootstrap in those languages should be quite simple.

You may also wish to download EPA's ProUCL software (available at [www.epa.gov/land-research/proucl-software](http://www.epa.gov/land-research/proucl-software)) and attempt to work with these data. The raw data are provided in the worksheet named "Raw data." For the bootstrap exercise, only detections were used. The dataset contains non-detects. These can be handled by ProUCL. The bootstrap implemented here is not definitive, but rather was done to give you an idea of how Monte Carlo methods and resampling techniques work.

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## CHAPTER 5

# Hazard Characterization and Dose–Response Assessment

The Dose makes the Poison.

**Paracelsus**

The dose–response assessment or toxicity assessment provides a means of understanding whether the magnitude of human exposure to environmental contaminants is sufficient to produce adverse health effects. The difference between dose–response assessment and hazard identification is that dose–response assessment is the process of quantifying (rather than identifying) the relationship between the dose of a particular chemical or hazard to which an individual or population is exposed and the likelihood of adverse health effects. Together, hazard identification and dose–response assessment are called hazard characterization.

The dose–response assessment most often relies on data from animal studies and extrapolates these data to humans. A major effort is underway to develop and validate results from high-throughput *in vitro* testing for use in risk assessment and ideally supplant animal testing. *In vivo* animal bioassay studies are most often conducted using very high doses relative to the environmental exposures experienced by humans—hence, extrapolation from both high doses to low doses and between different species are required. Extrapolation of high doses in an epidemiologic study to lower environmental doses is also needed when the dose–response assessment for a chemical was based on high-exposure epidemiology data, such as that in occupational or observational studies.

Traditionally, the US Environmental Protection Agency, Health Canada, and other regulatory agencies have developed two types of quantitative toxicity criteria for oral exposure: reference doses (RfDs) or tolerable daily intakes (TDIs), and cancer slope factors (CSFs). RfDs are also known as toxicity reference values. Reference doses are developed for non-cancer effects and embody the concept of a threshold in which a biological factor must be depleted or overcome for disruption of normal homeostatic mechanisms and resulting adverse effects. Cancer slope factors are developed based on the presumption that cancer responses lack a threshold. The non-threshold approach of a cancer slope factor is used because EPA presumes that any

level of exposure, even as small as a single molecule, poses finite probability of generating a carcinogenic response. Right or wrong, this presumption has enjoyed wide acceptance and has had a significant effect on environmental regulation throughout the history of risk assessment. This assumption is known as the linear no-threshold (LNT) hypothesis, and will be discussed at length later in the chapter.

The first section of this chapter will provide a discussion of the concept of mode of action (MOA). Then, a survey of computational methods that have come to be used in hazard characterization will be presented. Next, an in-depth description of the calculation of toxicity factors will be provided. MOA will be revisited, and its application to understanding toxicity in the 21st century will be also explored.

The changing nature of societal concerns, considerations of animal welfare, and our ever-increasing knowledge of the biological basis of disease are changing the manner in which toxicity and dose-response are assessed. The primary focus of environmental regulatory toxicology in the first half of the 21st century is to develop non-animal testing methods such as high-throughput *in vitro* testing and prediction models for developing quantitative toxicity factors from these high-throughput data.

## 5.1 MODE OF ACTION (MOA)

Mode of action provides the central organizing principle for understanding the biological underpinnings of toxicity. In US government guidance documents, MOA was first mentioned in the National Research Council's 1993 document *Issues in Risk Assessment*.<sup>1</sup> This publication considered three issues: the use of the maximally tolerated dose (MTD) in animal bioassays for cancer, the two-stage initiation/promotion model of carcinogenesis as a regulatory tool, and a paradigm for ecological risk assessment. Mode of action was mentioned with regard to the use of the MTD in animal bioassays. The report concluded that bioassays employing the MTD would need additional studies to determine “mode-of-action, pharmacokinetics and applicability of results to the human experience.”<sup>1</sup>

Chapter 1 discussed at length the considerable uncertainty in determining the human relevance of results from cancer bioassays in animals.<sup>2,3</sup> The 1993 National Research Council (NRC) report indicated the use of the MTD was a necessary evil to be able to obtain protective estimates of risk from animal studies.

### 5.1.1 Mode of Action and Cancer

Cancer is still viewed in a monolithic way—as a single disease; thinking of cancer as a group of diseases with multiple interacting causal factors is more accurate. The hallmarks of cancer were identified in the early 21st century, and include sustaining a blood supply, cells acquiring a limitless ability to replicate, insensitivity to controls on growth, the ability to escape programmed cell death, and other features. These acquired hallmarks provide malignant cells with a Darwinian selective advantage over normal cells: in short, cancer cells can scavenge resources, are essentially

immortal, and in a very real sense, parasitize the host. The six original hallmarks of cancer are:

- self-sufficiency in growth signals;
- evasion of apoptosis;
- insensitivity to anti-growth signals;
- sustained angiogenesis;
- tissue invasion and metastasis;
- limitless replicative potential.<sup>4</sup>

The four next-generation hallmarks added in 2011 are:

- dysregulation of cellular energetics;
- avoidance of immune destruction;
- genomic instability and mutation;
- tumor-promoting inflammation.<sup>5</sup>

These hallmarks are acquired capabilities of cells that are necessary for tumor growth and progression. The hallmarks are intended to serve as a general set of clinical targets for development of new drugs and treatment protocols. The authors also mention epigenetic changes, but in 2010 did not have sufficient information on the relationship of epigenetics and cancer to add another hallmark.

The “war on cancer” was conceived and carried out during the mid-20th century when the biology of cancer was relatively unknown.<sup>6,7</sup> In the 21st century, the pathogenesis, key events and causal factors leading to cancer are much better understood—in large part, due to the emphasis on mode of action in regulatory toxicology.<sup>8–16</sup>

How much detail is needed to specify a mode of action for a particular type of cancer—whether in humans or in animals? EPA indicates that data richness is generally a prerequisite for determining MOA, and defines the term as follows:

The term “mode-of-action” is defined as a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation. A “key event” is an empirically observable precursor step that is itself a necessary element of the mode-of-action or is a biologically based marker for such an element. Mode-of-action is contrasted with “mechanism of action,” which implies a more detailed understanding and description of events, often at the molecular level, than is meant by mode-of-action. The toxicokinetic processes that lead to formation or distribution of the active agent to the target tissue are considered in estimating dose but are not part of the mode-of-action as the term is used here. There are many examples of possible modes of carcinogenic action, such as mutagenicity, mitogenesis, inhibition of cell death, cytotoxicity with reparative cell proliferation, and immune suppression.<sup>17</sup>

EPA’s 2005 *Guidelines for Carcinogen Risk Assessment*, from which the above passage was taken, indicates that consideration of mode of action should be the centerpiece of any cancer risk assessment. While data richness is highly desirable, even sparse data can be considered in a MOA analysis and, perhaps more important,

cancer occurs through a finite number of pathogenic mechanisms. These mechanisms necessarily limit the number of MOAs that may be operative for a given tumor type.<sup>18–22</sup>

Consideration of MOA will generally enable understanding of the human relevance of tumor responses observed in animals, the identification of potentially sensitive sub-groups or life stages, and more importantly for regulatory purposes, the determination of whether low-dose extrapolation should be conducted using a linear non-threshold approach or a nonlinear approach that uses a presumed threshold and application of safety factors.<sup>23</sup>

### 5.1.2 Mode of Action versus Mechanism of Action

These two biological concepts—mode of action and mechanism of action—may seem quite similar; only the level of available biological details distinguishes them from one another. What is most important is the weight of evidence that serves to identify the actual biological occurrences that contribute to the adverse outcome—in other words, the key events (KEs) and the key event relationships between upstream and downstream events that constitute the pathogenesis of disease.

Mechanism of action refers to the specific sequence of events at the molecular, cellular, organ, and organism level leading from the absorption of an effective dose of a chemical to the production of a specific biological response in the target organ.<sup>23,24</sup> To understand the mechanism of action underlying a particular adverse outcome, one would need knowledge of the likely causal and temporal relationships between the events at the various levels of biological organization, including those events that lead to an effective dose of the chemical at the site of biological action. To specify a mechanism of action, data are needed regarding:

- metabolism and distribution of the chemical in the organism affecting the dose delivered to the molecular site of biological action;
- molecular target(s) or sites of biological action;
- biochemical pathways affected by interaction of the chemical with the site of biological action;
- cellular- and organ-level consequences of affecting these biochemical pathways;
- target organs/tissues in which the molecular sites of action and biochemical effects occur;
- physiological responses to these biochemical and cellular effects;
- target organ response to the biochemical, cellular, and physiological effects;
- the overall effect on the organism;
- likely causal and temporal relationships between these various steps;
- dose–response parameters associated with each step.

In contrast, mode of action is a more general description of the toxic action of a chemical action.<sup>23,25,26</sup> Mode of action refers to the type of response produced in an exposed organism or to only those key events that constitute necessary and critical aspects of the particular biological response. Hence, mode of action is known if the full mechanism is known, but the reverse is not true. The distinctions between

mode and mechanism are important for understanding and describing the biological effects of chemicals, including both environmental chemicals and drugs. However, it is important to remain aware that many risk assessors may be less than rigorous in the use of these terms.

In April 1996, EPA published its *Proposed Guidelines for Carcinogen Risk Assessment*, the first update to the 1986 guidelines stemming from the recommendations in the “Red Book.”<sup>27,28</sup> These proposed guidelines recommended consideration of the biological events underlying the carcinogenic process and the incorporation of new information, especially given the rapid pace of ongoing cancer research. The 1986 Cancer Guidelines acknowledged that insights gained from this research would be useful and important for MOA considerations and that MOA would play a greater role in cancer risk assessment—unfortunately, the details of how to apply this knowledge to gain an understanding of MOA were left unclear.<sup>29,30</sup>

Specifically, the proposed guidelines expressed a preference for biologically based dose–response models based on mode of action rather than the empirical dose–response models that had hitherto been used for cancer dose response. The International Life Sciences Institute (ILSI) convened an expert panel to evaluate the proposed guidelines and apply them in case studies of two specific chemicals—chloroform and dichloroacetate.<sup>30–32</sup> The findings of this expert panel resulted in the eventual acceptance by EPA’s National Center for Environmental Assessment that a nonlinear toxicity criterion for chloroform would be protective of the carcinogenic endpoint—even though achieving this acceptance required legal action.

### 5.1.3 An Example of Mode of Action

Lynn Turner, a 911 operator living in Forsyth County, Georgia, poisoned her husband with ethylene glycol in 1995 and then, in 2001, poisoned her live-in boyfriend the same way. After the boyfriend’s death, the husband’s body was exhumed, and the autopsies discovered that both men died from ethylene glycol poisoning.<sup>33</sup>

Just how does ethylene glycol, the chemical used in the majority of automobile antifreeze/coolant mixtures, produce toxicity and, ultimately, death? Mammalian kidney cells metabolize ethylene glycol to calcium oxalate monohydrate that forms crystals within renal tubular cells. These cells rupture, the kidneys cease their function, and death quickly ensues.<sup>34</sup>

Understanding the mode of action of ethylene glycol is quite easy from this example. Every summer, sadly, dogs may drink spilled antifreeze and also die. The mechanism, and thus the mode of action, are the same for both man and man’s best friend.

### 5.1.4 Applying the Mode of Action Concept

As noted in Chapter 1, in the absence of mode of action information, EPA’s regulatory policy for cancer assumed that the dose response was linear in the low-dose region. Implicit in the assumption that the dose response of a chemical is linear all the way down to zero dose is the outlandish notion that a single molecule of a

substance may produce adverse effects—a health-protective but biologically incorrect assumption. EPA and the state of California adopted an even more stringent but also incorrect assumption—chemicals that cause cancer by a mutagenic mode of action—i.e., heritable changes in DNA sequence—act rapidly, and exposure during childhood may produce risks that persist throughout life.<sup>35,36</sup>

Unfortunately, EPA never followed the recommendations of the expert panel that reviewed the 1996 revision of the proposed cancer guidelines. The failure to provide detailed guidance regarding consideration of mode of action has led to an extremely simplistic interpretation by many regulators. The most recent example of such a simplistic misinterpretation is the incorrect suggestion in a journal article by EPA staff that hexavalent chromium produces cancer by a mutagenic mode of action.<sup>37</sup> While EPA's 2005 *Guidelines for Carcinogen Risk Assessment* provided an unequivocal statement that MOA should be the centerpiece of all risk assessments, details of exactly how to incorporate and use the information were unfortunately lacking.<sup>23</sup>

#### **5.1.4.1 Mode of Action of Oral Exposure to Hexavalent Chromium**

For years, toxicologists have known that hexavalent chromium is carcinogenic to humans by the inhalation route. Workers in chromite processing facilities experience higher rates of lung cancer than the general population.<sup>38–40</sup> Many regulatory toxicologists believed that hexavalent chromium was also carcinogenic to humans by the oral route—although this belief turned out to be incorrect. From the initial supposition that hexavalent chromium (Cr(VI)) might be a human carcinogen by the oral route,<sup>41</sup> it took until 2008 for the National Toxicology Program to publish the results of a two-year cancer bioassay conducted in mice and rats.<sup>42</sup> Mice developed small intestinal tumors, and rats developed tumors of the oral epithelium.

Notwithstanding EPA's unequivocal recommendations to use consideration of mode of action as the centerpiece of all risk assessment,<sup>23</sup> these bioassay results were interpreted in a highly simplistic fashion by a number of regulatory agencies between their publication and proposal and elucidation of the actual MOA in 2012.<sup>35,36,43</sup> The details of the MOA were demonstrated in a clever series of experiments and published in 2012 and 2013 along with a risk assessment based on the findings.<sup>44–53</sup>

The lining of the small intestine consists of myriad tiny finger-like projections called villi (singular villus). The function of the villi to increase the epithelial surface area available for the absorption of nutrients. Between the villi are invaginations called crypts of Lieberkuhn. The enterocytes, cells of the villi, slough off into the intestinal lumen and are replaced about every three days by new cells migrating upwards from the crypts. The normal state of crypt cells is to proliferate and replace villous enterocytes. Chemical signaling via specific signaling molecules known as cytokines originating from the villous cells and elsewhere regulates the proliferative activity of the crypt cells.<sup>54–56</sup>

The MOA for intestinal tumors in mice from Cr(VI) exposure includes aspects of toxicokinetics. Cr(VI) is chemically reduced to trivalent chromium in the stomach. Trivalent chromium is poorly absorbed in mammals. The human stomach is much more acidic (pH ~ 1.5) than the stomachs of rats (pH ~ 3), thus in humans

the reduction of hexavalent chromium to trivalent chromium occurs to a much greater extent than in rats; rats have a more acidic stomach than mice ( $\text{pH} \sim 4.5$ ), thus mice reduce Cr(VI) to a lesser extent than do rats. Hence, a greater amount of Cr(VI) is available for absorption by villous enterocytes in mice than in either rats or humans. The absorbed Cr(VI) produces cytotoxicity of the cells in the intestinal villi, observed histologically as short, blunted villi, much smaller than normal. The need for replacement of the damaged villous enterocytes produces increased proliferation of stem cells in intestinal crypts. During such a hyperproliferative state, there is less time between cell divisions for DNA repair mechanisms to complete repair of spontaneous DNA damage, and mutations resulting from faulty DNA repair have a greater chance of revealing themselves as tumors.<sup>57–60</sup>

In mice, a distinct threshold was observed for crypt cell hyperplasia, and a reference dose developed for hyperplasia was also protective of cancer.<sup>44,45,47,49–52</sup> The increased stem cell divisions leading to tumors is an example of the “bad luck” hypothesis discussed in Chapter 3.<sup>60</sup>

## 5.2 NON-MONOTONIC DOSE RESPONSE, THRESHOLDS, AND HORMESIS

Continued existence for any organism is a matter of maintaining homeostasis in the face of an unremitting array of stressors. Evolutionarily successful organisms have developed redundant systems and capacities to deal with many different stressors, but these capacities are finite. When one or more of these capacities are exceeded, a departure from homeostasis, usually in the form of disease or death, occurs. The fact of biological thresholds is implicit in Paracelsus’ dictum that the dose makes the poison.<sup>61</sup>

In this chapter, the linear no-threshold hypothesis will be discussed at some length. As noted, this hypothesis assumes that even an infinitesimal dose of a carcinogen poses a finite, albeit small, risk and has provided the basis for the regulation of carcinogenic chemicals since the 1970s. Much of the animal testing that has been done in the past has had the goal of demonstrating whether a particular chemical produced cancer in rodents over their lifetime.

### 5.2.1 What Is Hormesis?

Paracelsus, the “first” toxicologist, whose famous quotation begins this chapter, noted that toxic substances may be beneficial in small amounts.<sup>62</sup> This phenomenon results in a J-shaped dose–response relationship and has been amply demonstrated in animals.<sup>62,63</sup> As a scientific concept, hormesis has yet to gain general acceptance, and there are likely political and economic agendas for this lack of acceptance.<sup>64</sup>

The phenomenon of hormesis was first noted in 1887 when small applications of disinfectant were observed to stimulate the growth of yeast, whereas large applications killed the yeast. Evidence seems to be mounting for the universality of hormesis as a phenomenon.<sup>65–68</sup> However, the acceptance of hormesis in risk assessment has yet to occur.<sup>69–74</sup>

### 5.2.2 Why Non-Monotonic Dose–Response Curves Appear

A useful way of thinking about hormesis is as a means of inducing biological resilience. Dr. Laura N. Vandenberg of the University of Massachusetts School of Public Health published a review article in 2012 about low-dose endocrine effects and the occurrence of non-monotonic dose–response curves in which the response does not necessarily increase with dose; high responses may occur at low and high doses. She indicated that such low-dose responses were potentially important when considering human health effects for endocrine-active substances, those labeled endocrine disruptors.<sup>75</sup> Essentially, the message of this paper was a restatement of the retracted Arnold paper that led to the additional 10 $\times$  factor used in the EPA’s Food Quality Protection Act discussed in Chapter 1.

Vandenberg received her Ph.D. in 2007, working in the laboratory of Dr. Ana Soto at Tufts University on the estrogenic effects of bisphenol A occurring in adult mice from exposure *in utero*.<sup>76,77</sup>

Modeling studies of generalized tumor responses suggest that J-shaped dose–response curves could occur in rodent tumor bioassays at a greater frequency than linear dose responses.<sup>78</sup> Hormesis can also be observed in models of specific cellular processes, including induction of DNA repair and control of the cell cycle checkpoint that prevents damaged cells from replicating.<sup>79</sup> Individuals exposed to residual radiation from the nuclear attacks on Hiroshima and Nagasaki during World War II also show a J-shaped or hormetic dose response for longevity.<sup>80</sup> The biological basis for hormesis may be related to changes in the process of autophagy, a critical cellular maintenance process through which cells recycle damaged protein and organelles.<sup>81</sup> Hormetic mechanisms may also be involved in the pathogenesis of type II diabetes and in repair of oxidative DNA damage<sup>49,82</sup>

## 5.3 MODE OF ACTION HUMAN RELEVANCE FRAMEWORK

Dose–response analysis and extrapolation to estimated or measured human exposure levels is a central issue in risk assessment. Risk assessment necessarily uses extrapolations—from doses at which effects are observable down to much lower doses—and from effects observed in animals to an understanding of the relevance or lack thereof of those same effects in humans.

To accomplish these extrapolations in a scientifically credible way, mode of action frameworks have been developed for application of knowledge of MOA as a means of deciding whether effects in animals are relevant to humans and as a way to understand the role of key events within the overall progression to the adverse outcome or apical toxic event.<sup>83–87</sup>

Quantitative MOA information can reduce uncertainty in risk assessments. Where applicable, quantitative data can be used to replace defaults and to choose the most appropriate dose–response models.<sup>88</sup> Hence, an understanding of the MOA is becoming a fundamental component of risk assessment, especially when it comes to classifying carcinogens and making judgments about whether a threshold

approach is appropriate or whether the default linear no-threshold assumption must be used.<sup>23</sup>

Information about toxicokinetics and metabolism can provide information about the active form of the chemical—indeed, if the toxic moiety is a metabolite of an administered parent chemical, then metabolic activation would clearly be a key event in the MOA. On the other hand, metabolism may also function as a mechanism for detoxification. By taking into account metabolic key events as part of the overall MOA, the influence of induction or inhibition of metabolism of the chemical and variations in patterns of toxicity with metabolic profiles across individuals, species, strains, and sexes can be factored into the risk assessment.

### 5.3.1 Counterfactual Identification of Key Events

The identification of activation by metabolism as a key event may permit a powerful counterfactual demonstration that strongly supports the identification of metabolism as a key event. If metabolic activation is indeed a key event, then blocking metabolism should also block the occurrence of the adverse outcome. This sort of counterfactual thinking can be applied to other types of KEs as well, and can provide powerful evidence in support of a proposed MOA. Genetically modified “knockout” animals missing genes that provide for specific KEs can also support this type of counterfactual identification.<sup>89</sup>

Even in the absence of such a counterfactual demonstration, consideration of MOA also allows for an understanding of potentially susceptible subgroups and different life stages so that the most appropriate adjustments can be factored into quantitative risk assessments. An example is the polymorphism in the folate carrier or glutathione transferase that may predispose certain individuals to colon cancer.<sup>90,91</sup>

### 5.3.2 History of Mode of Action

The MOA framework was originally developed over a decade ago by the World Health Organization (WHO) International Program for Chemical Safety (IPCS) and specifically focused on chemical carcinogenesis.<sup>87</sup> The original framework was expanded to include a human relevance component and information about the susceptibility of various life stages.<sup>83,86,92</sup> The framework was restructured in 2009 to enable a systematic examination of the key events that occur between the initial dose of a bioactive agent and the effect of concern.<sup>93</sup> The Bradford Hill considerations have been tailored for application to assessing the likelihood of different modes of action.<sup>94</sup>

### 5.3.3 Mode of Action and the Linear No-Threshold Hypothesis (LNT)

When the mode of action by which a chemical produces toxicity is unknown, regulators believe they must use highly health-protective default assumptions for the extrapolations—to account for differences between the test species and humans, the

range of human susceptibility, and to select linear low-dose extrapolation and derivation of a cancer slope factor.

Linear low-dose extrapolation assumes that the response for chemical carcinogens is linear in the low-dose range all the way down to zero. Hence, no dose, however small, exists that can be deemed without effect. Likely, you recognize this assumption as the linear no-threshold hypothesis.

### 5.3.4 MOA in Regulatory Guidance

EPA is well aware of the utility of the MOA, as evidenced by the 2005 Cancer Guidelines.<sup>23</sup> In addition, EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* also relies on assessing the MOA.<sup>95</sup> The draft *Framework for Determining a Mutagenic Mode-of-action for Carcinogenicity* also relied upon MOA—stating that assuming a mutagenic MOA for a cancer endpoint that would dictate the use of linear low-dose extrapolation should not a default position, but rather would require biological evidence in support.<sup>96</sup> This guidance document was written by Dr. Rita Schoeny, who served as Senior Science Advisor to a number of offices within EPA during her 30-year career.<sup>97</sup> The fact that this guidance has never been finalized demonstrates the unfortunate lack of consensus in risk assessment about the use of the LNT, the difference between genotoxicity and mutagenicity, and more fundamentally, the appropriate degree of conservatism in risk assessment resulting from confusion between the two types of ethics—intention and consequence—discussed earlier.

Even today, many, including both risk analysts and even medical professionals, automatically assume that DNA-reactive chemicals are mutagenic and thus also carcinogenic, even chemicals produced naturally by metabolism within the body. This assumption of universal mutagenicity of substances associated with cancer is emphatically wrong and is a holdover from the 1970s when regulatory scientists adopted the linear no-threshold hypothesis before the fact of DNA repair mechanisms became common knowledge.<sup>98–107</sup>

The European Commission has also incorporated using MOA in its risk assessment guidance for industrial chemicals and biocides.<sup>108</sup> The European Food Safety Authority includes a MOA assessment in its guidance on harmonizing cancer and non-cancer risk assessment approaches.<sup>109</sup> Consideration of MOA is recommended in the European Community REACH Regulation guidance for conducting a chemical safety assessment, and in the new “classification, packaging and labeling” regulation on chemical substances and mixtures.<sup>110</sup> The Organisation for Economic Co-operation and Development (OECD) recommends using MOA to support the building of chemical categories or when using read-across approaches.<sup>111</sup> With the push for using more systematic and weight of evidence approaches in risk assessment, the use of mode of action/human relevance framework (MOA/HRF) and key events dose–response framework approaches will likely increase correspondingly. Hopefully, the adverse outcome pathways (AOPs) will find a use through integrated approaches to testing and assessment (IATAs), but the utility of AOPs remains to be demonstrated.

### 5.3.5 Tools for Understanding MOA

The development of a proposed or hypothesized MOA will necessitate identification of key events and understanding the dose–response and temporal relationships between these key events and the adverse outcome. The purpose of the Dose–Time Concordance table is to show clearly the relationships in both with increasing dose and passage of time between the hypothesized key events. The Dose–Time Concordance table allows one to gain a highly useful understanding of dose–response and temporal relationships between the key events and the apical event and also among the various key events. Table 5.1 shows an example of a Dose–Time Concordance table for the occurrence of small intestinal tumors in mice in response to hexavalent chromium administered in drinking water.<sup>48,49</sup>

The human relevance of a hypothesized MOA may depend on both qualitative and quantitative factors. EPA's Office of Pesticide Programs clearly recognizes this

**Table 5.1 Dose–Time Concordance Table**

Dose–Time Concordance for the MOA of hexavalent chromium and mouse small intestinal tumors				
Time		8 days	90 days	720 days
Increasing Dose (mg/L in drinking water)	Increasing Time	Duodenum		
	4		Absorption	No data
	14	Absorption (presumed)	Absorption Redox Changes	Absorption Redox Changes (presumed) Villous Cytotoxicity Crypt Proliferation
	60	Absorption (presumed) Redox Changes	Absorption Redox Changes Villous Cytotoxicity	Absorption Redox Changes (presumed) Villous Cytotoxicity Crypt Proliferation <b>Tumors</b>
	170	Absorption (presumed) Redox Changes Villous Cytotoxicity	Absorption Redox Changes Villous Cytotoxicity Crypt Proliferation	Absorption Redox Changes (presumed) Villous Cytotoxicity Crypt Proliferation <b>Tumors</b>
	520	Absorption Redox Changes Villous Cytotoxicity Crypt Proliferation	Absorption Redox Changes Villous Cytotoxicity Crypt Proliferation	Absorption Redox Changes (presumed) Villous Cytotoxicity Crypt Proliferation <b>Tumors</b>

fact and the need for assessing both qualitative and quantitative concordance of key events between animals and humans.<sup>112</sup>

For example, in the early 1990s, a technical panel from EPA concluded that male rat renal tubule tumors from chemicals that induced accumulation of  $\alpha_{2u}$ -globulin were likely not relevant to humans, based on qualitative considerations.<sup>113</sup> Naphthalene produces respiratory tract tumors in rats, but the MOA for these tumors is not relevant to humans, for both qualitative and quantitative reasons.<sup>114</sup> Table 5.2 shows an example (albeit with rather few entries) of one way to set up a Dose–Response Species Concordance table. In one place and ideally on a single page, such a table can provide information about both qualitative and quantitative concordance of key events between animals and humans and also quantitative dose–response information in both animals and humans.<sup>84,85,93,112,115,116</sup>

### **5.3.6 Qualitative Concordance of Key Events between Humans and Animals**

Human relevance of the apical endpoint is best determined using a hypothetico-deductive weight of evidence approach.<sup>117</sup> To address human relevance of the MOA, qualitative concordance between humans and animals for each key event needs to be considered. *In vitro* data may also be available from human or animal cells or tissues; concordance should be considered for these data as well.<sup>118,119</sup> Ideally, the data will be sufficient to determine which of the key events is relevant to humans, and these data may then be used to support statements about the relevance to humans of the hypothesized MOA in animals.

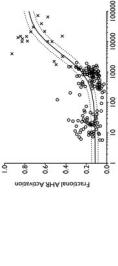
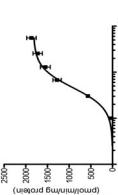
### **5.3.7 Quantitative Concordance of the MOA between Humans and Animals**

Quantitative examination of both the dose response and timing of key events is necessary to determine human relevance. For example, a MOA may be operative in both animals and humans, but extremely unlikely occur in humans because of quantitative toxicokinetic or toxicodynamic differences.<sup>93</sup> If a key event has the potential to occur in humans, then this quantitative examination can be used to inform animal-to-human extrapolation. Hence, the quantitative concordance should provide information about point of departure values such as no observed adverse effect levels (NOAELs) or lowest observed adverse effect levels (LOAELs) for as many key events as possible in both humans and the animal test species.

### **5.3.8 Understanding MOA in Terms of Timing and Species Concordance**

In general, events that occur at low doses and/or at early stages in the progression toward the apical event may represent: (1) the start of a temporal progression, (2) the initial stages of a developing change, or (3) a factor that potentially causes other key events that occur at higher doses or at a later time in the progression. Generally,

Table 5.2 An Example of a Dose–Response Species Concordance Table

Event or Factor	Qualitative Concordance			Quantitative Concordance and Quantitative Dose Response		
	Animals	Humans	Concordance	Strength	Animals	Humans
Key Event #1 Enzyme Induction	Occurs in animals <i>in vivo</i>	Also occurs in humans <i>in vivo</i>	Humans are less sensitive than animals	+++		NA
Key Event #2 Liver Toxicity	Occurs in animals <i>in vivo</i>	No evidence in humans	When observed in humans, this key event occurs only at high doses	+		NA
Apical Event	Known to occur in animals <i>in vivo</i>	Has not been shown to occur in humans	Concordance cannot be made because there is no human data			

showing that a particular event is necessary is experimentally difficult; however, this demonstration may be possible in some cases, as noted earlier, using transgenic or knockout animals or blockade of metabolic activation. Such a counterfactual demonstration provides powerful evidence for the identification of the KE.<sup>120</sup>

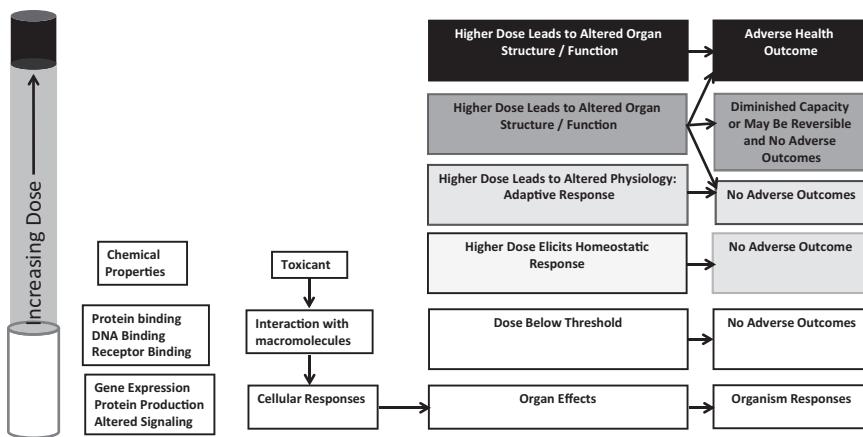
The exact nature of a KE cannot be necessarily understood from either its dose response or its timing of occurrence. Some early KEs may need to be sustained in order for later KEs or the apical event/adverse outcome to occur. One can easily think of this by considering the relationship between sugar consumption and cardiometabolic disease—a single candy bar as an occasional treat for a child will likely not produce adverse health effects; daily consumption of foods with high sugar content and failure to maintain cardiorespiratory fitness will over time very likely lead to cardiometabolic disease.<sup>121</sup>

Toxicokinetic factors affect the timing of key events as well. Lipid-soluble chemicals remain in adipose tissue for months or years and produce effects on an ongoing basis; for similar reasons, the dose of a bioaccumulative chemical may be measured as body burden or tissue concentration. In such a case, the area under the curve (AUC) in units of concentration time would likely represent the ongoing accumulation in both dose and time better than body burden or tissue concentration at a single time point. Sequestration of a chemical by protein binding may also be represented best by the AUC. A monotonic dose–response relationship between the AUC and a biomarker for a putative key event such as enzyme induction indicates that exploring the quantitative relationship between this biomarker and the apical event/adverse outcome may likely help elucidate details of the MOA.

In other cases, the occurrence of some early KEs may trigger a cascade of other events. These early KEs then either resolve themselves or become no longer empirically observable. However, the cascade of triggered events continues and leads ultimately to the apical event/adverse outcome. This embodies the concept of tipping points in which the upstream KE has to reach a specific duration and/or magnitude to produce the downstream KE. This concept is embodied in Figure 5.1, showing the exposure–response discontinuum. The transition from adaptivity to adversity likely occurs at the organ or tissue level of biological organization.<sup>122</sup> Quantitative aspects of identifying a tipping point will be considered in the section on dose–response modeling later in the chapter.

### 5.3.9 Weight of Evidence Considerations

A sequence of key events represents a progression over both dose and time. Knowing the relationship between the various key events in both dose and time along with an understanding of biology will contribute to the understanding of the role of particular key event within the MOA. Often, the counterfactual information discussed above is not available; without such information, it may be very difficult to demonstrate the necessity of a particular proposed key event. The understanding of biology can likely contribute, but conclusive support of necessity will be a data gap.



**Figure 5.1** Exposure-response discontinuum. The upright cylinder labeled “Increasing Dose” shows the transition from adaptation to adversity with increasing dose. This figure is similar to Figure 4.1, but explicitly includes the idea of the dose-dependent transition from adaptation to adversity. (Many thanks to Dr. Richard A. Becker for this figure. Dr. Becker also wrote the foreword to this book.)

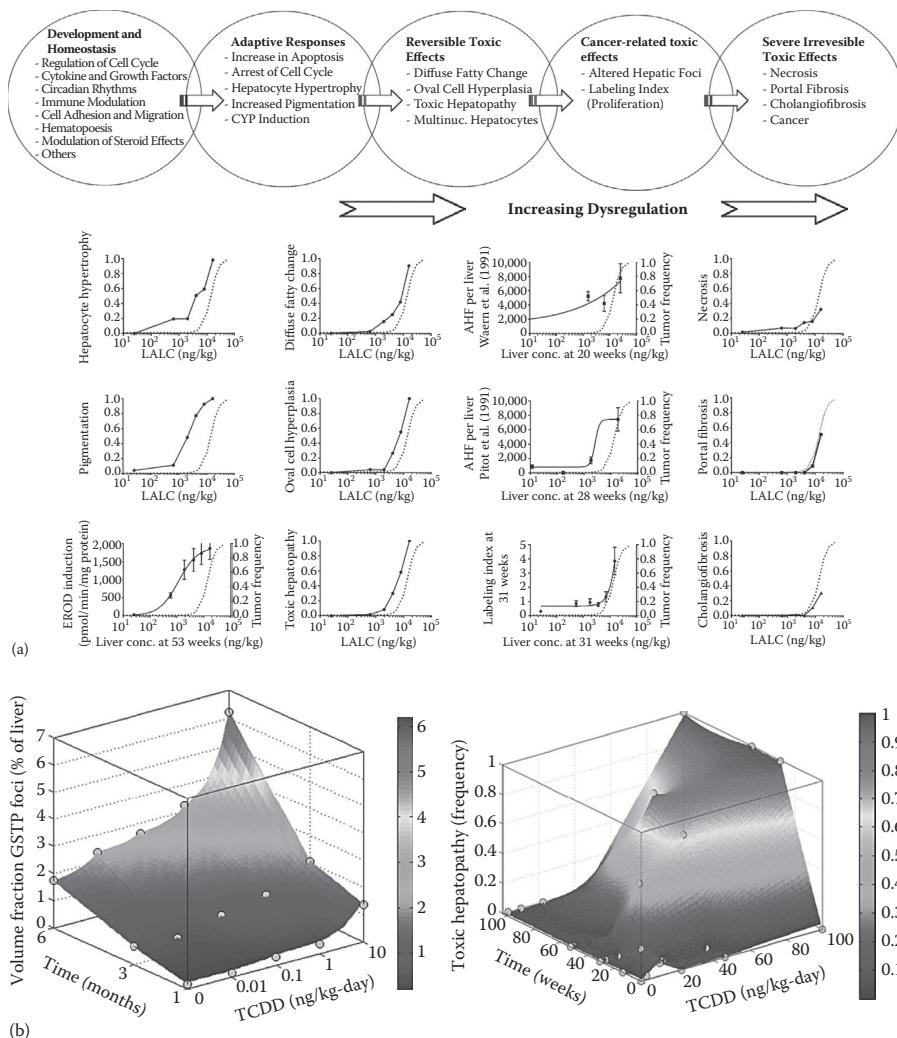
Identifying a key event is based on the confidence one has that this event is necessary for the apical event/adverse outcome and is based on an overall weight of evidence evaluation of qualitative and quantitative aspects of the MOA as well as whether the hypothesized roles of the key events are consistent with the biological basis of the adverse outcome.

The Bradford Hill considerations have been adopted for use in understanding mode of action. Sir Austin Bradford Hill in 1965 termed these “viewpoints” or “features to consider” rather than criteria.<sup>123</sup> Bradford Hill’s considerations are emphatically not a checklist, and necessitate rigorous scientific thinking. They have been quite correctly called “guideposts on the road to common sense.”<sup>120</sup> Hence, the consideration of MOA requires a rigorous and reasoned weight of evidence approach to reach an understanding of the overall mode of action.<sup>124</sup>

Recently, a number of schemes have been developed for assessing the likelihood of two or more hypothesized modes of action. These schemes involve scoring of KEs and KE relationships by scientists familiar with the specific toxicant or endpoint. At present, these quantitative scoring methods are being tested with panels of experts to evaluate their fitness for regulatory use.<sup>125–128</sup>

### 5.3.10 Quantitative Dose–Response Modeling and Key Event Relationships

Examining quantitative dose–response information from as many relevant sources as possible (e.g., human, animal, or *in vitro* data) is often informative about the progression of events within the MOA. Graphic display of the dose–response plots of KEs and of the adverse outcome on similar plots can be helpful for understanding



**Figure 5.2** Dose-response modeling of key events as a way of understanding the MOA. A: Progression of key events in the MOA for TCDD-induced liver tumors in rodents. The dotted line in all plots shows the modeled tumor response. B: Examples of modeling key events in both dose and time. Left: 3D plot of volume fraction of altered GSTP+ hepatic foci in a six-month low-dose study of TCDD. Right: 3D plot of toxic hepatopathy occurring in rats administered TCDD in a two-year bioassay.

with the same dose range on the x-axis in all the plots. An example of such an analysis based on the National Toxicology Program bioassay for 2,3,7,8-tetrachlorodibenzodioxin (TCDD) is shown in Figure 5.2A.<sup>129</sup>

Modeling key events in dose and time may also be useful. Figure 5.2B shows another example based on TCDD. Again, data in both dose and time were available for an early key event, inhibition of apoptosis within altered hepatic foci, and for

another key event, occurring later—toxic hepatopathy. These dose–time relationships helped reach the conclusion that the MOA for both combined liver tumors—cholangiocarcinoma and hepatocellular adenoma—was nonlinear.

### 5.3.11 MOA and High-Throughput *in Vitro* Testing

One of the purposes of the development of adverse outcome pathways is to provide sufficient context and understanding that the data from high-throughput *in vitro* testing assays can be aligned with key events in a mode of action.

Disruption of thyroid function affects most, if not all, of the systems in the body.<sup>130–134</sup> The production of thyroid hormone depends on iodine, and many people in both the developed and developing world do not have sufficient iodine intake.<sup>135–137</sup> In addition, exposures to perchlorate, thiocyanate, and nitrate are ubiquitous in food and drinking water, and these substances block the entry of iodine into the thyroid gland.<sup>138</sup>

Thyroid hormone (TH) acts on all tissues in the body to affect metabolism of food and vitamins, development of the nervous system, and other body functions. The two important enzymes in the production of TH are the sodium/iodide symporter (NIS) that moves iodide into thyroid follicular cells and thyroperoxidase, the enzyme that couples iodine to tyrosine and produces TH.<sup>139,140</sup>

Thyroid hormone homeostasis involves negative feedback to both the hypothalamus in the brain and the pituitary gland, to control synthesis and release of TH from the thyroid. These three together are commonly referred to as the hypothalamic–pituitary–thyroid (HPT) axis.

The secretion of TH by the thyroid is directly modulated by the action of thyroid-stimulating hormone (TSH). The paraventricular nucleus in the hypothalamus at the base of the brain produces thyrotropin-releasing hormone (TRH), a tripeptide, which is transported to the pituitary gland. TRH stimulates the pituitary gland to produce thyroid stimulating hormone (TSH) or thyrotropin, a 30 kD glycoprotein. TSH is released into the general circulation and stimulates the thyroid to produce TH.<sup>141</sup> Secretion of both TRH and TSH is controlled by negative feedback from circulating TH.<sup>142</sup>

In the developed world, all infants are given a heel stick to obtain blood for TSH screening. This testing is performed about 72 hours after birth, to ensure proper thyroid function and to identify those needing further testing to determine whether they might need treatment for congenital hypothyroidism. In adults, either too much or too little TH can produce other adverse effects. Grave's disease is an autoimmune condition that causes the majority of hyperthyroidism.<sup>143</sup> Insufficient intake of iodine and Hashimoto's thyroiditis, another autoimmune disease, are the major causes of hypothyroidism.<sup>144</sup>

As part of the ToxCast™ suite of high-throughput *in vitro* assays, EPA's National Center for Computational Toxicology has developed assays for thyroperoxidase inhibition and a high-throughput pharmacokinetic/pharmacodynamic model to determine the potential health effects of reduced thyroid hormone due to chemicals in food such as thiocyanates from vegetables, triclosan, a disinfectant in personal care

products, and propylthiouracil, a medicine used to treat hyperthyroidism. The complexity of thyroid homeostasis suggests this effort may lead the way in the task of finding ways to develop and contextualize non-animal data<sup>139,145</sup>

## 5.4 ANIMAL TOXICITY TESTING: PAST AND FUTURE

The nature of toxicity testing is clearly undergoing rapid change. The growing realization that high-dose experiments in animals yield little information with which to predict low-dose effects in humans along with concerns for animal welfare and the increasingly prohibitive cost of animal testing have spurred the development of new methods.

Nonetheless, significant challenges remain in the application of these new methods for risk assessment, and traditional animal testing will likely still be conducted for high-profile chemicals.

### 5.4.1 Animal Toxicity Tests

The first assumption upon which animal testing is based is that effects observed in laboratory animals are relevant to humans, with appropriate qualification. The second assumption that has received considerable scrutiny in recent times is that high-dose experiments in laboratory animals are a valid means of hazard identification and that observed effects will also occur in humans. In Chapters 1 and 2, the issues with this assumption about hazard identification were considered in some detail. In this regard, animal toxicity testing cannot demonstrate that a chemical is safe—only what toxic effects could possibly result from exposure. In this section, the nature and methods of some of the available animal bioassays will be considered. This selection is far from complete, and various toxicology texts will provide additional details to these and other assays. The purpose is to provide an idea of the range of studies that can currently be performed to measure specific aspects of biology.

#### 5.4.1.1 Chronic Bioassays

These studies are usually performed in rodents, and can last from six months to two years. Chronic bioassays are used to determine whether a chemical is carcinogenic over the lifetime of the animal, and generally have a duration of two years. Dose selection is critical in these studies. Chronic bioassays are most often performed by the National Toxicology Program. In some studies, many biochemical, histopathological, and other measurements deemed relevant are made in animals sacrificed at interim time points. Doing so requires a large number of animals and significantly increases the cost of the study. However, such information may help to inform the mode of action and may be extremely valuable.

For example, the National Toxicology Program (NTP) bioassay for 2,3,7,8-tetrachlorodibenzodioxin was carefully conducted with interim sacrifices and

measurements of enzyme induction, cell proliferation, and histopathology, and provided a great deal of MOA information (e.g., Figure 5.2).<sup>146</sup> In contrast, the NTP bioassay for hexavalent chromium did not include intermediate sacrifices, and thus presented tumor and histopathology data at two years only. A poor job was done on the Cr(VI) study design, likely because of political pressures—the unfortunate result was that this bioassay actually raised more questions than it answered.<sup>41,147–151</sup>

#### **5.4.1.2 *Developmental and Reproductive Toxicity Testing***

Several types of endpoints are considered in these studies. Teratogenic effects or birth defects may be induced by exposure during development *in utero*. Reproductive toxicology refers to adverse effects on the male or female reproductive system due to exposure to toxins or other stressors. Developmental toxicology refers to adverse effects that interfere with any developmental process in an organism that results from exposure to either or both parents of the organism or to the organism, during either the pre- or post-natal period.

Teratogenic effects occur most often when a chemical is administered during organogenesis in the first trimester of pregnancy. Often, fetuses are removed one day prior to delivery by Caesarian section. The dams are sacrificed and the uterus examined for resorbed dead and live fetuses. Fetal anomalies, usually of the skeleton, are recorded.

In fertility and reproductive performance tests, males are given the agent 60 days prior to mating and the females 14 days prior. Administration continues throughout gestation and the period of lactation. The offspring are assessed up to three weeks of age for their growth, weight, survival, and general condition. In addition, the fraction of females becoming pregnant and the number of stillborn and live offspring are reported.

Multigenerational studies are conducted across three generations. At around 30–40 days of age, rodents are administered the chemical, and dosing continues throughout breeding, gestation, and lactation. These parents are the F0 generation. The offspring, or F1 generation, are also administered the chemical from birth up through breeding, gestation and lactation. For the F2 generation, the number of live births, litter sizes, and viability counts are recorded. Pup weights are also recorded at intervals up to 21 days of age.

#### **5.4.1.3 *Mutation Assays***

The number of types of these toxicity studies is growing rapidly. For example, mutations can be assessed using the PIG-A gene. This X-linked gene codes for cell membrane proteins linked to phosphatidylinositol glycans in hematopoietic cells.<sup>152</sup> Somatic mutations in PIG-A can be measured using polymerase chain reaction or flow cytometry using antibodies specific for the PIG-A gene products. The PIG-A gene has been used to measure the baseline mutation rate in humans and in laboratory animals administered DNA-reactive chemicals.<sup>153,154</sup>

#### 5.4.1.4 Other Types of Testing

A large variety of testing methods are used to assay specific effects. The short-term uterotrophic assay, in which uterine growth is measured in either juvenile or ovariectomized female rodents, is the standard for estrogenicity.<sup>155</sup> For assessing androgens and anti-androgens, the short-term Hershberger assay uses castrated or immature male rodents.<sup>156</sup>

Genotoxicity is the ability of substances to damage DNA and/or cellular components regulating the fidelity of the genome—such as the spindle apparatus, topoisomerases, DNA repair systems, and DNA polymerases. The oldest, least expensive, and least predictive test is the bacterial reverse mutation assay, or Ames Test. The *in vitro* micronucleus test uses mammalian cell lines or cultures of primary human cells and looks for micronuclei or chromosomal aberrations. Micronuclei are infrequent third nuclei formed during cell division that contain chromosome fragments. The dose-dependent frequency of micronuclei suggests potential genotoxicity. *In vivo* genotoxicity tests are most often performed in transgenic animals and look for specific effects depending on the transgenic species.<sup>157</sup>

The type of testing used depends on the investigator's time and resources. Neurobehavioural effects in juvenile rodents and accompanying changes in the morphology of neurons in their brains following *in utero* exposure to various substances are being examined for their ability to predict the potential for autism.<sup>158,159</sup> Whether these approaches are fruitful remains to be seen.

A number of approaches for toxicity testing are available and depend greatly on the data needed. Risk analysts need to be aware of the role of good laboratory practice (GLP) for any toxicity testing for regulatory purposes. In non-clinical research, GLP is a system of audit and control to ensure uniformity, consistency, and integrity of test results.<sup>160</sup>

#### 5.4.2 Threshold of Toxicological Concern: A Simple and Pragmatic Risk-Based Screen That Uses Animal Testing Data

The threshold of toxicological concern (TTC) concept involves the establishment of a dose below which no appreciable risk to human health would be expected. The TTC is defined as the 5th percentile value of the distribution of NOAEL and LOAEL values of a large number of chemicals, to which is applied a safety factor of 100.<sup>161</sup> TTC is a pragmatic risk assessment tool, and has been used for evaluation of food additives, food contact agents, cosmetics, and genotoxic impurities in pharmaceuticals. TTC is a rapid, low-cost computational approach, and enables the appropriate allocation of resources for health risk assessment. TTC was never intended, however, to supplant testing or chemical-specific risk assessment where required.<sup>162–165</sup>

The TTC approach for carcinogenicity data was developed based on a large database of chemical carcinogenicity.<sup>166,167</sup> The TTC approach for non-carcinogens compared structural information of untested chemicals with the toxicological data of chemicals using a decision tree approach.<sup>168</sup> Substances are

classified into one of three categories on the basis of a decision tree containing three question sets:

- Cramer Class I are substances of simple chemical structure with known metabolic pathways and innocuous end products which would suggest a low order of oral toxicity, e.g., butyl alcohol.
- Cramer Class II contains substances that are intermediate, i.e., they possess structures that are less innocuous than in Class I, but they do not contain structural features that are suggestive of toxicity like those of Class III. Members of Class II include compounds such as allyl propionate or methyl 2-octynoate, thus they may contain reactive functional groups.
- Cramer Class III are substances of a chemical structure that permit no strong initial impression of safety and may even suggest a significant toxicity. Examples include benzoin or 2-phenyl-3-carbethoxyfuran.<sup>169</sup>

TTC values are adjusted for body weight and expressed as a daily dose, i.e.,  $\mu\text{g}/\text{day}$ . The TTC values established are:

- Cramer Class I: 1800  $\mu\text{g}/\text{person}/\text{day}$  (30  $\mu\text{g}/\text{kg}/\text{d}$ );
- Cramer Class II: 540  $\mu\text{g}/\text{person}/\text{day}$  (9  $\mu\text{g}/\text{kg}/\text{d}$ );
- Cramer Class III: 90  $\mu\text{g}/\text{person}/\text{day}$  (1.5  $\mu\text{g}/\text{kg}/\text{d}$ ).

Highly potent genotoxic carcinogens include aflatoxin-like, azoxy-, and N-nitroso-compounds, dioxin-like chemicals and steroids, whereas two groups containing substances that were considered nongenotoxic carcinogens—2,3,7,8-dibenzo-p-dioxin (TCDD) and its analogues (dioxins), as well as steroids—were assigned a TTC value 0.15  $\mu\text{g}/\text{person}/\text{day}$ , or 0.0025. For organophosphate and carbamate pesticides, a human exposure threshold of 18  $\mu\text{g}/\text{person}/\text{day}$  was derived. The TTC values in units of per person per day were based on a body mass of 60 kg.

Recently, the TTC approach was used to evaluate the set of heuristic high-throughput exposure estimates for almost 8000 chemicals used in commercial products. Less than 2% of the substances had median exposure estimates greater than the Cramer Class III TTC of 1.5  $\mu\text{g}/\text{kg}/\text{d}$ . For those chemicals identified by their structure as potentially genotoxic, only 79 of the substances had median exposure values greater than the TTC value of 0.0025  $\mu\text{g}/\text{kg}/\text{d}$ , assumed for potent carcinogens.<sup>170</sup>

## 5.5 COMPUTATIONAL METHODS IN HAZARD ASSESSMENT

Computational methods have been applied in toxicology for many years with growing sophistication. In the 1980s, physiologically based pharmacokinetic models were used to predict the distribution of volatile organic chemicals in the body from inhalation exposure. A number of these models were used in risk assessments.<sup>171–174</sup>

Pharmacokinetics is the study of the quantitative relationships between the absorption distribution, metabolism, and elimination (ADME) of chemicals in

biological systems. This study is also called toxicokinetics when applied to toxic chemicals. Pharmacodynamics or toxicodynamics is the study of events at the cellular, biochemical, and molecular levels that occur in response to perturbation by a chemical agent or other stressor.

Mathematical models of ADME of a large number of chemicals have been developed for use in environmental risk assessment and in the pharmaceutical industry. Early models concentrated on the estimation of vapors from volatile organic chemicals.<sup>171,172,175–177</sup> These models range in complexity and are referred to as either physiologically based pharmacokinetic (PBPK) models or physiologically based toxicokinetic (PBTK) models. Recently, biologically based dose–response models have incorporated both toxicokinetics and toxicodynamics. As biological measurements become more sophisticated, the field of systems biology has emerged. Systems biology is the use of mathematical and computational models that may incorporate not only toxicokinetics and toxicodynamics, but also data from bioinformatics, genomics, proteomics, and newer technologies such as chromatin immunoprecipitation (ChIP) or fluorescence resonance energy transfer (FRET), from which the direct interaction of molecules inside cells may be obtained. Organisms, tissues, cells, and molecules are all biological components with dynamic and complex behavior. The description and prediction of this behavior is the field of systems biology.

### **5.5.1 PBPK Modeling**

PBPK modeling was introduced in Chapter 3. For use in risk assessment, the risk analyst needs to select the modeled result—tissue concentration, flux, or chemical across a boundary, amount of metabolite produced, or some other quantity related to the effective dose of the toxic moiety within the target tissue. Finding an appropriate surrogate dose metric may present one of the main challenges in adapting a model for use in risk assessment. Choosing a dose metric is important—this quantity must be related in a quantitative fashion to one or more key events and the adverse outcome being assessed.<sup>178</sup>

PBPK models help greatly to ascertain the dose metric in the target tissue most appropriate for the toxicity being considered. For example, if a particular chemical produces liver toxicity, then oral exposure will likely produce effects at lower administered doses than either dermal or inhalation exposure. The reason is that chemicals absorbed from the gastrointestinal tract enter the hepatic portal system and move first to the liver. Consideration of fat solubility is important as well: highly lipid-soluble chemicals may tend to bioaccumulate in adipose tissue and possibly produce effects on an ongoing basis. The AUC for adipose tissue concentration might be the most appropriate dose metric for such bioaccumulative chemicals. Another chemical might be absorbed by the intestine and thus produce cellular damage in the enterocytes before entering the bloodstream: the example here is hexavalent chromium, and in this case, flux of the chemical from the intestinal lumen into the tissue would be an appropriate dose metric.<sup>179,180</sup>

### **5.5.1.1 An Early PBPK Model Is Still Used for Risk Assessment of Lead**

Early in its history, EPA recognized that children were exposed to lead through a variety of environmental media and exposure routes. To account for multi-media exposures (e.g., air, water, food, and soil), a model of lead pharmacokinetics would be needed. Hence, Alan Marcus of EPA created a set of lead PBPK models during the 1980s.<sup>181–184</sup> Other PBPK models of lead in children were also developed around this time.<sup>185–188</sup>

At the same time, evidence was mounting that exposure to lead affected mental and social development of children, and there was no evidence of a threshold for these effects.<sup>189,190</sup> Until recently, the US Centers of Disease Control provided an action level for blood lead in children of 10 µg/dL for continued monitoring. However, in 2012, this action level was reduced to 5 µg/dL because research since the 1980s has not revealed a blood lead level in children without effect.<sup>191–193</sup>

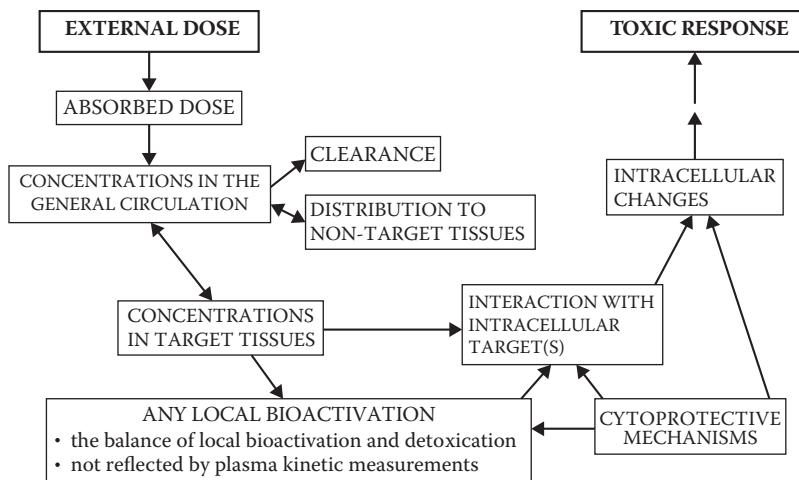
The mode of action for the neurodevelopmental effects of lead likely involves disruption of synaptic transmission changes in calcium homeostasis via a number of mechanisms, leading to alterations in the development of neural networks in the developing brain. Both the complexity of these mechanisms and their individual variability likely contribute to the inability to observe a threshold.<sup>194–198</sup>

In the 1980s, EPA developed the Integrated Uptake Biokinetic model to assess multimedia lead exposure in children. This model is still used, and is one of the successful pharmacokinetic models in risk assessment.

### **5.5.2 Toxicodynamics**

Toxicodynamics is the consideration of how a xenobiotic chemical interacts with tissues, cells, or biomolecules as part of the toxic response. Once a chemical distributes to the target tissue via ADME processes, it interacts with cells of that tissue to produce effects. For example, the binding of a DNA-reactive chemical to nucleic acid would be a toxicodynamic process. The initial biochemical event has been referred to as the molecular initiating event.<sup>199</sup> This toxicodynamic event will certainly be a key event in the mode of action. Some risk analysts consider the MIE as too strong a term when insufficient evidence is available to link this presumably first biochemical event to downstream KEs; hence, the term initial molecular event may be more apt.

The difference between toxicodynamics and toxicokinetics is evident in a very recent risk assessment of the organophosphate (OP) pesticide chlorpyrifos. The MOA for OPs is well known— inhibition of cholinesterases, with toxicity manifested as central and peripheral cholinergic effects.<sup>200</sup> Thionophosphorus OPs such as chlorpyrifos do not directly inhibit acetyl cholinesterase (AChE), but must first be metabolized to the oxygen analog, or oxon, by CYP450 mixed-function oxidases, mainly occurring in the liver. Paraoxonase 1 (PON1) is an arylesterase that metabolizes organophosphate compounds. Chlorpyrifos oxon is inactivated by the enzyme paraoxonase (PON1) in the liver and other tissues.<sup>201,202</sup> Genetic polymorphisms exist in the PON1 gene, and lifestyle factors such as the use of cholesterol-lowering medications and alcohol consumption may increase PON1 activity.<sup>203–206</sup>



**Figure 5.3** Schematic of processes underlying a toxic response.

The chlorpyrifos risk assessment used a biologically based dose–response model that incorporated both the toxicokinetics of chlorpyrifos and its toxicodynamics in terms of cholinesterase inhibition. However, the daily intake of chlorpyrifos has been estimated at less than 11 ng/kg/d in adults and 3.4 ng/kg/d in children. In 3-year-old children, the greatest reduction in cholinesterase activity for typical dietary intake was 0.001%. In addition, the intakes were too low for genetic or lifestyle variations in sensitivity to have an effect.<sup>207,208</sup>

The value of this example is that it clearly shows the difference between toxicokinetics and toxicodynamics. The interaction of chlorpyrifos oxon with cholinesterase would be represented by the boxes on the right of Figure 5.3, whereas the ADME considerations would be on the left.

### 5.5.3 Structure–Activity Relationships/Quantitative Structure–Activity Relationships

Structure–activity relationships/quantitative structure–activity relationships ((Q)SAR) include computational methods that use chemical properties to predict toxicity. These provide a means of estimating toxicity without animal or *in vitro* testing. The Organisation of Economic Cooperation and Development has embraced (Q)SAR as one means of addressing the large number of untested chemicals in commerce.

The OECD Validation Principles for (Q)SAR both provide a useful framework for interpreting (Q)SAR information in the context of regulatory purposes and offer a comparable and additional perspective of how to validate and interpret assays and data from emerging technologies.<sup>209</sup>

The five (Q)SAR validation principles are as follows:

1. a defined endpoint;
2. an unambiguous algorithm;
3. a defined domain of applicability;
4. appropriate measures of goodness of fit, robustness, and predictivity;
5. a mechanistic interpretation, if possible.

(Q)SAR provides a means to understand the link between chemical structure and biological activity as a means for preliminary screening of chemicals.<sup>210,211</sup> The field has grown considerably, with increasing reliance on data mining, statistics, and artificial intelligence. As part of an overall strategy to address chemical hazards, prediction models need to be validated whether these models are based on chemical properties or *in vitro* testing results.<sup>212</sup>

#### 5.5.4 Read-Across

Read-across assumes that chemical structure determines toxicity, and in the analog approach, the method uses data from one or two tested chemicals to predict the toxicity of an untested chemical. In the category approach, read-across uses chemical category with a number of tested chemicals and trends in the chemical properties to increase the confidence in the toxicity predictions for the untested chemicals.<sup>213,214</sup> A necessary part of read-across is the identification of analogs or categories.<sup>215,216</sup>

As experience with systems biology and computational modeling increases, the number of computational methods for predicting toxicity will likely increase as well. The OECD QSAR validation principles at present provide a common platform for assessing the confidence in the prediction of these models.<sup>209</sup>

The number of chemical characteristics is huge. Thus, QSAR models may be overfit. QSAR predictions may be based on either statistical modeling, a knowledge-based system, or a hybrid of these two approaches. For a given endpoint, QSAR predictions of toxicity need to be validated against an accepted traditional assay. For example, predictions of estrogenic activity based on structure or similarity to other substances need to be validated against the uterotrophic assay.<sup>155,217</sup> Because of the ban on animal testing for cosmetics in the European Union, any read-across or QSAR method for cosmetic ingredients will require validation, likely by comparison to the local lymph node assay or the guinea pig maximization test.<sup>218,219</sup>

### 5.6 DERIVING TOXICITY REFERENCE VALUES: POINT OF DEPARTURE, LOW-DOSE EXTRAPOLATION, AND SPECIES EXTRAPOLATION

Elucidating and understanding the MOA enables one to determine the type of regulatory toxicity factor to develop—linear or nonlinear—depending on the method of low-dose extrapolation. In addition to these characteristics, the route of exposure—oral, inhalation, or dermal—also determines the type of toxicity factor

developed. For each critical adverse health effect, MOA is used to determine whether the dose–response relationship in the low-dose region is threshold or non-threshold. Box 5.1 provides definitions needed for this section.

### 5.6.1 Reference Values and Tolerable Daily Intakes

The general method of determining nonlinear toxicity factors is to obtain a point of departure (POD) from the dose–response relationship. The POD is that point on the dose–response curve that marks the upper end of the low-dose region and thus the starting point for low-dose extrapolation. The POD should be based on the lowest dose at which an adverse effect is observed and should be within the range of observation. Not all effects are necessarily adverse: for example, exposure to a chemical may result in enzyme induction that may actually be an adaptive response.

#### BOX 5.1 DOSE-RESPONSE CHARACTERISTICS AND DEFINITIONS

*Low-dose region:* The dose range below the lowest experimental dose. The shape of the dose–response relationship in the low-dose region is unknown, and must be presumed.

*Point of departure (POD):* The POD is that point on the dose–response curve from which low-dose extrapolation is performed. Often, the POD for dichotomous effects such as cancer is a 10% response level. For continuous effects, the POD should be a level that reflects a level of response known to be adverse.

*Threshold:* The dose or exposure below with no adverse or deleterious effect is expected to occur.

*Nonlinear dose response:* This type of response shows a pattern of frequency or severity that does not vary directly with dose. If the dose–response relationship for a given chemical is nonlinear, a threshold will likely be observed such that doses below the threshold are not expected to cause adverse effects. Chemicals that produce effects other than cancer are called systemic toxicants and typically exhibit nonlinear dose–response relationships. MOA information indicates that some carcinogens also exhibit a nonlinear dose response.

*Linear dose response:* This type of response shows a pattern of frequency or severity that varies directly with dose. Carcinogens have typically been assumed to exhibit a linear dose response in the low-dose region. If the dose–response relationship of a chemical is assumed to be linear, the presumption is that no threshold exists, meaning that any dose, even as small as a single molecule, produces an increase in the probability of a response.

*No observed adverse effect level (NOAEL):* The highest dose or concentration at which there are no biologically or statistically significant increases in the frequency or severity of an adverse effect over background.

*Lowest observed adverse effect level (LOAEL):* The lowest dose or exposure concentration at which increases in the frequency or severity of adverse effects occur. These increases should be both biologically and statistically significant.

*Benchmark dose or benchmark concentration (BMD or BMC):* A dose or concentration that produces a predetermined level of an adverse response defined by the point of departure.

*BMDL or BMCL:* The statistical lower confidence limit on the dose or concentration at the BMD, generally at the 95% level of confidence.

*Reference value:* An estimate of an exposure, designated by duration and route, to the human population, including susceptible subgroups, that is likely to be without an appreciable risk of adverse health effects over a lifetime.

*Reference dose (RfD):* An estimate of oral exposure (with uncertainty spanning perhaps an order of magnitude or greater) of a daily oral exposure level for the human population, including sensitive subpopulations, that is likely to be without an appreciable risk of deleterious effects during a lifetime. Reference doses may be developed for chronic, subchronic, or acute durations. RfD is expressed in units of dose, generally mg/kg BW/day.

*Reference concentration (RfC):* An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects during a lifetime. RfCs are expressed in units of concentration, generally mg/m<sup>3</sup>.

*Cancer slope factor (CSF):* An upper-bound estimate of the probability of developing cancers per unit intake of a chemical over a lifetime. CSFs are used to estimate the upper-bound probability of an individual developing cancer resulting from a lifetime of exposure to a particular dose of a potential carcinogen. CSFs result from the application of linear low-dose extrapolation and are expressed in units of risk per dose, or (mg/kg/d)<sup>-1</sup>.

*Inhalation unit risk (IUR):* The upper-bound excess lifetime cancer risk estimated to result from continuous exposure to a chemical at a concentration of 1 µg/m<sup>3</sup> in air, expressed in units of (µg/m<sup>3</sup>)<sup>-1</sup>.

### **5.6.1.1 Choosing a Point of Departure for Threshold Effects**

Choosing a POD is an absolute requirement for proceeding with dose-response assessment. Yet the choice is dependent on the definition of adversity. EPA defines an adverse effect as “resulting in functional impairment and/or pathological lesions that may affect the performance of the whole organism, or that reduces an organism’s ability to respond to an additional challenge.”<sup>220</sup>

The POD can be a NOAEL, a LOAEL, or a BMDL, as defined in Boxes 5.1 and 5.2. It is important to ensure the LOAEL or BMDL are based on truly adverse effects. Generally, the LOAEL will be the lowest exposure at which adverse events occur that are both statistically different in severity or frequency than background and biologically significant.

The approach of using NOAELs or LOAELs as the POD has been criticized because only a single value is used rather than the entire set of dose-response data.<sup>221–225</sup> In addition, the values of the NOAEL are dependent on study design and the doses chosen. Hence, some studies can only identify a LOAEL—a so-called “hanging” LOAEL because the value of the unknown NOAEL could be as low as zero. Multiple studies may provide a range of NOAEL and LOAEL values.<sup>226</sup>

For dichotomous data, the POD is a chosen frequency of the critical effect. Most often, the value of 10% is chosen because it is about the lowest value that can be statistically distinguished from background.<sup>227</sup> For continuous data, EPA suggests the default BMD be one standard deviation above the mean of the controls, but this level should be interpreted in terms of biological significance as well.<sup>228–230</sup> The need for biological significance was also recognized in the redefinition of the benchmark response (BMR) for continuous data as the “critical effect size.”<sup>231–233</sup>

To understand adversity, the distinction between biological and statistical significance must be considered. For an effect to be biologically significant, it should have a substantial or noteworthy effect on the well-being of the organism. Care is urged when relating a statistical finding to a truly adverse biological effect.<sup>234</sup> The term “adversity” implies some impairment of functions or development of pathology that affects the performance of the organism or reduces the organism’s capability to withstand additional stressors.<sup>235</sup>

Prior to the explosion of knowledge of the biological basis of health and disease that began around 2000, EPA’s Integrated Risk Information System (IRIS) program would, as a matter of science policy, identify a critical effect as that effect occurring at the lowest dose, and would select the study using the most sensitive species as the critical study.<sup>†</sup> From these data, the NOAEL and LOAEL would be selected. These two values are experimental bounds on the unknown threshold.

The difficulty in determining adversity can be illustrated by EPA’s IRIS database entry for the pesticide oxadiazon ([https://cfpub.epa.gov/ncea/iris/iris\\_documents/documents/subst/0253\\_summary.pdf#nameddest=rfd](https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0253_summary.pdf#nameddest=rfd)). Rats were administered diets containing 0, 10, 100, 1000, or 3000 parts per million (ppm) oxadiazon. At a dietary concentration of 100 ppm, increased levels of serum proteins in 18% of females and increased liver weights in 31% of both sexes were observed, and these were chosen as the critical effect. The NOAEL was 10 ppm and the LOAEL was 100 ppm. At 1000 ppm, hepatotoxicity, hemolytic anemia, and kidney effects were observed. Were the serum protein changes and increase in liver weights in the minority of animals

<sup>†</sup> The IRIS program within the National Center for Environmental Assessment at EPA headquarters develops toxicity criteria used by many programs within EPA.

tested truly an adverse effect? Perhaps these represented an adaptive or compensatory response within the biological capacity of the animals. Certainly, hepatotoxicity and anemia are adverse. Perhaps these higher-dose effects would be more appropriately chosen as adverse rather than adaptive effects. Compare these effects with the critical effect of mortality chosen for dibutyl phthalate ([https://cfpub.epa.gov/ncea/iris/documents/documents/subst/0038\\_summary.pdf#nameddest=efd](https://cfpub.epa.gov/ncea/iris/documents/documents/subst/0038_summary.pdf#nameddest=efd)). Which effect do you think is truly adverse?

The determination of adversity became such a flashpoint that in 2007, the Agency for Toxic Substances and Disease Registry (ATSDR) of the Centers for Disease Control provided a classification of endpoints as non-adverse, less serious, and serious.<sup>236</sup> In 2015, the Texas Commission on Environmental Quality modified this list, as shown in Table 5.3.<sup>237</sup>

#### **5.6.1.2 Dose–Response Modeling for Threshold Continuous Effects**

The benchmark dose approach was proposed as an alternative to the NOAEL/LOAEL approach in response to the issue mentioned above.<sup>226</sup> In BMD modeling, an empirical mathematical model is fit to the entire dose–response data for a chemical. The BMD corresponding to a prescribed level of response (benchmark response) and the statistical lower limit on the BMD (BMDL) are determined; generally, the BMDL is used as the POD.

Because predicting the dose–response relationship in the low-dose region is the focus of the modeling, the lowest POD that is within the range of observation, i.e., somewhere above the lowest dose, should be used.<sup>23</sup> The lower plot in Figure 5.4 shows an idealized dose–response curve and the details of linear extrapolation from the BMDL. The use of the BMDL is a protective approach that depends on the statistical uncertainty in the BMD and provides an unknown degree of conservatism in the assessment.

**Table 5.3 Classification of Endpoints by ATSDR and the Texas Commission on Environmental Quality**

Classification	Endpoint
Non-Adverse Effects	Weight loss or decrease in body weight gain of less than 10% in adult animals
	Weight loss or decrease in body weight gain in less than 5% in fetuses
	Changes in organ weight of non-target organ tissues that are not associated with abnormal morphologic or biochemical changes
	Increased mortality over controls that is not statistically significant ( $p > 0.05$ )
	Some adaptive responses

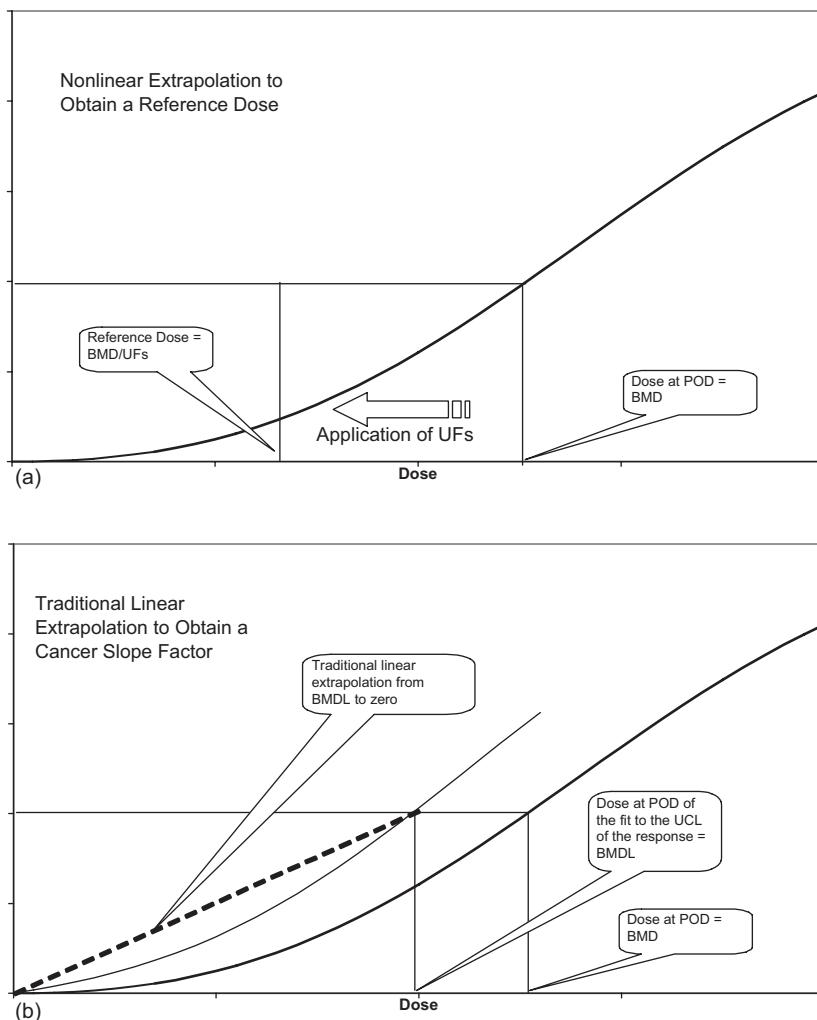
*(Continued)*

Table 5.3 (Continued)

Classification	Endpoint
Less Serious Effects	Reversible cellular alterations at the ultrastructural level (e.g., dilated endoplasmic reticulum, loss of microvilli, myelin figures) and at the light-microscopy level (e.g., cloudy swelling, hydropic degeneration, fatty change)
	Mild necrosis (dependent upon location, distribution, and magnitude), metaplasia, or atrophy with no apparent decrement of organ function
	Mild to moderate serum chemistry changes (e.g., increased 1–3 and 3–20 times the normal ranges of serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) are considered mild and moderate, respectively)
	Organ weight change in known target organ tissue that is not associated with morphologic or biochemical alterations
	Mild behavioral effects as measured by behavioral function tests
	Weight loss or decrease in body weight gain of 10–19% (assuming normal food consumption and when weight loss is due to a systemic effect of toxicant)
	Some adaptive responses (e.g., hepatic CYP p-450 induction)
	Death
	Clinical effects of significant organ impairment (e.g., convulsions, icterus, cyanosis)
	Moderate to severe morphologic changes (such as necrosis, metaplasia, or atrophy) in organ tissues that could result in severe dysfunction (e.g., marked necrosis of hepatocytes or renal tubules)
Serious Effects	Moderate to major behavioral effects as measured by behavioral function tests
	Weight loss or decrease in body weight gain of 20% or greater (assuming normal food consumption)
	Major serum chemistry changes (e.g., increased > 20 times the normal ranges of SGOT and SGPT)
	Major metabolic effects (e.g., ketosis, acidosis, alkalosis)
	Cancer effects

Because BMD modeling uses all the data, this method can reduce uncertainty due to small sample sizes. BMDL values are generally comparable to NOAELs.<sup>221–223,226,227,229,233,238–245</sup>

The nature of the data collected during the study and the quality of the experimental study both determine whether the data are amenable to modeling. Since the mid-1990s, EPA has provided BMDS software to perform benchmark dose modeling and guidance on dose–response modeling.<sup>246–248</sup> This software uses a range of models and determines parameters by maximum likelihood estimation. In 2000, EPA released an external review draft of the *Benchmark Dose Technical Guidance Document*. This draft was finalized in 2012, including additional information.<sup>247</sup>



**Figure 5.4** Nonlinear versus linear low-dose extrapolation. The upper panel shows the procedure for nonlinear extrapolation in which uncertainty factors are applied to a point of departure. The point of departure may be a no observed adverse effect level (NOAEL) or a lowest observed adverse effect level (LOAEL). In dose-response modeling such as that in EPA's Benchmark Dose Software, the POD may be the dose corresponding to a specific response benchmark, i.e., the benchmark dose. The lower panel shows the procedure for linear extrapolation in which the slope of the line from the lower confidence limit on the benchmark dose and the corresponding POD to the origin at zero dose and zero response is used as an estimate of the risk of exposure in the low-dose region.

EPA continues to provide updates to BMDS, and the current version is 3.1. For many years, BMDS was maintained by Dr. R. Woodrow Setzer. Upon his recent retirement, BMDS was completely rewritten with an Excel interface; the current EPA scientists who maintain BMDS are Dr. Jeff Gift, Dr. Todd Blessinger, and

Mr. J. Allen Davis. The software is in transition, with the goal of incorporating a Bayesian inferential approach. BMDS 3.1 runs as an Excel macro under Windows 10. As of May 2019, the user manual was not complete and using BMDS is a challenge. EPA's webpage at [www.epa.gov/bmds/benchmark-dose-software-bmds-version-3-support-articles](http://www.epa.gov/bmds/benchmark-dose-software-bmds-version-3-support-articles) describes some of the difficulties with the latest version of BMDS. These problems notwithstanding, EPA has a long history of providing excellent support for benchmark dose modeling, and the expectation is that the user manual will be updated.

A competing software package to BMDS is PROAST available from the Dutch National Institute for Public Health and the Environment (RIVM). PROAST is available as an R package in three versions—a menu-driven version, a GUI version, and a web version. The web version is the least user-unfriendly; the menu-driven R version in which the user answers a series of choices is the most flexible, but not at all user-friendly. You can access PROAST at <https://proastweb.rivm.nl/>. Unfortunately, the web version of PROAST does not provide sufficient guidance for users as did earlier versions of EPA's BMDS.

One of the major conceptual differences between PROAST and BMDS is the assumption in PROAST that responses are lognormally distributed; BMDS assumes a normal distribution for responses. Summarized data are generally reported as arithmetic means and arithmetic standard deviations. Transforming these to the counterparts in log space will not produce the same result as fitting a lognormal distribution to the original data, and may cause difficulties in obtaining a useable fit.<sup>249</sup>

Dr. Kan Shao of Indiana University has fortunately created a web application that performs Bayesian benchmark dose modeling at <https://benchmarkdose.org>. This application uses the Python computing language and Andrew Gelman's Bayesian computation package STAN to obtain distributions for BMDs for both quantal and continuous data. The application will also derive reference doses using Bayesian methods for application of uncertainty factors. The web interface is intuitive and easy to use. A user guide with worked examples is provided.

The traditional reference dose will likely be around for years. Based on *Science and Decisions: Advancing Risk Assessment* from the National Academies of Sciences (NAS), a more complete characterization of the health impact of chemical exposure could be obtained by disaggregating risk into three components: severity or magnitude of effect, population incidence at this degree of severity, and overall uncertainty.<sup>250</sup> Hence, the concept of the RfD is changing. The new idea is a human dose associated with a given magnitude or severity (M) and a specified population incidence, and has been defined and described in guidance from the World Health Organization and in the scientific literature.<sup>225,251,252</sup>

### **5.6.1.3 Dose–Response Models Used for Continuous Responses**

Table 5.4 provides the equations for continuous responses used in BMDS and PROAST. These are empirical equations without a biological basis that have been used for many years, and will fit most dose–response patterns observed in animal testing.

**Table 5.4 Dose–Response Models for Continuous Responses**

Model Type	Equation	Constraints
Polynomial	$y(dose) = \beta_0 + \beta_1 dose + \beta_2 dose^2 + \dots + \beta_n dose^n$	none
Power	$y(dose) = \gamma + \beta dose^\delta$	$0 < \gamma > 1, \beta \geq 0$
Hill	$y(dose) = \gamma + \frac{\nu dose^n}{k^n + dose^n}$	$\nu \geq 0, k > 0, 0 < n \leq 18$
Exponential 2	$y(dose) = \nu \exp(\beta dose)$	$\nu > 0$
Exponential 3	$y(dose) = \nu \exp(\beta dose^\delta)$	$\nu > 0, \delta \geq 1$ or preset lower limit
Exponential 4	$y(dose) = \nu [\gamma - (\gamma - 1) \exp(-\beta dose)]$	$\nu, \gamma, \beta > 0$
Exponential 5	$y(dose) = \nu [\gamma - (\gamma - 1) \exp(-(\beta dose)^\delta)]$	$\nu, \gamma, \beta > 0, \delta \geq 1$ or preset lower limit

#### 5.6.1.4 Traditional Application of Uncertainty Factors

Uncertainty factors are used to extrapolate from the POD to lower doses to account for a number of uncertainties inherent in the assessment. UFs are intended to account for:

- unknown variation in sensitivity among the members of the human population (intraspecies variability);
- uncertainty in extrapolating animal data to humans (interspecies variability);
- uncertainty in extrapolating from data obtained in a shorter term study to lifetime exposure (subchronic to chronic);
- uncertainty in extrapolating from an LOAEL rather than from an NOAEL;
- uncertainty associated with extrapolation from animal data when the toxicity data-base is incomplete.

The default value of each of these UFs is 10.<sup>†</sup> These values are based on an initial estimate from the US Food and Drug Administration, suggesting that acceptable daily intakes for contaminants in food should be based on a chronic animal no observable effect level or NOAEL divided by a 100-fold uncertainty factor. This 100-fold factor was intended to account for both intraspecies and interspecies variability as well as possible synergistic effects between the many intentional or unintentional food additives or contaminants in the human diet.<sup>253–255</sup>

The majority of work on the conceptual development of UFs was accomplished by Dr. Michael Dourson, who began his career at EPA and later founded Toxicology

<sup>†</sup> The reason for this is the same that for the emergence of mathematics based on a decimal system—humans have ten fingers! A waggish toxicologist once stood up at a symposium on UFs and held his hands in the air with only three fingers extended. He then claimed he was Zorg from the planet Krypton, and that he believed the default UF should be 6!

Excellence in Risk Assessment, an independent non-profit organization whose mission is to foster scientific collaboration and transparency in support of the science underlying risk assessment. Dourson attempted to refine the scientific basis of uncertainty factors.<sup>256,257</sup> During the same period of time, European scientists, also dismayed at the lack of a science basis for UFs, were attempting to provide this basis.<sup>163,258–271</sup> These scientists recognized that both interspecies and intraspecies UFs could be split into toxicokinetic and toxicodynamic components. The interspecies UF was split into factors of 4 and 2.5 to account for TK and TD respectively; the intraspecies UF was split into two equal factors of 3.16 ( $\sqrt{10}$ ).<sup>272</sup>

This recognition enabled the extensive use of PBTK models in risk assessment for species extrapolation—with such use, only the toxicodynamic portion of the UF would need to be applied.

In 2001, the International Programme on Chemical Safety of the World Health Organization published guidance on chemical-specific adjustment factors, and in 2011, EPA's Risk Assessment Forum published draft guidance on data-derived extrapolation factors. These documents were quite similar and provided guidance on the use of data to derive chemical-specific values for the interspecies and intraspecies UFs.<sup>273,274</sup>

#### **5.6.1.5 Bayesian Methods for Application of Uncertainty Factors**

In 2014, the National Research Council published its *Review of EPA's Integrated Risk Information System (IRIS) Process* that considers methods EPA uses for developing toxicity criteria for continuous dose–response data, generally associated with systemic toxicants. These criteria are the reference dose for oral exposure and reference concentration for inhalation exposure. The NRC review suggested using Bayesian methods for application of uncertainty factors to adjust the point of departure dose or concentration to a level considered to be without adverse effects for the human population. The NRC foresaw that Bayesian methods would be potentially useful for combining toxicity data from disparate sources—high-throughput assays, animal testing, and observational epidemiology. UFs represent five distinct areas for which both adjustment and consideration of uncertainty may be needed. The NRC suggested UFs could be represented as Bayesian prior distributions, illustrated the use of a lognormal distribution to represent the composite UF, and combined this distribution with a lognormal distribution representing uncertainty in the point of departure to reflect the overall uncertainty. Here, we explore these suggestions and present a refinement of the methodology suggested by the NRC that considers each individual UF as a distribution.<sup>275</sup>

When NOAELs or LOAELs are used as PODs, their value is unavoidably skewed by study design; the BMD or BMDL as a point estimate of the POD is also imprecise. Toxicological responses follow the laws of thermodynamics, and logarithms are the most appropriate expression of dose.<sup>276–279</sup> When the sample size of the underlying study is sufficiently large, by the central limit theorem, the maximum likelihood estimator of the BMD will approximate a normal distribution; this normal approximation is also the case for this estimator of the POD on a logarithmic scale.

In practice, the use of lognormal distributions is robust against variation skewed toward the heavy right tail when the sample size is small to moderate because lognormal distributions have a lower bound of zero. Hence, using normal distributions of the BMD is not advisable in practice because substantial bias would occur in estimating BMDLs, especially in small datasets.<sup>247,280</sup>

Within a Bayesian framework, each individual UF is represented by a prior distribution with a mean and variance. The general assumption about the default values for UFs is that they are protective at the 95% level. Mathematically, dividing the POD by an UF of 1 is equivalent to subtracting zero from the logarithm of the POD; hence, the log mean of UF distributions is 0. The 95th percentile of the UF distribution corresponding to a default value of 10 would be 10, and the log standard deviation would be 1.4. For the default of 3, the corresponding log standard deviation would be 0.668.\* The composite UF includes the uncertainty in the BMD as well as the UFs.<sup>281</sup>

$$\sigma_{combined} = \sqrt{\sigma_{BMD}^2 + \sigma_{UFS}^2 + \sigma_{UFL}^2 + \sigma_{UFA}^2 + \sigma_{UFH}^2 + \sigma_{UFD}^2} \quad (5.1)$$

Benchmark dose modeling platforms either provide distributional parameters for the BMD or the value of both the BMD and BMDL. The log standard deviation of the POD can be calculated as:

$$\sigma_{POD} = \frac{\log(BMD) - \log(BMDL)}{abs(Z_\alpha)} \quad (5.2)$$

where  $Z_\alpha$  = Z-score at BMDL percentile, i.e.,  $Z_{\alpha=0.05} = -1.645$

The reference dose is calculated as:

$$RfD = \exp\left(\log(BMD) - Z_\alpha \sqrt{\sigma_{BMD}^2 + \sigma_{UFS}^2 + \sigma_{UFL}^2 + \sigma_{UFA}^2 + \sigma_{UFH}^2 + \sigma_{UFD}^2}\right) \quad (5.3)$$

Box 5.2 provides an example of RfD derivation using traditional and Bayesian methods.

### 5.6.2 Cancer Slope Factors and Inhalation Unit Risks

A linear dose response is an artificial construct associated with the linear no-threshold hypothesis. This precautionary approach is not based on any science; rather, it represents a policy that attempts to address the fact that the shape of the dose-response relationship in the low-dose region is unknown.

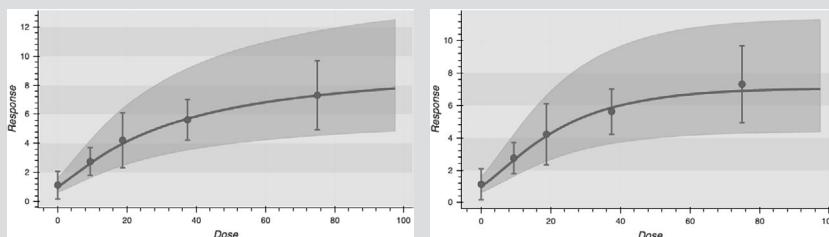
\* You can check these values yourself—the exponentiation of the Z-score at 0.95 or 1.645 multiplied by the log standard deviation will equal the default value of the UF. So  $\exp(1.645 \times 1.4) = 10$  and  $\exp(1.645 \times 0.668) = 3$ .

### BOX 5.2 DERIVATION OF A REFERENCE DOSE USING TWO METHODS

Nitrobenzene produces methemoglobinemia, in which red blood cells have a decreased oxygen-carrying capacity due to the formation of methemoglobin (MetHb) from hemoglobin. MetHb is normally maintained at <1% of total Hb by NADH-diaphorase. Premature babies and individuals with chronic congenital methemoglobinemia due to an inherited deficiency in this enzyme are especially susceptible to metHb-generating chemicals, such as nitrate or nitrobenzene. In humans, cyanosis or other clinical symptoms become apparent at metHb levels of 6–10%.

Male rats were exposed to doses of 0, 9.38, 18.75, 37.5, and 75 mg/kg/d. Values (mean  $\pm$  SD) for % metHb were  $1.13 \pm 0.58$ ,  $2.75 \pm 0.58$ ,  $4.22 \pm 1.15$ ,  $5.62 \pm 0.85$ , and  $7.31 \pm 1.44$ . These data were fitted to a variety of models for continuous (as opposed to quantal) responses using the Dr. Kan Shao's app at <https://benchmarkdose.org>.

The two best-fitting models were the Hill model (left) and the 5-parameter exponential model (right), with the corresponding equations shown below.



$$f(\text{dose}) = a + \frac{b \times \text{dose}^g}{c^g + \text{dose}^g}$$

$$f(\text{dose}) = a \times [c - (c-1) \times e^{-(b \times \text{dose})^g}]$$

Model	Post-Prediction p-value	Model Weight	BMD (mg/kg-d)	BMDL (5th percentile)
Hill	0.404	53.1%	4.14	2.90
Exponential-5	0.399	46.9%	4.32	3.13
Model Average	NA	NA	4.28	3.37

The use of Bayesian model averaging accounts for the increase in the BMDL with reduction in uncertainty with increasing information.

To derive a traditional RfD, the Hill model results and a combined UF of 300 were used. The UFs represented animal-to-human extrapolation (10),

intraspecies extrapolation (10) and subchronic to chronic extrapolation (3). The resulting RfD was 0.01 mg/kg/d.

Bayesian application of UFs with values using log SD values of 1.4, 1.4, and 0.668 for the three UFs and 0.145 for the log SD of the BMD was carried out as follows:

$$RfD = \log(BMD) - Z_{p=0.05} \sqrt{\sigma_{BMD}^2 + \sigma_{UFA}^2 + \sigma_{UFH}^2 + \sigma_{UFSC}^2}$$

The resulting RfD from Bayesian application of UFs is 0.5 mg/kg/d. A useful exercise would be to repeat these calculations at <https://benchmarkdose.org> and compare the RfD values calculated here to the  $HD_M^1$  (human dose producing a given effect magnitude and at a given population incidence) value on the web application.

Since 1977, the practice of cancer risk assessment has been to use linear low-dose extrapolation to predict cancer risk at the regulatory target of 1 in 1,000,000 based on the observed cancer incidence in high-dose animal experiments. Low-dose extrapolation is necessitated by the limited number of animals in a standard cancer bioassay, typically 50 per dose group, a number sufficient to detect a 10% risk of cancer with a measure of statistical confidence, but not nearly enough to meet the regulatory target risk of 1 in 1,000,000. As noted earlier, the primary and biologically incorrect assumption of linear low-dose extrapolation is that even a single molecule—an amount obviously too tiny to measure—will still pose a quantifiable risk of cancer. This has become known as the LNT hypothesis.

The LNT became accepted as the norm for cancer risk assessment during the second half of the 20th century and persists today. The reason is likely a statement made by Hermann J. Muller in his Nobel Prize acceptance speech on December 12, 1946.

Muller was a pioneer in radiation genetics, and in 1926 he examined the use of radiation in producing mutations in fruit flies. Although others had tried radiation earlier, Muller was the first to be successful in inducing mutations and rushed his work into publication without presenting his data in 1927. At the same time, Lewis J. Stadler used radiation as a mutagen in corn, but Muller published a few months earlier and established priority. Later in 1927, Muller presented the data in detail at the International Congress of Genetics in Berlin and returned to the US with international scientific stature. Even as a doctoral student at Columbia, Muller was a “priority hog” and had difficulty crediting others for having their own ideas. He appeared to be insecure, jealous of his fellow graduate students, and reluctant to share his insights with them.<sup>282</sup>

In his Nobel address, Muller argued that the dose response for radiation-induced mutations was linear and there was “no escape from the conclusion that there is no threshold.” A recent examination of the letters between Muller and his colleagues Ernst Caspary and Curt Stern indicates that Muller was deceptive in his lecture, possibly because of a precautionary philosophy, possibly to protect his scientific reputation.<sup>283</sup> At the time of Muller’s speech, correspondence reveals that he knew about data that showed a threshold inconsistent with the LNT.<sup>283,284</sup>

The story of Hermann Muller is a cautionary tale about the importance of scientific integrity. If Muller’s deception was indeed based on precautionary thinking, this story highlights the wrongness of the backwards thinking embodied in the precautionary principle. The precautionary principle was first stated at the Rio Declaration of 1992:

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.

*(www.unesco.org/education/pdf/RIO\_E.PDF)*

The precautionary principle was given voice with the best of intentions—to encourage policies that protect human health and the environment in the face of uncertain risks. However, the desire for protection in the face of incomplete knowledge also has its perils—that an action taken without sufficient understanding may have unintended consequences that actually make matters worse.<sup>285</sup>

In the early 1930s, at what should have been the pinnacle of Muller’s scientific career, his life began to unravel over difficulties in his marriage, professional jealousy of his colleagues at the University of Texas, and his outspoken political stance that caused the FBI to investigate him as a communist. In 1932, he attempted suicide by taking an overdose of barbiturates. Muller was an obviously troubled man.<sup>6</sup> In his mind, he may have justified his attempt to protect his reputation with the good intentions of a precautionary statement. Muller was known as a gadfly and was never hesitant to speak out on science policy issues such as eugenics or nuclear weapons—it is likely that his political views on the hazards of radiation may have blurred his vision of the science–policy interface and inappropriately altered his scientific judgment.<sup>282</sup>

For chemical risk assessment, the 1977 Safe Drinking Water Committee of the National Academies of Sciences unwittingly accepted Muller’s “no escape/no threshold” statement and recommended the adoption of linearity at low dose for risk assessment of chemical carcinogens. The reasons for this adoption are poorly documented in their report, and it is likely that the committee’s choice was also based on a protectionist-precautionary philosophy.<sup>286</sup>

It is not difficult to understand or sympathize with the fear of cancer that has become ingrained in society. For many years, cancer was poorly understood and the medical treatments in the early 20th century were horrific, often disfiguring, and largely unsuccessful.<sup>6</sup> The fear of cancer is reflected in the adoption of the Delaney

Clause by the US Congress in 1958, which states that no food additive that has been shown to induce cancer in man or experimental animals can be considered safe. This fear was also clear in the anger of Congressman Andy McGuire, who represented New Jersey's 7th district from 1975 to 1981, upon learning that nitrosamines were present in pesticide samples that EPA had failed to withdraw from the marketplace.<sup>285</sup> The adoption of the LNT for cancer dose response by the Safe Drinking Water Committee is a response to the fear of cancer, but it does not reflect the state of knowledge of cancer biology in the 21st century.

### **5.6.2.1 Why the Linear No-Threshold Hypothesis Is Wrong**

Adoption of the LNT occurred prior to the advent of research on DNA repair. DNA damage is not, by itself, a mutational event, but in the late 1970s, prior to the advent of research on DNA repair, it seemed reasonable that DNA damage itself was mutagenic.

Even today, many scientists commonly believe that the dose response of a carcinogen that acts by damaging DNA does not exhibit a threshold, and in their minds equate genotoxicity with mutagenicity. There is, however, ample experimental evidence that carcinogens that act by damaging DNA exhibit dose thresholds and these thresholds are likely due to DNA repair and other compensatory processes.<sup>287</sup>

Evolutionarily successful organisms have developed redundant systems that provide both immediate capacity and fail-safe mechanisms to deal with many different stresses. DNA repair is just such a fail-safe mechanism.<sup>243,288–295</sup> However, these capacities are finite, and when one or more of these capacities are exceeded, a departure from homeostasis, usually in the form of disease or death, occurs. As noted earlier, DNA repair may be incomplete when cells are in a hyperproliferative state. The fact of biological thresholds is implicit in the statement by Paracelsus upon which the science of toxicology is based—the dose makes the poison.

Low-dose linearity has been justified by the notion that normal physiological processes reflect a pathological continuum toward cancer or other diseases and that exposure to a stressor will act in an additive fashion with these ongoing pathological processes.<sup>296</sup> Statistical rather than biological arguments are used to attempt to explain away the occurrence of thresholds, and these arguments ignore the need of all organisms to maintain homeostasis.<sup>297–299</sup>

The reductionist hypotheses inherent in the empirical dose–response models commonly used in risk assessment render them scientifically inadequate given the individual differences in phenotype, exposure history, and defense or repair capacities.<sup>300–302</sup> Indeed, a stronger experimental and regulatory focus on biological mechanisms would enable greater flexibility in the regulation of carcinogens without compromising human health.<sup>78,79</sup> More recently, advances in the biological sciences, including systems biology, high-throughput screening methods, and chemical genomics, suggest that the increased understanding of biological responses from these advances will be consistent with the assumption of thresholds and will also clarify the distinction between adaptive and adverse responses.<sup>65</sup>

Had the Safe Drinking Water Committee been aware of DNA repair, the policy of linear low-dose extrapolation for cancer risk assessment might never have been adopted. In sum, the linear no-threshold hypothesis is incorrect for both radiation and chemical carcinogenesis, and its use has driven risk assessment practice for the past 60 years, with the result of unnecessary fear on the part of the general public and needless expenditure of resources to comply with regulations that may do more harm than good.<sup>303,304</sup>

A recent special issue of the journal *Chemico-Biological Interactions* provided both a historical perspective on the LNT and new thinking about the actual biological implications for dose response of both chemicals and radiation.<sup>20,98,99,101–107,305</sup> With continuing efforts such as this, late 21st-century risk analysts will look back on the history of the LNT, roll their eyes, and wonder what indeed their predecessors might have been thinking.

In summary, the adoption of the LNT and its continued use is likely motivated by fear. Many in today's world have an economic motivation to foster the fear of cancer.

#### **5.6.2.2 Low-Dose Synergies and the Hallmarks of Cancer: Another Incorrect Notion**

In 2015, a series of papers appeared in a supplementary issue of the journal *Carcinogenesis* as part of the Halifax project. The purpose of the Halifax project and these papers was to determine if exposure to multiple chemicals that are not considered to be carcinogens could trigger the formation of a sufficient number of the hallmarks of cancer. This work was sponsored by Leroy Lowe of the organization Getting to Know Cancer. Dr. Lowe witnessed the death of his grandfather and his aunt to cancer; both were beloved family members, and his grief likely motivated the Halifax project. The goal of the project was to understand the carcinogenic potential of mixtures by investigating the development of the cancer hallmarks in response to chemical mixtures.<sup>4,5,306</sup> The goal of the 12 papers that comprise the Halifax project had the goal of delving into the biological bases of the hallmarks of cancer.

The first author of the summary paper was William H. Goodson, MD, an oncologist specializing in breast cancer. The goal of the 12 papers was to select chemicals found ubiquitously in the environment but not known to be carcinogenic and to link such chemicals to the formation of one or more of the hallmarks. The other message of the papers was that yet-undiscovered synergies between non-carcinogenic chemicals were capable of fostering one or more hallmarks. Mode of action as an organizing framework for hazard characterization was dismissed as inadequate to deal with these yet-undiscovered synergies.<sup>307</sup>

Obviously, the demonstration of associations between non-carcinogenic chemicals and the hallmarks was necessary for this train of logic; the supporting papers, however, were not able to present such associations, and instead described the biology of hallmark formation and the association with identified carcinogens, such as arsenic, aflatoxin and benzo[a]pyrene.<sup>308–310</sup>

### 5.6.2.3 A Simpler Theory of Carcinogenesis

In Chapter 3, we considered the “bad luck” hypothesis of cancer, with random mutations in normal stem cell replication being a causal factor in cancer pathogenesis. Three papers appeared in the journal *Regulatory Toxicology and Pharmacology* in early 2019. The first of these presented a unified theory of carcinogenesis: cancer results from DNA coding errors that arise either by direct interaction of a chemical with DNA to cause a mutation or indirectly by sustained stem cell proliferation with random mutations. Further, those chemicals that acted indirectly could induce proliferation via activation of biological pathways or by cytotoxicity and proliferation to replace damaged cells.<sup>19</sup>

The second paper indicated that the three categories of mode of action by which chemicals can induce cancer—(1) direct interaction with DNA or DNA replication including DNA repair and epigenetics, (2) receptor-mediated induction of cell division, and (3) non-specific induction of cell division due to cytotoxicity—have undermined the idea of separating chemicals into carcinogens and non-carcinogens. Hence, considering carcinogenicity as a separate process from toxicities already described by known modes of action provides no additional public health protection.<sup>21</sup>

The third paper pointed out the folly of the time-consuming, costly, and animal-intensive two-year bioassays in assuming that such testing can predict human carcinogens. Instead, the authors propose a decision tree based on the premise that cancer is the consequence of DNA coding errors that arise either directly from mutagenic events or indirectly from sustained cell proliferation. The first type of investigation would be *in silico*, i.e., QSAR; the second would be *in vitro* testing and then comparison with the threshold of toxicological concern; the last step would be targeted testing to identify chemicals that might be associated with hallmarks that are precursors of the carcinogenic process such as immunosuppression, cell proliferation, or estrogenicity.<sup>18</sup>

### 5.6.2.4 Dose–Response Modeling for Dichotomous Effects

Given the foregoing discussion on the lack of a scientific basis for the LNT, why even present this material? The reason is—right or wrong, linear extrapolation is norm for regulatory agencies throughout the world and will be used for as long as the LNT is considered valid. Hence, those planning to work in the field of risk assessment need to know how linear low-dose extrapolation is performed.

Toxicity factors based on linear low-dose extrapolation are in essence a ratio between risk and dose. Ideally, consideration of mode of action should guide the choice of whether to use linear or nonlinear extrapolation for any endpoint. Once these prior steps are complete and the decision to use linear extrapolation is made, the following steps are used to develop an oral cancer slope factor or inhalation unit risk value:

- adjustments to the data and selection of a risk metric;
- dose–response modeling;

- selection of a point of departure;
- adjustments to the POD to account for animal-to-human differences and differences in exposure duration and timing;
- linear low dose extrapolation;
- evaluation of potential for a mutagenic MOA.

These will each be considered in detail.

#### 5.6.2.4.1 Adjusting for Lifespan, Added Risk, and Extra Risk

Two-year cancer bioassays in rodents are designed to estimate the lifetime risk of cancer. Hence, the number of animals at risk in each dose group is adjusted for lifespan. If an animal survives to study termination, generally 720 days for rats, or if a tumor is present at the time of death, the time-at-risk weight for that animal is 1; should an animal die before study termination from some other cause, the time-at-risk weight is calculated with a process known as poly-3 adjustment as follows:

$$\alpha_{ij} = \left( \frac{t_{ij}}{T} \right)^3 \quad (5.4)$$

where  $\alpha_{ij}$  = time-at-risk weight for the  $i^{\text{th}}$  animal in the  $j^{\text{th}}$  dose group

$t_{ij}$  = time of death of the  $i^{\text{th}}$  animal in the  $j^{\text{th}}$  dose group

T = study duration

The sum of the time-at-risk weights in each dose group are summed and used in lieu of the number of animals.<sup>311</sup>

EPA defines two types of risk estimates—additional risk and extra risk. In the glossary in the 2012 *Benchmark Dose Technical Guidance*, additional risk is defined as follows:

Additional risk is the difference in risk (or in the probability of a response) between subjects exposed and those not exposed to a hazard (herein, a particular dose or concentration of a chemical). In the context of a bioassay and its dose-response analysis, it is the increment by which the probability of an adverse response exceeds background probability, calculated as  $P(d) - P(0)$ , where  $P(d)$  is the probability of a response risk at a dose  $d$  and  $P(0)$  is the probability of response as zero dose (i.e., background risk).<sup>247</sup>

In that same glossary, extra risk is defined as:

A measure of the proportional increase in risk of an adverse effect adjusted for the background incidence of the same effect. In other words, the ratio between the increased risk above background for a dose ( $d$ ) divided by the proportion of the population not responding to the background risk. Extra risk is calculated as follows:  $[P(d) - P(0)]/[1 - P(0)]$ .<sup>247</sup>

In the guidance, an implied but clear preference is shown for extra risk; the term “additional risk” occurs only twice in the document, in the glossary and in a footnote on page 8.<sup>247</sup> Exactly when these terms cropped up in the history of cancer risk assessment is difficult to discover, although Dr. Kenny S. Crump, a statistician and pioneer of dose-response modeling, defines what EPA calls “extra risk” as “additional risk over background.”<sup>312</sup>

#### 5.6.2.4.2 Dose-Response Models for Dichotomous (Quantal) Data

Dose-response modeling seeks to fit a mathematical model to dose-response data that describes the dataset, especially at the lower end of the observable dose-response range. Empirical dose-response modeling is a curve-fitting exercise and should be clearly distinguished from a biologically based dose-response modeling effort.<sup>313</sup> Table 5.5 shows the models used for benchmark dose modeling of dichotomous endpoints.

For dichotomous or quantal data, such as frequency of cancer from an animal bioassay, the software and web applications already discussed provide a number of models to fit the data. These generally include the gamma, logistic, log-logistic, multistage, probit, log-probit, quantal linear, Weibull, and dichotomous Hill models.

**Table 5.5 Dose-Response Models for Dichotomous Responses**

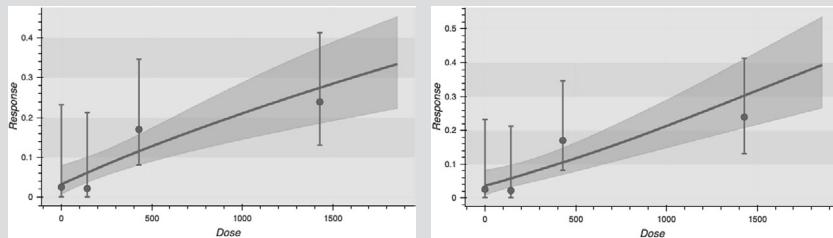
Model Type	Equation	Constraints
Quantal linear	$p(dose) = \gamma + (1 - \gamma)(1 - \exp[-\beta dose])$	$\beta \geq 0, 0 \leq \gamma \leq 1$
Multistage	$p(dose) = \gamma + (1 - \gamma)(1 - \exp[-\sum_i \beta_i dose^i])$	$0 \leq \gamma \leq 1, \beta_i \leq 0, i = 0, 1, 2, 3, \dots, n$
Weibull	$p(dose) = \gamma + (1 - \gamma)(1 - \exp[-\beta dose^\alpha])$	$0 \leq \gamma \leq 1, \beta \geq 0, \alpha \geq 1$ or lower limit
Gamma	$p(dose) = \gamma + \frac{(1 - \gamma)}{\Gamma(\alpha)} \left[ \int_0^{\beta dose} t^{\alpha-1} e^{-t} dt \right]$	$0 \leq \gamma \leq 1, \beta \geq 0, 0 < \alpha \leq 18$
Dichotomous Hill	$p(dose) = \gamma + \frac{\nu(1 - \gamma)}{1 + \exp[-\alpha - \beta \log(dose)]}$	$0 \leq \gamma \leq 1, 0 \leq \nu \leq 1, \beta > 0$
Logistic	$p(dose) = \frac{1}{1 + \exp[-\beta_0 - \beta_1 dose]}$	$\beta_i \geq 0$
Log-Logistic	$p(dose) = \gamma + \frac{(1 - \gamma)}{1 + \exp[-\beta_0 - \beta_1 \log(dose)]}$	$0 \leq \gamma \leq 1, \beta_i \geq 0$
Probit	$p(dose) = \Phi(\alpha + \beta dose)$	$0 \leq \beta \leq 18$
Log-Probit	$p(dose) = \gamma + (1 - \gamma)\Phi[\beta_0 + \beta_1 \log(dose)]$	$0 < \gamma < 1, 0 \leq \beta \leq 18$

Box 5.3 provides an example of BMD modeling for a dichotomous endpoint. This example is provided to illustrate the dose–response modeling and computations involved in development of a cancer slope factor. Standard doses of *Ginkgo biloba* in humans range from 120 to 800 mg/d. Please note the use of allometric scaling using body weight to a fractional power as part of animal-to-human extrapolation.<sup>314</sup>

### BOX 5.3 EXAMPLE OF CANCER SLOPE FACTOR DERIVATION

This example uses data from the frequency of hepatoblastoma in female B6C3F1/N mice administered *Ginkgo biloba* by corn oil gavage at doses of 0, 200, 600, or 2000 mg/kg for five days per week for 105 weeks. These data were obtained from the draft report from the National Toxicology Program. Hepatoblastomas were observed at frequencies of 1/50, 1/50, 8/50, and 11/50. Poly-3 adjustment yielded group sizes of 39, 45, 47, and 46 animals.

These data were fitted to a variety of models for dichotomous responses using Dr. Kan Shao's app at <https://benchmarkdose.org>. The two best-fitting models were the quantal linear (left) and 2nd order multistage (right) models, with the corresponding equations shown below.



$$f(\text{dose}) = a + (1 - a) \times (1 - e^{-b \times \text{dose}})$$

$$f(\text{dose}) = a + (1 - a) \times (1 - e^{-b \times \text{dose} - c \times \text{dose}^2})$$

Model	Post-Prediction p-value	Posterior Model Weight	BMD @ 10% (mg/kg-d)	BMDL @ 10% (5th percentile of BMD)
Quantal-linear	0.713	68%	547	348
Multistage (2nd order)	0.684	32%	624	388
Model Average	NA	NA	586	414

In the absence of other means for species extrapolation, the ratio of body weights to the 1/4 power would be used to obtain a human-equivalent dose (HED) at the POD of  $414 \text{ mg/kg/d} \times 0.144 = 60 \text{ mg/kg/d}$ .

To perform linear extrapolation and obtain the CSF, the HED is divided into the BMR of 10% as follows:  $0.1/60 = 0.002 \text{ per mg/kg/d}$ .

Using this value, the risk-specific dose for *Ginkgo biloba* corresponding to a cancer risk of 1 in 1,000,000 is  $1\text{E-}06/0.002 = 5\text{E-}04 \text{ mg/kg/d}$ .

As an exercise, you may wish to estimate the cancer risk for a 75 kg adult consuming *Ginkgo biloba* on a daily basis for, say, 30 years. However, bear in mind that the cancer slope factor developed in Box 5.3 was to illustrate dose-response modeling and calculation of a slope factor—as such, performed in the absence of any MOA analysis and without any consideration of the evidence, its strength or its weight. It is emphatically not provided to suggest that *Ginkgo biloba* is a human carcinogen. In this regard, *Ginkgo biloba* appears to be carcinogenic to mice. As part of this exercise, please take a look at the two-year bioassay for *Ginkgo biloba* at [https://ntp.niehs.nih.gov/ntp/htdocs/lt\\_rpts/tr578\\_508.pdf](https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr578_508.pdf) and draw your own conclusions.

### **5.6.3 Adjustments to the POD for Linear Extrapolation and Use of Uncertainty Factors**

#### **5.6.3.1 Differences in Exposure Duration**

The POD may need to be adjusted for differences in exposure between that used in the study and that in exposed humans. For example, in an inhalation bioassay, animals may be exposed for six hours a day and five days a week. This exposure would be adjusted to represent continuous exposure by multiplying by 6/24 and 5/7. In animal bioassays employing oral gavage for five days per week, the administered daily dose would be similarly multiplied by 5/7.

These adjustments reflect the application of Haber's Rule, developed early in the 20th century to address issues of the toxicity of poison gas used as a weapon of war. At that time, scientists observed that both concentration and time interacted to produce toxicity, and Haber's Rule indicates that concentration and exposure time are both factors in producing an effect—briefly,  $c \times t = k$ , where  $k$  is proportional to the effect. In essence,  $k$  represents the AUC for exposure. Hence, an inhalation exposure to 10 ppm for one hour will be equivalent to an exposure to 1 ppm for ten hours. Haber's Rule has been shown to be applicable for both the inhalation and oral routes of exposure.<sup>315</sup>

In fact, application of Haber's Rule is valid only when repeated exposures used in an inhalation study result in steady-state internal concentrations. Rapid clearance

may render the duration of exposure negligible.<sup>316</sup> Notwithstanding, Haber's Rule is used by most regulatory agencies as a default procedure when chemical-specific information is not available.

### **5.6.3.2 Allometric Scaling and Species Differences**

For inhalation exposure, mathematical dosimetry models are used to account for differences in pulmonary anatomy, disposition of chemical within the airway, and target tissue interactions.<sup>220,317,318</sup>

Two methods are currently used for species extrapolation. The first is the application of uncertainty factors, as discussed earlier in this chapter. In contrast to the application of uncertainty factor, for cancer slope factors derived by linear extrapolation, most regulatory agencies use body weight scaling to the 3/4 power. This adjustment may be performed on the doses in an animal experiment, on the point of departure value, or on the slope factor; however, interspecies scaling should only be performed once. Body weight to a fractional power is generally representative of surface area, and is generally predictive for scaling of toxicity data.<sup>314,319–322</sup> EPA's Risk Assessment Forum recommended the combined use of  $BW^{3/4}$  as a scaling factor along with a reduced values of uncertainty factors to derive human-equivalent doses for reference doses.<sup>323</sup> You've already seen the example of this scaling in Box 5.3.

If the POD represented a dose metric from a physiologically based pharmacokinetic model, a model with parameter sets specific to both humans and animals could be used for the toxicokinetic portion of species extrapolation. This, in fact, is the most scientifically sound approach for animal-to-human dosimetric adjustment: the use of a validated PBPK model or chemical-specific adjustment factors in lieu of defaults to estimate the human external dose (mg/kg-day) corresponding to an appropriate dose metric identified from consideration of the MOA.<sup>178,273,274</sup>

## **5.7 TOXICITY REFERENCE VALUES FROM EPIDEMIOLOGY STUDIES**

Epidemiologic studies may provide the most appropriate data from which to develop toxicity reference values for humans. Data on biomarkers of effect related to disease progression would be ideal; these biomarkers could then be put into an evidence map as used for pharmaceuticals.<sup>324</sup> Such biomarkers are available for only a few chemicals.

### **5.7.1 Dose–Response Modeling for Dichotomous Endpoints**

A dichotomous outcome, i.e., disease or no disease, is used in the majority of human cancer studies. These studies deal with # cases, # controls and the total in an exposure group.

### 5.7.1.1 Measures of Response

Risk is calculated as the # Cases/# Total, designated as P(risk). The risk in the reference quantile is also calculated as this ratio. Relative risk (RR) is the ratio of the risk in a given quantile and the risk in the reference quantile. The uncertainty in relative risk is given by the standard error and calculated as:

$$SE \text{ of } \log(RR) = \sqrt{\frac{1}{Cases_i} - \frac{1}{Total_i} + \frac{1}{Cases_{Ref}} - \frac{1}{Total_{Ref}}} \quad (5.5)$$

The upper and lower confidence limits of RR are calculated as:

$$CI_{RR} = R \text{Re}xp(Z_{1-\alpha} SE_{RR}) \quad (5.6)$$

Z-score values of  $\pm 1.645$  correspond to the upper and lower 95% one-sided CI.

The odds of having the disease in a given quantile is  $P(\text{risk})/(1-P(\text{risk}))$ . The odds ratio is the ratio of the odds in a given quantile and the odds in the reference quantile. The uncertainty in the number of cases is binomially distributed and can be modeled as random binomial variable. Hazard ratio differs from relative risk only in the inclusion of time in the denominator; hence, for a given exposure bin, instead of the total number of persons at risk, a value such as person-years at risk is used.

### 5.7.1.2 Exposure–Response Modeling

A relatively simple model for dichotomous outcomes is an exponential model, shown below with parameters  $\beta_0$  and  $\beta_1$ .

$$\Pr(disease) = 1 + \exp(\beta_0 + \beta_1 \log(dose)) \quad (5.7)$$

Although more complex models exist, Equation 5.7 is widely applicable to all risk measures that compare exposure groups to the baseline or control group, such as relative risk, odds ratio or hazard ratio. The expression inside the exponential is called the link function, and the linear link function shown in Equation 5.7 is one of the simplest. The use of the logarithm of dose/exposure simply reflects the very wide exposure range often observed. Other link functions include quadratic or power functions. Smoothing techniques such as splines or moving averages may also be used.<sup>325</sup>

### 5.7.1.3 Relative Risk and Extra Risk

The tricky part of using these ratio measures as relative risk or odds ratio is that they hide the actual risks that are used for regulatory purpose, i.e., 1 in 1,000,000 risk of cancer. Exposure quantiles are most often presented as ranges, and once a fit is achieved, the relative risk corresponding to the lower bound on the reference exposure group is used as the lower bound for linear extrapolation.

PODs are selected as relative risk values. For example, the National Research Council suggested a relative risk value of 1.1 as the POD for dose–response modeling of arsenic studies.<sup>326</sup> When using a relative risk value as a POD, this value should fall within the range of observation; for epidemiologic studies, the POD is most often chosen between the response of the second and third exposure quantiles.

The reference group bears a finite risk calculated as # Cases/# Total and zero risk, therefore, is not an appropriate lower limit for low-dose extrapolation. Instead, the relative risk at the lower end of the reference group is used and calculated as:

$$RR_{reference} = 1 + \exp(\beta_0 + \beta_1 \log(C_{lowest})) \quad (5.8)$$

The extra risk at the POD expressed as a relative risk is defined as follows:

$$Extra\ Risk\ at\ POD = \frac{\left( \frac{RR_{POD}}{RR_{reference}} - 1 \right) Risk_{reference}}{1 - Risk_{reference}} \quad (5.9)$$

Grid approximation can also be used with dichotomous endpoints. The POD needs be selected within the range of observation.<sup>23,326</sup> Box 5.4 shows an example of using grid approximation for arsenic-related pancreatic cancer. Table 5 in Hays et al.’s 2010 paper “Biomonitoring equivalents for inorganic arsenic” was used to convert the creatinine-normalized urinary concentrations to dose.<sup>327,328</sup>

### 5.7.2 Dose–Response Modeling of Continuous Responses

For non-cancer endpoints, the response may be continuous, such as reduction of IQ as a neurodevelopmental endpoint or birth weight for overall development. These continuous responses generally appear sigmoidal in shape when plotted against log dose. The Hill model or the exponential model may be appropriate.

An opportunity to work through the derivation of the distribution for the BMD of the effect of arsenic on full-scale IQ in Bangladeshi children is provided as an exercise at the end of this chapter. The exposure metric was urinary arsenic concentrations. Similar to Box 5.4, grid approximation is used to obtain BMD and BMDL values. Working with this relatively simple technique will help understand the Bayesian dose–response methods presented earlier.

## 5.8 TOXICITY REFERENCE VALUES FROM HIGH-THROUGHPUT *IN VITRO* STUDIES

For many years, regulators considered animal toxicity testing to be the so-called “gold standard.” In response to concerns about animal welfare, the need to assess the growing number of chemicals in commerce, and the growing realization that high-dose experiments in animals could not address potential effects in humans exposed

**BOX 5.4 CALCULATING A BMD/BMCL FROM AN EPIDEMIOLOGIC STUDY BASED ON RELATIVE RISK**

García-Esquinas et al. (2013) evaluated the association between arsenic exposure and pancreatic cancer mortality in 3932 Native Americans aged 45–74 years from Arizona, Oklahoma, and North/South Dakota who participated in the Strong Heart Study from 1989 to 1991 and were followed through 2008.<sup>329</sup> The exposure metric was creatine-normalized urinary arsenic in units of  $\mu\text{g As per g creatinine}$  and the response was relative risk (RR). For all the cancer types studies, the data were provided as tertiles (3 groups), as shown below.

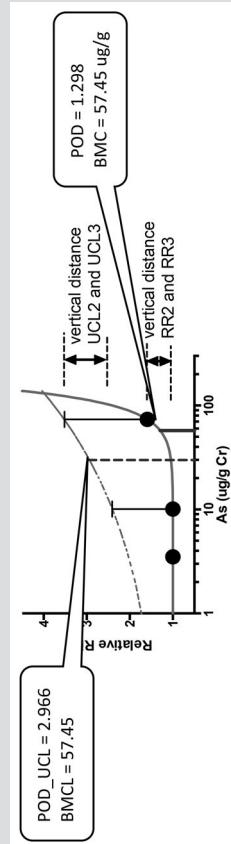
As (low)	As (high)	Mid-point	Positive	Negative	Total	Risk	RR	SE(RR)	(Equation 5.6)	LCL	UCL	(Equation 5.7)	(Equation 5.7)
0.4	6.91	3.5	7	1312	1319	0.005307	1	NA	NA	NA	NA		
6.91	13.32	10.1	7	1309	1316	0.005319	1.002	0.533		0.417	2.41		
13.32	133.6	73.5	11	1289	1300	0.008461	1.594	0.482		0.722	3.52		
Fit of Equation 5.7 to Central RR				$\beta_0 = -12.6$		$\beta_1 = 2.81$		POD = 1.298		BMC = 57.45			
Fit of Equation 5.7 to UCL RR				$\beta_0 = -0.337$		$\beta_1 = 0.294$		POD = 2.966		BMC = 29.93			

Notes: LCL = lower confidence limit; UCL = upper confidence limit.

The Excel Solver was used to fit Equation 5.7 for both the central and UCL values of RR. The exposure dose used was the average of the upper and low arsenic concentration ranges. The POD was chosen as the value halfway in between the RR values for the second and third quantiles.

The fits to the central values and UCL values of RR are shown in the table above. The parameters were used to calculate the central value and LCL of the distribution of concentration at the POD using Excel's GoalSeek function. The BMC was 57.45  $\mu\text{g/g Cr}$ , and the BMCL was 29.93  $\mu\text{g/g Cr}$ .

(Continued)



To convert these concentrations to doses, the value of 31.1 µg As/kg/d per µg/g Cr from Hays et al. (2010)<sup>327</sup> was used to obtain values of 1.85 and 0.96 µg/kg/d for the BMD and BMCL, respectively.

The RR value at the lower end of the reference range is  $1 + \exp(-12.6 + 2.81 * \log(0.4)) = 1.00000026$ .

From Equation 5.6, the extra risk at the POD as calculated with Equation 5.9 is 0.00159, or 1.6E-03

The cancer slope factor is calculated by dividing the extra risk at the POD by the BMCL round to 1 significant figure is 0.00159/(1 × 0.001) = 1.6 per mg/kg/d. This value is very close to that derived by EPA in 1995 for skin cancer ([https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?&substance\\_nmbr=278](https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?&substance_nmbr=278)). This similarity suggests that the mode of action of arsenic for all endpoints is similar, as suggested by Cohen et al. (2013).<sup>328</sup>

to much lower doses, the prospects for the use of *in vitro* testing for risk assessment has grown.<sup>329,330</sup>

EPA has initiated a number of activities in an effort to incorporate the use of high-throughput/high-content (HT/HC) assays into risk assessment. The most visible of these is ToxCast™, consisting of a battery of both commercial and publicly developed HT/HC assays. Initially, the ToxCast™ approach has been designed to utilize the vast array of commercially available HT/HC assays to screen substances of interest to EPA. These assays were initially developed for use in the pharmaceutical industry. One distinct and obvious advantage is that these assays can be robotically automated to generate data very quickly. Another advantage is that they were already available.

There are also significant disadvantages, however. One of the most problematic and challenging aspects of this approach is that many of these commercial methods are proprietary, so details about development, replicability, sensitivity, and specificity of the individual assays are not necessarily available for independent evaluation and scientific peer review. Hence, these proprietary assays are “black boxes” in many ways. From a scientific point of view, the choice of assays based on convenience does an “end-run” around the concept of MOA. Ideally, the selection of assays would begin with the identification of toxicity pathways and assays would then be chosen because their results reflect the occurrence of key events in those pathways.

What is lacking here is the knowledge of those pathways. For example, how many toxicity pathways exist? The comment by Dr. Melvin Andersen in Chapter 2 (p. 93) about “false accuracy” is apt here. As the number of enzymes and cellular targets for toxicity are finite, the number of pathways is also likely finite.<sup>331</sup> Although there are evolutionary and energetic constraints on the complexity of human biology,<sup>332</sup> a question that will remain unanswered is whether the ToxCast™ assays or any other set that is used in risk evaluations will cover the entire domain of toxicity pathways—or indeed, just what fraction of that domain is represented.

The prediction models used for screening, hazard identification, or hazard characterization of *in vitro* data are slowly maturing. In 2012, when the predictive performance of more than 600 *in vitro* assays was examined across 60 *in vivo* endpoints using 84 different statistical classification methods and compared to the predictions based solely on chemical descriptors, the predictive power of the *in vitro* assays was no better than that of the chemical descriptors.<sup>333</sup> The first author of this paper was Dr. Rusty Thomas, who worked at the Hamner Institute for many years until EPA wisely offered him the job of leading the National Center for Computational Toxicology. This group at EPA has partnered with the National Toxicology Program, the National Center for Advancing Translational Science, and the Food and Drug Administration to address five distinct areas of focus:

- developing alternative test systems that are predictive of human toxicity and dose response;
- addressing the technical limitations of the current *in vitro* test systems;

- curating and characterizing extant *in vivo* toxicity studies;
- establishing scientific confidence in the *in vitro* test systems;
- refinement of *in vitro*-to-*in vivo* extrapolation and the understanding of *in vitro* disposition.<sup>334,335</sup>

Twenty-first-century toxicology presents an exciting era for toxicologists, risk assessors, and researchers. Programs such as the EPA's ToxCast™ are laudable in that they demonstrate just how new technologies can be exploited to address the challenges of risk assessment. However, the new challenges are establishing credible validation/evaluation methods and understanding of the strengths and limitations for specific uses.

One way to approach the development of a plethora of new methods in toxicology is to apply evidence-based methodology to both the data and prediction models. This approach is loosely based on the work of the Cochrane Collaboration in medicine.<sup>336–338</sup> What is clear is that implementing such an evidence-based approach will not be an easy task.<sup>339–342</sup>

Recently, a team of researchers were able to collect cord blood and urine from a cohort of mothers in Durango, Mexico and developed BMCs and BMCLs for epigenetic biomarkers including DNA methylation, microRNA expression, messenger RNA expression, and protein expression. The BMC and BMCL estimates for urinary total arsenic were 58 µg/L and 45 µg/L.<sup>343</sup> A chance to examine changes in full-scale IQ changes in a cohort of Bangladeshi children is provided as an exercise at the end of the chapter, and thus presents an opportunity to compare these point of departure doses based on epigenetics with those based on a neuro-behavioral endpoint.

## 5.9 TOXICITY FACTORS USED FOR REGULATION

What is vital for regulation is the availability of high-quality peer-reviewed toxicity factors that enjoy wide support among regulators, the regulated community, and the public. A number of governments, international groups, and non-governmental organizations have developed sets of toxicity values.

### 5.9.1 Toxicity Databases in the US and around the World

In 1985, EPA created the Integrated Risk Information System to develop consensus opinions about the health effects that may result from chronic exposure to various substances in the environment, and to provide these opinions and accompanying quantitative toxicity factors in an accessible database. The goal was to reduce inconsistency in toxicity assessments. For the next ten years, IRIS consensus opinions were documented in IRIS Summaries, and EPA, state regulatory agencies, and others came to rely on IRIS information in decision-making. In 1997, EPA began publishing comprehensive Toxicological Review support documents and incorporating additional peer review into the development of IRIS toxicity values.

However, there were several highly controversial assessments that prompted requests for review of several chemical-specific assessments and the entire IRIS process by the National Academies of Sciences. The highly controversial assessments include those for 2,3,7,8-tetrachlorodibenzodioxin, the solvent trichloroethylene, and formaldehyde. In fact, in the last chapter of the NAS review of EPA's formaldehyde toxicity assessment, the panel recommended a comprehensive revamping of the IRIS process.<sup>344</sup> In 2012, EPA requested that the NAS begin a comprehensive review of the entire IRIS process that is currently ongoing.

During the 1990s, EPA considered IRIS the “gold standard” for toxicity criteria. However, data of sufficient quality were not available for all chemicals, and toxicity values based on this poorer-quality data were assembled in another database called the Health Effects Assessment Summary Tables (HEAST). HEAST tables can still be found on EPA's website.<sup>345</sup>

A small number of states in the US had toxicologists on staff and issued their own toxicity factors. The most active state in this regard was California, where a database of toxicity factors was developed by the Office of Environmental Health Hazard Assessment. This database can be found at <https://oehha.ca.gov/chemicals>. The state of Texas also has a vigorous program for developing toxicity factors with extensive guidance that provides procedures for toxicity factor development based on both animal and epidemiologic data. This guidance is available at [www.tceq.texas.gov/toxicology/esl/guidelines/about.html](http://www.tceq.texas.gov/toxicology/esl/guidelines/about.html).

What is interesting is that California and Texas regulators both have disagreements with some of the toxicity factors in IRIS. One of the exercises at the end of this chapter is to compare some of the toxicity values among these three sources.

In the US, Toxicology Excellence in Risk Assessment (TERA) maintains a database named International Toxicity Estimates for Risk Assessment (ITER). ITER is available in the list of TOXNET databases at <https://toxnet.nlm.nih.gov> (this URL may change because TOXNET will be migrated to PubChem, PubMed, and Bookshelf, all administered by the National Library of Medicine). ITER provides chronic human health risk assessment data from a variety of organizations worldwide in a side-by-side format, explains differences in risk values derived by different organizations, and links directly to each organization's website for more detailed information. Furthermore, it is the only database that includes risk information from independent parties whose risk values have undergone independent peer review.<sup>346</sup>

The European Union and the Organisation for Economic Co-operation and Development provide links to toxicity databases around the world—some from EPA, some from universities, and others from private consultants. These can be found at [www.eea.europa.eu/publications/GH-07-97-595-EN-C2/iss2c1h.html](http://www.eea.europa.eu/publications/GH-07-97-595-EN-C2/iss2c1h.html). The International Agency for Research on Carcinogens (IARC) of the World Health Organization does not develop quantitative toxicity criteria, but its monograph series claims to provide information about substances associated with cancer. Sadly, for about 10–15 years, IARC hazard evaluations have been very biased, and many toxicologists no longer consider them scientifically credible.

With its growing economy, China is becoming the largest importer of chemicals in the world and has realized the need for a governmental role in environmental risk

assessment.<sup>347</sup> However, China realizes the societal cost of the linear no-threshold hypothesis; whether this hypothesis becomes entrenched in Chinese government environmental policies remains to be seen.<sup>348</sup>

## 5.10 MIXTURES

For a number of years, the response provided by risk assessors to the question of whether chemical mixtures were more or less toxic than single chemicals was less than satisfactory. Usually, the answer would be something that stated that the science underlying risk assessment was not sufficiently advanced to meet the needs and challenges of modern-day problems. The study of mixtures has been plagued with generalizations from too few data, and with ambiguous use of terminology and consequent imprecise interpretation—the reasons behind the non-answer.

Chemicals in a mixture might interact to produce toxicity in two general ways. Additivity suggests that the effect of the mixture can be estimated directly from the sum of the doses or the sum of the responses of the individual chemicals in the mixture—the former is called dose addition and the latter response addition.<sup>349</sup>

Dose addition assumes a common mode of action, and if the MOA is not known, EPA recommends separating chemicals by the affected target organ. This recommendation falls short: hydrogen sulfide and cyanide both form methemoglobin adducts, and both prevent oxygen transport by red blood cells. Does this respiratory inhibition represent a common mode of action? Hydrogen sulfide is detoxified by sulfide oxidase, an enzyme that produces thiosulfate from hydrogen sulfide. Cyanide is detoxified by rhodanese, an enzyme that uses thiosulfate to convert cyanide to thiocyanate, which is also found in cruciferous vegetables like broccoli. The increased levels of thiosulfate accelerate detoxification of cyanide. Cyanide antidote kits used by poison control centers contain injectable thiosulfate, and here is an instance where two chemicals with a common MOA fail to be dose-additive and act as antagonists as defined below.<sup>24</sup>

Response addition assumes that the chemicals in the mixture have a dissimilar mode of action. An example of response addition is the common practice of summing cancer risks from individual chemicals estimated from cancer slope factors. Since these risks are probabilities, this practice is mathematically and conceptually correct—what is missing is any information about MOA. Dose addition is the basis of the toxic equivalence factors for dioxin-like chemicals that have been used for many years.<sup>350</sup>

Interactions between chemicals may also occur. Mixtures producing risks greater than expected by additivity are called synergistic, and those producing risks less than expected from additivity are called antagonistic. Hence, depending on whether one is thinking about dose addition or response addition, the appearance of synergism or antagonism may be quite different. Interactions are quantitative relationships, and demonstration of interactions requires a quantitative determination based on the quantitative dose response of single agents in the mixture. Further, interactions are defined quantitatively, and their presence or absence can be determined by experiment—whether or not the MOA is known. Recently, five criteria were stated

for determining whether interaction between two substances actually occurred. These criteria were quite stringent, and meeting all of them would require both large amounts of data and rigorous thinking.<sup>351</sup>

In the last decade, assessing the toxicity of mixtures has fallen under the rubric of cumulative risk assessment (CRA). In 2003, EPA released the *Framework for Cumulative Risk Assessment*.<sup>352</sup> “Cumulative risk” was defined therein as including multiple factors or stressors not limited to exposure to multiple chemicals. The goal was to enable risk management decisions to include a range of options so as to enhance the health of the exposed population to the greatest extent. Additivity is mentioned only twice in the document, both times in regard to previous EPA guidance. The inclusion of stressors, however, grew to include factors outside the ability of regulation to affect, and the practice of cumulative risk assessment remains aspirational.<sup>250,353</sup>

The ILSI Health and Environmental Sciences Institute is attempting to advance CRA using an explicit problem formulation and a tiered approach.<sup>354,355</sup> However, these approaches generally fall short in the area of the toxicity assessment. If the response to a binary mixture is the sum of the responses to individual components, this response is considered additive; if the response is greater than additive, the response is considered synergistic; and if less than additive, the response is considered antagonistic.

Conceptual differences between toxicology, epidemiology, and statistics, however, lead to different conclusions with regard to a response being additive, synergistic, or antagonistic.<sup>356</sup> Considerable effort has been devoted to reconciling these differences, but the approaches require sophisticated mathematics; hence, the simplest assumption—additivity—is almost always the regulatory default.<sup>357–364</sup>

For years, the toxicology of mixtures has been plagued by generalizations from too few data and ambiguous use of terminology, with consequent imprecision of meaning.<sup>365</sup> The most basic distinction is that chemicals in a mixture produce toxicity either by a common effect on a shared biological target or by independent action upon diverse biological targets.<sup>366–368</sup>

In general, dose addition or concentration addition assume the chemicals in the mixture act by a common mode of action on a common target, whereas response addition assumes that any combined effect is considered the result of statistically independent random events, likely on different biological targets.

### 5.10.1 EPA’s Approach to Mixture Risk Assessment

EPA has not issued guidance on mixtures since 2000. In short, EPA’s contributions to mixture toxicity are rooted in the past and have been supplanted by efforts by the European Commission, WHO/IPCS and other international bodies.

### 5.10.2 Approaches to Mixture Toxicity by the European Commission

In 2011, the European Commission issued its report *Toxicity and Assessment of Chemical Mixtures* and incorporated many of the advancements in the scientific

literature since EPA's 2007 publication.<sup>369</sup> The Joint Research Centre (JRC) is the European Commission's science and knowledge service through which scientists provide independent scientific advice and support to EU policy.

In 2014, the JRC issued *Assessment of Mixtures: Review of Regulatory Requirements and Guidance*. In this document, toxicologic interactions between chemicals were split into three categories: (1) dose or concentration addition, (2) response addition or independent action, and (3) interaction, which includes synergism and antagonism.

In 2015, the JRC issued *Scientific Methodologies for the Assessment of Combined Effects of Chemicals: A Survey and Literature Review*.<sup>370</sup> The authors of this document realized that testing the infinite range of chemical mixtures was a non-starter. Further, they noted that in almost all cases, the approach of dose addition had become a *de facto* default because of lack of guidance and experience. The report went on to suggest new approaches, including adverse outcome pathways along with integrated testing and assessment, *in vitro* testing coupled with *in vitro*-to-*in vivo* extrapolation, omics techniques, chemoinformatics, read-across, physiologically based pharmacokinetic/pharmacodynamic models, dynamic energy budget models, and the use of the threshold of toxicological concern. The report also included results of a survey of risk assessment experts on their use of these approaches.

In 2016, these same authors, working through the JRC, produced yet another report, *Review of Case Studies on the Human and Environmental Risk Assessment of Chemical Mixtures*.<sup>371</sup> Twenty-one case studies were identified, with a range of approaches including dose addition, relative potency, WHO/IPCS categorizations (see below), and the use of the maximum cumulative ratio and a decision tree.<sup>362,372-375</sup>

### **5.10.3 Up-to-Date Approaches to Mixture Risk Assessment from the Scientific Literature**

McCarty and Borgert (2006) provide a comprehensive review of the regulatory practice for mixture risk assessment and point out that the blend of convention and empiricism that characterizes guidance from EPA and other regulatory bodies reflects the lack of cohesion in the science of mixtures.<sup>376</sup> Furthermore, they lament the lack of a widely accepted conceptual framework and note such a framework will likely be needed for progress in the understanding of mixture effects. The underpinning of this conceptual framework would be a classification scheme for mode of action. The adverse outcome pathway effort may in time provide the comprehensive mode of action information needed to predict the effects of chemical mixtures.<sup>377</sup>

Most of the recent mixtures work has been conducted on the effects of environmental chemical mixtures on aquatic organisms—for obvious reasons: exposure can be determined by analytical results of the water. Concentration addition was shown to be an appropriate means of prediction after scaling the environmental concentration of each component in the mixture to its effect concentration.<sup>378</sup>

The maximum cumulative ratio (MCR) is the ratio of the cumulative toxicity received by an individual from exposure to multiple chemical stressors to the largest toxicity from a single chemical stressor, and provides an estimate of the extent to

which a chemical-by-chemical approach could underpredict toxicity when compared to a mixture approach.<sup>379</sup>

The European Chemical Industrial Council Mixtures Industry Ad-hoc Team (MIAT) developed a decision tree that incorporates both the WHO/IPCS framework and the MCR.<sup>373,380</sup> The MIAT/MCR approach has been used successfully to identify the significant contributors to overall risk present in a mixture.<sup>374,381</sup>

The regulatory approach to mixtures has become sufficiently “balkanized” between different countries and different regulatory sectors that the European Union has just begun a project to develop a pragmatic approach for risk assessment of combined exposure to multiple chemicals derived from multiple sources. The 2020 Horizon project European Test and Risk Assessment Strategies for Mixtures (EuroMix) aims to develop and verify testing and tiered assessment strategies for mechanism-based approaches to understanding the risk of chemical mixtures.<sup>382</sup>

In summary, recent work suggests that little progress has been made toward resolving the confusing blend of empiricism and convention that runs throughout mixture risk assessment.<sup>359,383</sup> Mixtures thus present a significant conceptual and practical challenge for risk assessment.

## 5.11 ADVERSE OUTCOME PATHWAYS: A CHEMICAL-AGNOSTIC APPROACH

The idea of adverse outcome pathways was first proposed in 2010. An AOP is a conceptual scheme based on biological knowledge that uses the extant knowledge between a molecular initiating event (MIE), the initial key event in a toxicity pathway or mode of action, and a linked series of KEs leading to an adverse outcome at a level of biological organization (e.g., tissue, organism, population) relevant to risk assessment.<sup>199</sup>

Predictive toxicology, as exemplified by AOPs, is an appealing concept. The 2007 report from the National Research Council, *Toxicity Testing in the 21st Century*, provided the road map that eventually led to AOP development. The predictive aspect of AOPs is intrinsic to the idea of key event relationships (KERS)—to what extent does an upstream KE need to manifest in order to produce a downstream KE? The idea of tipping points or thresholds is embodied in KERS. To provide support for the MIEs, KEs, and KERS, the Bradford Hill considerations for causality have been tailored to provide a weight of evidence analysis for transparent communication of the specific lines of evidence supporting an AOP.<sup>94,384</sup> The current sticking point with AOPs is their assembly into AOP networks to describe multiple pathways and complex toxicological processes with several different outcomes.<sup>385,386</sup>

AOPs differ from MOA in that AOPs are “chemically agnostic”; this term means that one need not consider a specific chemical when discussing the toxicity pathways described by an AOP. As a result, AOPs can be thought of as hypotheses for how specific chemicals produce effects via specific biological pathways. Quantitative and statistical methods have been envisioned for using AOPs as a prediction tool to

provide a complete hazard characterization and prediction of risks to humans, ideally without animal testing.<sup>387-393</sup>

### **5.11.1 Adverse Outcome Pathways and Mode of Action**

Obviously, considerable overlap exists between the related concepts of AOPs and MOA. AOPs are considered chemical-agnostic, meaning that they consist only of response–response relationships that result from sufficient perturbation of a MIE by an unidentified stressor; if this idea seems overly flexible, the goal of AOPs is to interpret the effects of multiple stressors operating on multiple pathways. The link to specific chemicals may be facilitated with QSAR techniques, toxicokinetics, or even *in vivo* data.<sup>394</sup> The use of AOPs in this way is part of an integrated approach to testing and assessment or IATA.<sup>392,395</sup> An IATA for a specific chemical is essentially a value-of-information exercise to understand where data gaps exist and the cost and feasibility of additional data collection. The goal, of course, is a risk assessment informed by the most appropriate interpretation of the most up-to-date science in an efficient and cost-effective manner.

## **5.12 CONCLUSION**

This chapter is long—both to read and to have written—and considerably longer than the corresponding chapter in the first edition of this book. I felt it was necessary to incorporate the many changes that have occurred in the intervening years.

## **5.13 EXERCISES FOR THOUGHT AND DISCUSSION**

### **5.13.1 Benchmark Dose Modeling for a Cancer Endpoint**

The web application at <http://benchmarkdose.org> from Dr. Kan Shao is recommended here. Alternatively, you can download and install EPA's BMDS software, available at [www.epa.gov/bmds/benchmark-dose-software-bmds-version-27-materials](http://www.epa.gov/bmds/benchmark-dose-software-bmds-version-27-materials). The recommendation here is to use version 2.7 because it does not have as many issues as the newer versions. For those of you knowledgeable in R, you can try PROAST.

Whatever software you choose, please find the animal bioassay reports from the National Toxicology Program at <http://ntp-server.niehs.nih.gov/>. Navigate to the section on reports and publications, and find the long-term study reports. You can obtain data from any of the reports, but the recommended ones are TR-521 on TCDD administered by corn oil gavage and TR-546 on hexavalent chromium in drinking water. Both of these have plenty of data to model. You should be able to fit a number of models to these data. This exercise will help you become familiar with both the NTP reports and with benchmark dose modeling.

### 5.13.2 Benchmark Dose Modeling for Non-Cancer Effects

Obtain the NTP report on Wy-14,643 (TOX-62) from <http://ntp-server.niehs.nih.gov/> and use the continuous models in BMDS to model the dose-response data in Table 7 on steroids and blood lipids. Think about your experience modeling these continuous data versus that modeling the quantal (frequency) data in the first exercise.

### 5.13.3 Comparison of Toxicity Criteria

Pick your favorite five chemicals. Use the internet to try to find at least three toxicity criteria. Compare the basis of these criteria. What are the strengths and weaknesses of each?

### 5.13.4 Grid Approximation to Obtain a BMD/ BMDL for a Continuous Endpoint

Please find in your library the following paper: Hamadani et al. (2011), “Critical windows of exposure for arsenic-associated impairment of cognitive function in pre-school girls and boys: a population-based cohort study,” *Int J Epidemiol* 40(6):1593–1604.<sup>396</sup>

Table 2 in that paper provides four different datasets showing IQ reduction in Bangladeshi children associated with arsenic exposure in drinking water. The exposure medium was urine and exposure quartiles of total urinary arsenic concentration are provided for exposure during early and late gestation and at 1.5 and 5 years old. Choose any of these datasets and calculate the IQ reduction from the lowest quantile. Assume the IQ data are normally distributed. You’ll need to calculate the standard deviation of the difference of two normal distributions as

$$\sigma_{difference} = \sqrt{\frac{\sigma_1^2}{n_1} + \frac{\sigma_2^2}{n_2}}$$

You should be able to calculate the 5th and 95th percentile values of urinary arsenic concentration within each quantile using the number within each quantile (n) and the plotting position or percentile calculated as  $pp = (i - 0.5) / (n + 0.5)$ , where i is an integer between 1 and n. You can calculate Z-scores using the NORM.S.INV function in Excel.

Using the 5th, 50th, and 95th percentiles of urine arsenic concentration and IQ change in each quantile, you can fit a simple dose-response equation using the Solver in Excel to each of the nine combinations of percentiles of dose and response. The equation that will likely fit all these combinations is a modified form of the Hill model,  $\Delta IQ = v \times C / (k + C)$ , where C = concentration and v and k are model parameters. Once you have values for v and k, use these to calculate the urinary arsenic concentration associated with a one-point change in IQ. Then calculate the plotting position for each of the sorted nine values and use rank order statistics as shown in

Box 4.2 to calculate a lognormal distribution of the urinary arsenic concentration associated with a one-point IQ drop. This will be the benchmark concentration associated with this effect.

To convert values from this distribution to a benchmark dose in mg/kg/d or  $\mu\text{g}/\text{kg}/\text{d}$ , please find Table 5 in Hays et al.'s 2010 paper "Biomonitoring equivalents for inorganic arsenic"<sup>327</sup> and use the appropriate conversion factor to calculate both the BMD and BMDL.

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## CHAPTER 6

# Risk Characterization

Security is mostly a superstition. Life is either a daring adventure or nothing.

**Helen Keller**

Life is being on the wire, everything else is just waiting.

**Karl Wallenda**

This chapter will provide a number of exemplar risk assessments. The first two follow guidance from EPA and can be considered traditional. The others are not so traditional and give examples of “thinking outside the box.” The direction of risk assessment methodology in years to come is uncertain; however, the general protocols established in the late 20th century will likely not be the tools of choice for analyzing and assessing risks as the 21st century continues.

The 1983 “Red Book” specifies risk characterization as the final component in a risk assessment and indicates that this activity is “the description of the nature and often the magnitude of human risk, including attendant uncertainty.” However, the document does almost nothing to define what a risk characterization should look like, except in the vaguest of terms.<sup>1</sup> However, the 1994 “Blue Book” provides much helpful guidance on risk characterization.<sup>2</sup> Four elements make up a risk characterization:

- quantitative estimates of risk;
- qualitative and, if available, quantitative descriptions of uncertainty;
- presentation of the risk estimates in their appropriate context;
- communication of the results of the risk analysis.

These four elements will be discussed in detail.

### 6.1 QUANTITATIVE ESTIMATES OF RISK

Two different methods of developing quantitative risk estimates exist—one for chemicals producing adverse effects considered to have a threshold, and the other for those for which no risk-free level of exposure is believed to exist based on the

linear no-threshold hypothesis (LNT). EPA uses the threshold method and reference doses for substances not associated with cancer and slope factors or unit risk levels for those substances considered carcinogenic.

The general equation for estimating risk for non-carcinogens is:

$$HQ = (1/RfD) \times (C \times CR \times EF \times ED) / (BW \times ED \times 365) \quad (6.1)$$

where:

$HQ$  = Hazard Quotient (unitless)

$RfD$  = Reference Dose (Toxicity Criterion) (mg/kg-d)

$C$  = Concentration (mg/kg or mg/L)

$CR$  = ContactRate or IngestionRate (amount per day)

$EF$  = Exposure Frequency (days/year)

$ED$  = Exposure Duration (years)

$BW$  = Body Weight (kg)

The general equation for estimating risk for carcinogens is:

$$Risk = CSF \times (C \times CR \times EF \times ED) / (BW \times AT) \quad (6.2)$$

where:

$CSF$  = Cancer Slope Factor (1/(mg/kg-d))

$AT$  = Averaging Time, usually 25,550 days, or 70 years

Equation 6.1 yields a unitless value for the hazard quotient after dividing the average daily dose in units of mg/kg-d by the reference dose (RfD), also in units of mg/kg-d. Values greater than unity indicate the potential for systemic toxicity leading to adverse effects. Equation 6.2 yields a unitless value for the probability of cancer, i.e., risk, after multiplying the average lifetime daily dose in units of mg/kg-d by the CSF in units of 1/(mg/kg-d). You may wish to conduct unit analysis on these equations to satisfy yourself that all units cancel to yield a unitless value for hazard or risk.

### 6.1.1 Estimating Risk for Systemic Toxicants (Not Associated with Cancer)

For each chemical-producing systemic toxicity, the dose estimate is divided by the RfD to obtain a hazard quotient (Equation 6.1). If the hazard index is less than 1, the risk for that chemical is considered unlikely to lead to adverse health effects. If the hazard index is greater than 1, adverse health effects are more likely, and suggest that risk management should be considered. For multiple chemicals, hazard quotients can be summed to estimate an overall hazard index (HI). For exposure by the dermal route, the RfD is adjusted to reflect an absorbed dose, as detailed in Appendix A of EPA's *Risk Assessment Guidance for Superfund, Volume I, Part A*.<sup>3,4</sup>

For exposure by the inhalation route, the reference concentration (RfC) is used in lieu of the RfD.<sup>5</sup>

EPA's *Risk Assessment Guidance for Superfund, Volume I, Part A* indicates that hazard quotients should be summed by either target organ or mechanism of action. Further, this document points out that the hazard index is thus not an actual measure of risk and that summing the HQ values over chemicals that act by different mechanisms would likely overestimate the potential for adverse effects.<sup>3</sup>

The real difficulty with the RfD concept is that while HI values appear to be quantitative measures of risk, they are more accurately regulatory "bright lines," appropriate for the determination of highly protective cleanup values, but inappropriate as accurate or "best" estimates of human health risk. The use of default values for uncertainty or safety factors in RfD derivation results in toxicity values that are very certain to be protective estimates of a human threshold, but the actual protectiveness remains unknown. The Agency for Toxic Substances and Disease Registry (ATSDR) of the Centers for Disease Control develops minimum risk levels (MRLs) by a process almost identical to that used to develop RfDs. MRLs are used in public health assessments to determine if people are likely to experience adverse effects. Toxicity criteria based on safety factors are inappropriate for such a public health assessment—indeed, the use of safety factors yields toxicity criteria that will result in protective cleanup levels, appropriate for engineers and environmental scientists engaged in remediation or standard setting, but inappropriate as a tool for predictive toxicology or public health.

### **6.1.2 Estimating Risk for Chemicals Associated with Cancer**

For each chemical presumed to be carcinogenic, the intake estimated as a dose, usually in units of mg/kg body weight/day, is multiplied by the slope factor in units of (mg/kg/d)<sup>-1</sup> (Equation 6.2). The resulting value will be a unitless probability value of the incremental risk of an individual developing cancer over a lifetime of exposure.

When exposure occurs by inhalation, unit risk values are used instead of slope factors. Usually, the most appropriate exposure value is a lifetime weighted average of air concentration, usually in units of  $\mu\text{g}/\text{m}^3$ . Multiplying by a unit risk value in units of  $(\mu\text{g}/\text{m}^3)^{-1}$  yields a unitless probability value of the incremental lifetime risk.

Because cancer risks are expressed as unitless probabilities, their summation across multiple chemicals and exposure routes is mathematically appropriate. Nonetheless, EPA cautions that summing risks across multiple exposure pathways should be carefully considered, and the authors of *Risk Assessment Guidance for Superfund, Volume I, Part A* were clearly aware of the problem of compounding conservatism discussed in Chapter 1.<sup>3</sup>

## **6.2 DEALING WITH UNCERTAINTY IN RISK ESTIMATES**

Knowledge will continue to be imperfect. Risk assessment is predictive—it tries to make statements about the future, but knowledge is based on the past and the interpretation of past events, and uncertainty is inescapable.

Risk estimates calculated using the “Red Book” paradigm of combining exposure and toxicity are conditional estimates based on many assumptions about exposure and toxicity.<sup>1</sup> Hence, characterization of uncertainty is also a necessary part of the overall risk characterization. Transparency in communicating the uncertainties and assumptions provides appropriate perspective, and may also identify data gaps for which additional research or data collection might be advantageous.

In some cases, quantitative statistical uncertainty analysis can provide some insights. A full treatment of quantitative uncertainty analysis is beyond the scope of this book. However, Chapter 3, which provides an introduction and some hopefully useful techniques, is a good place to begin.

Sadly, the general public, and even many scientists, have become increasingly innumerate; hence, the results of any quantitative analysis will likely be challenging to communicate.<sup>6–8</sup> In many cases, quantitative uncertainty analysis may not add much insight to the risk characterization. Value of information (VOI) is a type of uncertainty analysis that attempts to assess “bang for the buck” regarding the question of whether to conduct additional data collection or analysis.

### **6.2.1 The Nature and Classification of Uncertainty**

There are a number of ways to classify the types of uncertainties in a risk assessment. A number of authors have provided typologies of uncertainty over the past three decades, and no single scheme has come into general usage.<sup>9–11</sup>

Aleatory uncertainty or variability refers to the variation inherent in a population and just how well or how poorly the risk assessment represents this target population. For example, how well does the value of 70 kg for the body weight of an adult represent a target population in Memphis, Tennessee, reported to have the highest obesity rate of US cities, versus Portland, Oregon, reported to be the most fit city in the US. Aleatory uncertainty can be quantified, but not reduced, with additional data collection.

Epistemic uncertainty or incertitude refers to lack of knowledge or ignorance, and is most often called simply “uncertainty.” How sure can one be that the parameter values or model structure used to evaluate risks are correct? This type of uncertainty can be reduced by additional data collection. For example, one might wish to know just how much time children spend outside in their yards (front or back). The default generally used by EPA in Superfund-type risk assessments is 350 days per year. How accurate is this value today, when children have many indoor activities, such as video games and online activities, on which to spend time? Recent data obtained from children wearing Global Positioning System transmitters, video recording, or sampling by dedicated cell phones with a method called ecological momentary assessment suggests that the true value of time spent outside by children in the 21st century is much less. The epidemic of childhood obesity in the developed world is ample testimony to this fact.<sup>12–17</sup>

Another classification of uncertainty exists as well. Parameter uncertainty arises from measurement error or whether the parameter values used in a risk assessment represent the target population accurately. Model uncertainty arises from lack of an

adequate scientific basis for the theory underlying some aspect of the risk assessment. For example, page 165 of the “Blue Book” highlights the validity or lack thereof of the linear no-threshold model as an example of model uncertainty.<sup>2</sup>

Some uncertainty can be addressed on a purely statistical basis—conducting a Monte Carlo or probabilistic risk assessment is one way to address the issue of aleatory uncertainty. Some data are inherently uncertain and have been developed at great cost and effort. For example, the data on children’s soil and dust ingestion discussed in Chapter 4 are uncertain. Additional data collection may support these data, but this quantity and a number of other issues in risk assessment represent “deep” uncertainties, as recently characterized by the National Academy’s Institute of Medicine.<sup>18</sup>

Deep uncertainties are those that are unlikely to be resolved in the time frame in which a risk management decision is needed. This type of uncertainty occurs when fundamental disagreements exist among scientists about either the nature of biological or environmental processes or the methods to characterize these processes. Although expert elicitation may be considered as a means of addressing these deep uncertainties, that process (discussed below) does not always work.

When the stakeholders in a decision process have fundamental disagreements, a situation arises in which the decision may be subject to undue political influence. In such cases, risk assessors may be pressured to alter or revise the results of their analyses to support a desired outcome.

Hence, a caution is provided for the readers of this textbook—if you find yourself in such a situation and have provided an honest, transparent, and good faith risk characterization, resist any political pressure to change your results. Have good reasons to believe in your analysis and be able to communicate them. If you change your mind without a sufficient science-based reason, you will be perceived as waffling or indecisive—or worse, dishonest. New or additional information may alter your conclusions; in such a case, you must be able to present both the reasoning behind your original conclusion and your reason for the change of mind in a forthright, easy-to-understand, and transparent fashion.

### **6.2.2 Identification and Quantification of Uncertainty**

In all environmental risk assessments, considerable uncertainty exists regarding the numerical values of inputs and the quantitative estimates of risk—a range of an order of magnitude or more. Generally, identification of the key factors and assumptions that contribute most to the overall uncertainty will provide as much information as any attempt to quantify the overall uncertainty.

Uncertainty exists in both the exposure assessment and the toxicity assessment. Uncertainty regarding exposure exists in chemical monitoring data, in the understanding of the environmental fate of chemicals, and in the nature and extent of human contact with chemicals in various environmental media. Uncertainty regarding toxicity exists, largely because of the lack of information on the mode of action for most chemicals. Future changes in the science base of risk assessment also introduce uncertainty—no one can predict the future, and to a large degree, predicting the future is the primary task of risk assessment.

### 6.2.3 Presentation of Uncertainty in Risk Estimates

The results of risk assessments are often boiled down to single numbers. The “Red Book”, the “Blue Book,” and the 1992 risk characterization memo from F. Henry Habicht of EPA all opined on this inappropriate over-condensation of information.<sup>12,19</sup> William Ruckelshaus, EPA administrator during the Reagan administration, also lamented the use of what he derogatorily called “magic numbers”:

First, we must insist on risk calculations being expressed as distributions of estimates and not as magic numbers that can be manipulated without regard to what they really mean. We must try to display more realistic estimates of risk to show a range of probabilities. To help do this, we need new tools for quantifying and ordering sources of uncertainty and for putting them into perspective.<sup>20</sup>

Chapter 6 of *Risk Assessment Guidance for Superfund, Volume 3: Guidance for Probabilistic Risk Assessment*, provides a discussion of how to present quantitative estimates of risk and uncertainty to a variety of audiences. This source provides a good starting point.

Nonetheless, and already briefly mentioned, an overarching challenge exists—the general innumeracy of many audiences; these audiences would include the general public, upper-level managers, many attorneys, legislators, and others. According to the National Adult Literacy Survey, almost half of the general population are challenged by relatively simple numeric tasks.<sup>21</sup> Numeracy is an essential skill for understanding risk–benefit information and making appropriate judgments, and unfortunately, communicating quantitative risk information, especially information about uncertainty, to most audiences will require considerable “dumbing down.”<sup>22</sup> The field of risk communication evolved to develop ways to communicate complex information in ways that a variety of audiences can understand. In general, successful risk communication requires empathy, compassion, humility, and insight.

### 6.2.4 Quantitative Assessment of Variability and Uncertainty

Later in this chapter, examples are provided of full risk assessments. In the past, a piecemeal approach to uncertainty analysis has been adopted. In *Risk Assessment Guidance for Superfund, Volume 3: Part A* (see [www.epa.gov/risk/risk-assessment-guidance-superfund-rags-volume-iii-part](http://www.epa.gov/risk/risk-assessment-guidance-superfund-rags-volume-iii-part)), EPA indicated that application of the probabilistic methods to the toxicity assessment was not justified.<sup>23</sup> Appendix D of this guidance document does, however, provide details of methodology for quantitative assessment of variability and uncertainty in exposure assessment. In this book, Box 1.3 in Chapter 1 provides a relatively simple way to address quantitative uncertainty in both exposure and toxicity.

## 6.3 RISK ASSESSMENT AS A DESIGN PROBLEM

Uncertainties in the risk assessment need to be described and made fully transparent to all stakeholders. The communication of these uncertainties to the risk manager is most often a difficult task. Risk assessors should be aware that a risk manager

wants to arrive at the end of the process with a clear path forward—either a rationale for no action, a strategy for cleanup, or an explicit plan for additional data collection to address one or more of the areas of uncertainty. Value of information may also be challenging to communicate, but VOI may be the best means of deciding whether to address uncertainties by additional data gathering.

### 6.3.1 Value of Information Analysis

A practical and robust approach to environmental decision-making requires that the risk manager understand in which areas uncertainty is irreducible and in which uncertainty can be lessened by more data. The value of this information is required by the manager—only with this VOI information can the manager choose whether to delay a decision in order to collect more data or whether to proceed in order to obtain immediate but uncertain benefits in terms of public health protection.<sup>24</sup>

This conflict between delaying a decision to wait for more data or to continue with a plan to address an environmental hazard with the current state of knowledge is inherent in any science-based decision process. There is no end to the scientific process, and uncertainty, as noted in an earlier chapter, is its ever-constant hand-maiden.

In a popular science book titled *Doubt Is Their Product: How Industry's Assault on Science Threatens Your Health*, David Michaels characterizes any science produced by industry as flawed.<sup>25</sup> In 2012 and 2013, scientists at the Environmental Working Group and the National Resources Defense Council suggested to the National Academies of Sciences (NAS) in a public forum that any research program funded by the chemical industry should be considered fatally flawed and should not be used in any Integrated Risk Information System (IRIS) assessments conducted by EPA. These activists also suggested that EPA should move ahead as quickly as possible with IRIS assessments with whatever information was available.

Here's the counterargument: the chemical industry is concerned that its products are safe. The industry is in a unique position—in contrast to regulatory agencies or non-governmental organizations, chemical companies are able to afford the cost of research. This conflict puts regulatory agencies such as EPA in the role of arbiter of this most basic of quandaries when applying scientific information for decision-making: how much is enough?

There are no established “stopping criteria” in pure research. But sometimes decisions are required without having complete information. The difficulty in knowing how much is enough adds to this inherent societal conflict in which those who would attempt to limit the extent of scientific inquiry and debate to meet a regulatory deadline and those who believe that there may be significant value in the information expected from ongoing and incomplete research.<sup>24</sup> The Scylla and Charybdis of this dilemma represent the choice between blithely forging ahead with a decision that has unknown consequences versus “paralysis by analysis.”

The decision-theoretic process begins with analyzing what can be done given the current state of knowledge and what potential improvements in the decision can result from additional knowledge. In 2003, a risk assessor working at the Region 4 offices of EPA advised the project manager for the Barber's Orchard Superfund site in Waynesville, North Carolina to obtain site-specific bioavailability measurements

for arsenic. The site was an old apple orchard at which arsenical pesticides were used. The land was subsequently sold to a developer who built luxury homes worth over \$200,000 each. A decision document for the site was written in 2004 with a cleanup cost for the entire site of over \$30 million. The decision was not approved by the Superfund Remedy Review Board.<sup>26</sup> The project manager did eventually obtain site-specific information about arsenic bioavailability from an *in vivo* bioavailability study using monkeys conducted at the University of Florida.<sup>27</sup> The use of these bioavailability data reduced the cleanup costs from \$32,000,000 to about \$15,000,000.

### **6.3.2 Additional Thoughts about Expert Elicitation**

Formal expert elicitation (EE) is one of the means towards a structured and transparent way to address such uncertainties. When insufficient knowledge for decision-making is available, this process provides a structured approach to seek the published and unpublished knowledge of experts for the purpose of developing quantitative estimates for use in risk assessment. Hence, expert elicitation is a process to synthesize the limited available information before conclusive scientific evidence is developed. A formal systematic method for elicitation improves the transparency and reproducibility of the information.

In the 1980s, EPA's Office of Air Quality Planning used expert elicitation to assess exposure response relationships for lead and ozone.<sup>28</sup> The advantage of expert elicitation is that the process combines knowledge from different disciplines that likely have differing views on the issue being considered. When data limitation or incomplete understanding of the problem at hand prevents conventional approaches to uncertainty analysis, EE may be helpful as a formal process to quantify expert judgments in terms of probability. Both the "Red Book" and "Blue Book" provide support for EE.<sup>1,2</sup> Circular A-4 from the Office of Management and Budget concerning quantitative uncertainty analysis for regulatory decisions over \$1 billion also supports EE.<sup>29</sup>

#### **6.3.2.1 Methods for Expert Elicitation**

One of the earliest structured methods for EE was the Delphi method, developed in the 1950s at the RAND corporation and used by the US Air Force to address Cold War issues. The Delphi technique seeks to obtain the most reliable consensus of opinion from a group of experts using both questionnaires and feedback.<sup>30</sup>

In many expert elicitations, what is done is to suggest to the experts that they describe their estimates using gambling analogies as a means of encoding probabilities. Two kinds of experts are selected for participation in formal expert elicitation: substantive experts who possess knowledge of the subject matter being considered, and normative experts with expertise in decision analysis, psychology, and group facilitation.

Using a consensus technique to develop information may be viewed as circumventing the scientific method; nonetheless, expert elicitation is generally accepted as a reasonable tool for developing increased certainty about the information needed

for risk assessment. Expert elicitation is not often used—it is usually not practical or necessary for most decisions based on environmental risk assessment because of resource limitations and concerns about public and stakeholder acceptance of the results.

## 6.4 COMPARISON TO BACKGROUND

The term “background” is general, and refers to a reference against which to measure a difference. “Background” at hazardous waste sites means the concentrations in environmental media if site contamination were absent. For substances that occur ubiquitously in the environment and to which all humans are exposed, biomonitoring data provides the most direct measurement of exposure; in this instance, “background” means the level of a substance in the body that can be measured in different demographic groups, and the decision of which group constitutes “background” is specific to the situation. Background disease incidence provides yet another comparator. Risk from exposure to arsenic is considered several times in this chapter. Arsenic and tobacco smoke may synergize to increase lung cancer incidence.<sup>31</sup> Considering a group of smokers who are also exposed to arsenic, a group of non-smokers would be the “background” or reference for the effect of smoking, whereas for arsenic, the lowest exposure quantile would represent background. Additionally, one might want to perform the analysis twice—excluding and including smokers.

### 6.4.1 Comparison to Background at Hazardous Waste Sites

Before 2002, EPA used comparison to background as part of selection of chemicals of potential concern (COPC). In fact, this was performed in the second example below of the gold mine. Selection of the background dataset is critical to this process. However, an EPA guidance document on background comparison released in 2002 indicated in an appendix that background comparison should occur after risk characterization and that site-related risks should be compared to background risks.<sup>32</sup> Many risk assessors and project managers at EPA believed this policy would result in a confusing message—there would be at least two risk estimates, and risk comparisons have been shown to be difficult for the lay public to understand fully.<sup>22,33</sup>

In a number of instances, many EPA project managers and risk assessors disagreed with the advice in the guidance and continued to use comparison to background as part of COPC selection.

### 6.4.2 Comparison to Background Exposures Based on Biomonitoring Data

The National Health and Nutrition Examination Survey (NHANES) conducted by the Centers for Disease Control has collected a wealth of biomonitoring data. Data on blood and urine concentrations of metals, volatile organic compounds, steroid hormones, albumin, creatinine, and other analytes are available. These samples

can be used to assess external exposure. Urine samples are obviously easier to collect, but the analysis of urinary data may be a challenge due to inter- and intra-individual variation in urine volume, urine flow, and creatinine excretion that, apart from external exposure, all affect biomarker concentrations in urine.<sup>34-37</sup>

#### **6.4.3 Comparison to Background Incidence of Health Effects**

The 2009 publication from the National Research Council, *Science and Decision: Advancing Risk Assessment*, has been discussed earlier. One aspect deserves mention. This guidance offered three conceptual models for population dose response with not a scintilla of biological support, a significant flaw in this otherwise very good document. Variation in either background exposures and individual disease susceptibility were assumed to “linearize” the dose response.<sup>24</sup> This approach received considerable criticism in the scientific literature.<sup>38-43</sup>

Background disease incidence is obviously necessary to quantify as part of hazard assessment using epidemiologic data, as presented in Chapter 5. However, the use of background incidence as an argument for a linear dose response is not consistent with biological observations.<sup>44-46</sup>

### **6.5 RISK ASSESSMENTS FOR ENVIRONMENTAL CONTAMINATION**

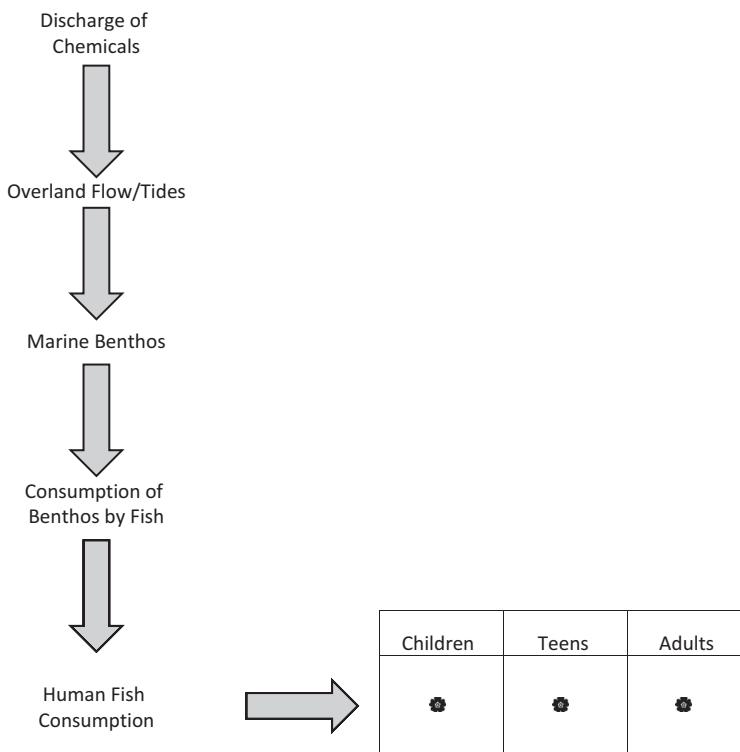
The remainder of this chapter will present several risk assessments, including the risk characterizations. These examples were developed from real world situations. The presentation has been tailored to illustrate both qualitative and quantitative uncertainty, and other aspects of the risk characterization.

In these examples, some narrative that might occur in a typical risk assessment is provided. Conclusions about the estimated level of risk are presented in such a way as to highlight the uncertainties. In addition, interactions between the risk assessor and the decision-maker are presented, to provide examples of how the risk assessment can aid decision-making without compromising its scientific basis.

#### **6.5.1 Consumption of Contaminated Fish**

In this example, marine fish contain bioaccumulative chemicals produced by legacy industrial processes. These fish are consumed by coastal anglers and others. The conceptual model for the site is shown in Figure 6.1. Because only a single exposure pathway is considered, this conceptual model is much simpler than that for the former gold mine example later in this chapter.

Chlorine has been a commodity chemical for over 100 years. Most often, chlorine is produced by the chlor-alkali process by electrolytic decomposition of brine or seawater. One of the past uses of chlorine was the production of pesticides, specifically the pesticide toxaphene, first introduced in 1945. Toxaphene was widely used as an insecticide on cotton, soybeans, and corn.<sup>47</sup>



**Figure 6.1** Conceptual site model for fish consumption risk assessment.

Toxaphene was produced by passing chlorine gas through a mixture of camphenes and bornanes derived from pine stumps in the presence of ultraviolet radiation.<sup>48</sup> This process resulted in the nonselective addition of chlorine to mainly bornane molecules, leading to a highly complex technical mixture of chlorinated camphenes and bornanes.<sup>49</sup> The total worldwide use of toxaphene is estimated to be 1.3 million tons, of which about 40% is used in the United States, primarily in the southeast.<sup>49</sup> Toxaphene was deregistered in the US in 1982 and banned in 1990. The most persistent toxaphene congeners in humans are known as p-26, p-50, and p-62. The sum of the concentrations of these three congeners is referred to as  $\Sigma 3PC$ , and provided the basis for a toxicity criterion developed in 2006.<sup>50</sup>

The chlorine used to produce toxaphene was produced at a nearby chlor-alkali plant. Both polychlorinated biphenyls and mercury are used in the electrolytic cells needed for the chlor-alkali process. Toxaphene, Aroclor 1268, a high-molecular weight polychlorinated biphenyl (PCB) mixture, and mercury were released during chlorine production and toxaphene manufacture. All three chemicals bioaccumulate in fish, and this example demonstrates the risk assessment of consumption of fish contaminated with these three chemicals. The last number in the Aroclor

designation represents the weight percentage of chlorine in the PCB mixture. The most highly chlorinated mixture is Aroclor 1268, with 68% chlorine by weight.

The high-molecular weight congeners tend to be less toxic than other PCB congeners. EPA does not have toxicity criteria for Aroclor 1268; because the toxicity of this mixture is lower than other PCB mixtures, both a cancer slope factor and reference dose specific to Aroclor 1268 have been developed and are published in the scientific literature.<sup>51,52</sup>

#### **6.5.1.1 Selection of COPCs**

The site where toxaphene was produced is located on the Atlantic coast in the southeastern US. Manufacture of the pesticide occurred from 1948 until 1980. In 1997, 2001, and 2005, fish were sampled and toxaphene tissue residues analyzed. Full datasets for toxaphene congeners in fish, including p-26, p-50, and p-62, were available from samples obtained in 1997 and 2005.

Fish samples are analyzed about every two years for mercury and PCBs as part of routine monitoring for fish advisories; samples are available from 2002 forwards. Datasets for Aroclor 1268 and mercury were available from samples obtained from 2002 through 2006.

Because the site is in a relatively rural location with no other industry around, toxaphene, Aroclor 1268, and mercury were the only chemicals of potential concern. Hence, for this example, the exposure and toxicity assessments will be emphasized, rather than COPC selection.

#### **6.5.1.2 Reduction in Total Toxaphene Concentrations in All Fish**

From data obtained in 1997, prior to any remediation, the concentration for total toxaphene residues from fish was  $5250.8 \pm 6531.3 \mu\text{g/kg}$  (mean  $\pm$  standard deviation).<sup>53</sup> In fish collected in 2001, the concentration of total toxaphene residues was  $1400 \pm 3500 \mu\text{g/kg}$ .<sup>54</sup> During the time between these two sampling events, dredging had been performed in a canal to remove sediment with the highest toxaphene concentrations—the likely reason for these reductions.

In addition to the reduction in total toxaphene (TTX) residues,  $\Sigma 3\text{PC}$  concentrations in all fish decreased from a mean of  $222.0 \mu\text{g/kg}$  in 1997 to a mean of  $21.0 \mu\text{g/kg}$  in 2005, about a ten-fold reduction. The average percentage of  $\Sigma 3\text{PC}$  in TTX in the 1997 fish samples was 4.14%. The average percentage of  $\Sigma 3\text{PC}$  in TTX in fish in the 2005 samples was 1.14%, an approximate 75% reduction. Hence, both the concentration of TTX and the percentage of persistent congeners decreased. Had single-congener analysis been performed on the 2001 samples, a trend analysis might have revealed a decreasing concentration term; however, such analysis was not performed.<sup>54</sup>

Because p-26, p-50, and p-62 are the congeners most resistant to metabolism, biotransformation, or abiotic weathering, the reduction in both the concentration of  $\Sigma 3\text{PC}$  in fish and the percentage of  $\Sigma 3\text{PC}$  in total toxaphene residues from 1997 to 2005 is somewhat surprising.<sup>50</sup> The expectation is that the percentage of  $\Sigma 3\text{PC}$  in

total toxaphene residues would increase because other congeners would be metabolized or degraded.<sup>55-57</sup>

One possible interpretation of this result is that the dredging perturbed the ecosystem in such a way that the fish sought prey items from other locations that were less contaminated. Supporting the hypothesis that the reduction in  $\Sigma 3PC$  is due to changes in feeding strategies or locations of some of the fish species is the fact that concentrations in Red Drum changed very little. Red Drum move in and out with the tides and feed over a wide area. This type of feeding strategy will tend to dilute the amount of  $\Sigma 3PC$  in the prey items with high concentrations of toxaphene. Large differences in individual concentrations were observed in fish species with smaller home ranges, such as Striped Mullet and Spot (Tables 6.1a, b, and c). Had congener analysis been available for more than two instances, the reduction in  $\Sigma 3PC$  might have been taken into account in the risk assessment in a quantitative fashion.

#### **6.5.1.3 Concentrations in Fish**

Tables 6.1a, b, and c show the data for the three COPCs in the various species of fish. Table 6.2 shows the statistics and exposure point concentrations (EPCs) for the various species.

#### **6.5.1.4 Exposure Assessment: Human Factors**

This portion of the exposure assessment deals with the choice to eat fish, which species are consumed, the portion size of fish and how often people consume self-caught fish.

##### **6.5.1.4.1 Proportion of Species Consumed**

The Marine Recreational Fisheries Statistics Program of the Office of Science and Technology within the US National Oceanic and Atmospheric Administration (NOAA) conducts the Marine Recreational Fisheries Statistics Survey (MRFSS) to produce catch, effort, and participation estimates and to provide biological, social, and economic data. EPA made use of these data obtained from 1986 to 1993 to determine estimates of consumption of marine fish presented in the *Exposure Factors Handbook*.<sup>58,59</sup>

The data (Tables 6.1a, 6.1b, 6.1c) consist of analytical results from fish species likely to be consumed by humans (e.g., Red Drum, Spotted Seatrout) as well as those less likely to be consumed (e.g., Spot Croaker, Striped Mullet). The likelihood of consumption of a given species is based on a relative species harvest analysis of the Marine Recreational Fisheries Statistics Survey data from 2001 through 2005 (Table 6.3).

The MRFSS consists of a telephone survey and an intercept survey conducted at two-month intervals. These two-month intervals are called waves. The period of two months was chosen because it was the maximum time for easy recall of past fishing trips. The intercept data from 2001 through 2005 were used here.

Table 6.1a Concentrations of Aroclor 1268, Methylmercury, and Toxaphene as  $\Sigma$ 3PC in Fish

	Atlantic Croaker						Red Drum					
	Aroclor 1268 (mg/kg)	Methylmercury (mg/kg)	Toxaphene (µg/kg)	$\Sigma$ 3PC	Aroclor 1268 (mg/kg)	Methylmercury (mg/kg)	Toxaphene (µg/kg)	$\Sigma$ 3PC	Aroclor 1268 (mg/kg)	Methylmercury (mg/kg)	Toxaphene (µg/kg)	$\Sigma$ 3PC
2002	0.17	2002	0.067	1997	5300	163.16	2002	0.16	2002	0.226	1997	490
2002	0.20	2002	0.462	1997	11000	334.19	2002	0.33	2002	0.550	1997	1400
2002	0.96	2002	0.156	1997	11000	296.69	2002	0.32	2002	0.230	1997	79
2002	0.60	2002	0.208	1997	6300	20769	2002	<0.05	2002	0.111	2005	596.0
2002	1.56	2002	0.168	2005	350	1.0	2002	0.19	2002	0.440	2005	955.5
2002	1.02	2002	0.112	2005	419	1.0	2002	<0.05	2002	0.312	2005	1774.5
2002	0.64	2002	0.195	2005	1085	3.0	2002	<0.05	2002	0.156	2005	361.0
2002	0.49	2002	0.351				2002	<0.05	2002	0.242	2005	221.0
2002	0.58	2002	0.139				2002	0.17	2002	0.195	2005	937.0
2002	0.71	2002	0.174				2002	<0.05	2002	0.276	2005	159.0
2002	0.90	2002	0.149				2002	<0.05	2002	0.165	2005	159.5
2002	0.81	2002	0.170				2002	<0.05	2002	0.136	2005	209.0
2002	2.24	2002	0.228				2002	<0.05	2002	0.062	2005	85.0
2002	0.87	2002	0.233				2002	0.46	2002	0.240	2005	75.5
2002	0.81	2002	0.155				2002	<0.05	2002	0.253	2005	59.5
2002	0.39	2002	0.018				2005	0.10	2005	0.377		5.88
2002	<0.05	2002	0.210				2005	0.03	2005	0.173		3.28
2002	1.04	2002	0.096				2005	0.11	2005	0.266		6.17
2002	1.06	2002	0.147				2005	0.05	2005	0.173		
2005	2.10	2005	0.522				2005	0.24	2005	0.398		

(Continued)

Table 6.1a (Continued)

		Atlantic Croaker			Red Drum		
Aroclor 1268 (mg/kg)	Methylmercury (mg/kg)	Toxaphene (µg/kg)		Aroclor 1268 (mg/kg)	Methylmercury (mg/kg)	Toxaphene (µg/kg)	
		TTX	Σ3PC	2005	2005	2005	
2006	0.58	2006	0.267				
2006	1.40	2006	0.163				
2006	0.36	2006	0.172				

Note: Please note the difference in units between the measurements.

Table 6.1b Concentrations of Aroclor 1268, Methylmercury and Toxaphene as Σ3PC in Fish

		Southern Kingfish			Spot		
Aroclor 1268	Mercury	Toxaphene (µg/kg)		Aroclor 1268	Mercury	Toxaphene (µg/kg)	
		TTX	Σ3PC				
2002	0.50	2002	0.235	1997	2100	94.90	2002
2002	0.31	2002	0.097	1997	230	10.09	2002
2002	0.68	2002	0.230	1997	370	16.19	2002
2002	0.51	2002	0.368	1997	840	38.08	2002
2002	0.68	2002	0.146	2005	546	5.18	2002
2002	1.19	2002	0.297	2005	3038	45.40	2002
2002	0.48	2002	0.430	2005	2417	84.47	2002
2002	0.48	2002	0.225	2005	1032	0.53	2002
2002	0.12	2002	0.288	2005	370	3.67	2002
2002	0.18	2002	0.483	2005	402	2.13	2002
2002	1.25	2002	0.260	2005	446	1.89	2002

(Continued)

Table 6.1b (Continued)

Aroclor 1268	Southern Kingfish			Aroclor 1268			Spot		
	Mercury	Toxaphene (µg/kg)		Mercury	Toxaphene (µg/kg)		TTX	Σ3PC	
		TTX	Σ3PC		TTX	Σ3PC		TTX	Σ3PC
2002	0.59	2002	0.240	2005	196	3.73	2002	1.30	2002
2002	0.35	2002	0.350	2005	746	6.00	2002	0.96	2002
2002	0.53	2002	0.275	2005	85	0.55	<0.05	2002	0.061
2002	0.39	2002	0.299				2002	0.93	2002
2002	0.70	2002	0.456				2002	0.68	2002
2002	0.28	2002	0.625				<0.05	2002	0.090
2002	<0.05	2002	0.275				2002	0.32	2002
2002	1.34	2002	0.448				<0.05	2002	0.067
2002	<0.05	2002	0.315				2002	<0.05	2002
2002	<0.05	2002	0.352				2002	<0.05	2002
2002	0.31	2002	0.308				2002	1.49	2002
2002	0.30	2002	0.325				2002	0.21	2002
2002	0.90	2002	0.506				2002	1.19	2002
2002	0.80	2002	0.450				2002	<0.05	2002
2005	0.89	2005	0.975				2002	<0.05	2002
2005	0.15	2005	0.382				2002	<0.05	2002
2005	0.20	2005	0.189				2005	0.63	2005
2005	0.18	2005	0.743				2005	0.06	2005
2005	0.34	2005	0.252						
2005	1.40	2005	0.617						
2005	0.42	2005	0.156						
2006	0.94	2006	1.130						

Note: Aroclor 1268 and methylmercury are in mg/kg, and Toxaphene Σ3PC is in µg/kg.

Table 6.1c Concentrations of Aroclor 1268, Methylmercury and Toxaphene as  $\Sigma$ 3PC in Fish

Aroclor 1268	Spotted Seatrout				Striped Mullet			
	Mercury	Mercury	Toxaphene ( $\mu$ g/kg)	$\Sigma$ 3PC	Aroclor 1268	Mercury	Toxaphene ( $\mu$ g/kg)	$\Sigma$ 3PC
2002	0.32	2002	0.460	1997	3300	193.29	2002	1.30
2002	0.98	2002	0.476	1997	4400	117.39	2002	1.18
2002	<0.05	2002	0.220	1997	3600	166.76	2002	1.32
2002	0.82	2002	0.288	1997	940	30.8	2002	2.70
2002	0.50	2002	0.360	1997	1300	37.84	2002	1.57
2002	0.36	2002	0.494	1997	1300	55.99	2002	0.10
2002	0.28	2002	0.350	1997	110	5.4575	2002	0.33
2002	0.50	2002	0.384	2005	1077	37.62	2002	1.05
2002	0.15	2002	0.408	2005	1478	32.96	2002	2.28
2002	0.17	2002	0.400	2005	686	31.50	2002	1.98
2002	0.83	2002	0.312	2005	1249	22.66	2002	4.42
2002	0.11	2002	0.418	2005	1134	9.92	2002	2.02
2002	0.35	2002	0.350	2005	566	8.61	2002	10.50
2002	0.55	2002	0.406	2005	179	7.77	2002	0.24
2002	0.78	2002	0.416	2005	258	7.24	2002	0.26
2002	<0.05	2002	0.252	2005	234	5.77	2002	<0.05
2002	<0.05	2002	0.207	2005	116	3.79	2002	<0.05
2002	<0.05	2002	0.252	2005	128	2.78	2002	<0.05
2002	<0.05	2002	0.288	2005	311	0.94	2002	<0.05
2002	<0.05	2002	0.288				2002	<0.05

(Continued)

Table 6.1c (Continued)

Aroclor 1268	Spotted Seatrout			Toxaphene (µg/kg)			Striped Mullet		
	Mercury	Toxaphene (µg/kg)		Aroclor 1268	Mercury		Toxaphene (µg/kg)		
		TTX	Σ3PC		TTX	Σ3PC			
2002	<0.05	2002	0.235		2002	0.50	2002	<0.01	
2002	<0.05	2002	0.288		2002	0.29	2002	<0.01	
2002	0.19	2002	0.336		2002	<0.05	2002	0.017	
2002	<0.05	2002	0.220		2002	1.29	2002	0.006	
2002	<0.05	2002	0.280		2002	1.00	2002	0.014	
2002	<0.05	2002	0.484		2002	3.78	2002	0.023	
2002	<0.05	2002	0.624		2002	0.19	2002	0.022	
2002	<0.05	2002	0.460		2002	0.27	2002	0.020	
2005	0.18	2005	0.428		2005	3.40	2005	0.041	
2005	0.19	2005	0.362		2005	2.20	2005	0.049	
2005	0.16	2005	0.641		2005	2.00	2005	0.051	
2005	0.43	2005	0.759		2005	1.70	2005	0.026	
2005	0.61	2005	0.941		2005	0.71	2005	0.026	
2005	0.20	2005	0.564		2005	0.03	2005	0.013	
2005	0.11	2005	0.300		2005	0.43	2005	0.014	
2005	0.09	2005	0.263		2005	0.47	2005	0.022	
2005	0.12	2005	0.217		2005	0.59	2005	0.036	

Note: Units as specified earlier.

Table 6.2 COPC Selection for Contaminants in Fish Tissue

Constituent/ Species	Frequency	Percent Detects	Range of SQLs		Average Detect Min–Max	Screening Level*	Alternate Screening Level	COPC (Y/N)?	UCL	Method (PROUCL)
			Det./Total	Min–Max						
<b>Atlantic Croaker</b>										
Aroclor 1268	22/23	96%	0.05–0.05	0.166–2.244	0.885	0.0016	0.056	Y	1.044	95% KM (BCA) UCL
Total Toxaphene	7/7	100%	0.35–11	5.065	0.0029	NA	Y	8.506	95% Student's t UCL	
Toxaphene as Σ3PC	7/7	100%	0.001–0.334	0.144	NA	0.027	Y/Y	0.25	95% Student's t UCL	
Mercury	23/23	100%	0.018–0.522	0.198	0.014	NA	Y	0.248	95% Approx. Gamma UCL	
<b>Red Drum</b>										
Aroclor 1268	13/22	59%	0.05–0.05	0.03–0.456	0.175	0.0016	0.056	Y	0.164	95% KM (t) UCL
Total Toxaphene	15/15	100%	0.0595–1.775	0.504	0.0029	NA	Y	0.851	95% Approx. Gamma UCL	
Toxaphene as Σ3PC	15/15	100%	0.00045–0.058	0.014	NA	0.027	Y/N	0.0244	95% Approx. Gamma UCL	
Mercury	22/22	100%	0.062–0.55	0.245	0.014	NA	Y	0.287	95% Student's t UCL	
<b>Southern Kingfish</b>										
Aroclor 1268	30/33	91%	0.05–0.05	0.12–1.4	0.579	0.0016	0.056	Y	0.649	95% KM (BCA) UCL
Total Toxaphene	14/14	100%	0.0845–3.038	0.915	0.0029	NA	Y	1.504	95% Approx. Gamma UCL	

(Continued)

Table 6.2 (Continued)

Constituent/ Species	Frequency	Percent Detects	Range of SQLs	Range of Detects	Average Detect	Screening Level*	Alternate Screening Level	COPC (Y/N)?	UCL	Method (PROUCL)
	Det./Total		Min–Max	Min–Max						
Toxaphene as Σ3PC	14/14	100%	0.00053– 0.0949	0.0223	NA	0.027	Y/Y	0.0483	95% Approx. Gamma UCL	
Mercury	33/33	100%	0.097–1.13	0.386	0.014	NA	Y	0.452	95% Approx. Gamma UCL	
<b>Spot</b>										
Aroclor 1268	18/29	62%	0.05–0.05	0.062–3.07	0.93	0.0016	0.056	Y	0.838	95% KM (% Bootstrap) UCL
Total	16/16	100%	0.191–23	6.61	0.0029	NA	Y	11.88	95% Approx. Gamma UCL	
Toxaphene	16/16	100%	0.0005–1.21	0.263	0.0029	0.027	Y/Y	0.623	95% Adjusted Gamma UCL	
Toxaphene as Σ3PC										
Mercury	29/29	100%	0.042–0.3	0.101	0.014	NA	Y	0.12	95% Student's t UCL	
<b>Spotted Seatrout</b>										
Aroclor 1268	23 37	62%	0.05–0.05	0.089–0.98	0.383	0.0016	0.056	Y	0.342	95% KM (% Bootstrap) UCL
Total	19/19	100%	0.11–4.4	1.177	0.0029	NA	Y	1.855	95% Approx. Gamma UCL	
Toxaphene	19/19	100%	0.00094–0.193	0.041	0.0029	0.027	Y/Y	0.0713	95% Approx. Gamma UCL	
Mercury	37 37	100%	0.207–0.941	0.39	0.014	NA	Y	0.434	95% Approx. Gamma UCL	

(Continued)

Table 6.2 (Continued)

Constituent/ Species	Frequency	Percent Detects	Range of SQLs		Average Detect Min–Max	Screening Level*	Alternate Screening Level	COPC (Y/N)?	UCL	Method (PROUCL)
			Det./Total	Min–Max						
<b>Striped Mullet</b>										
Aroclor 1268	31/37	84%	0.05–0.05	0.027–10.5	1.615	0.0016	0.056	Y	2.737	95% KM (Chebychev) UCL
Total Toxaphene	18/18	100%	0.126–26	4.203	0.0029	NA	Y	Y	7.732	95% Approx. Gamma UCL
Toxaphene as $\Sigma$ 3PC	18/18	100%	0.0005–1514	0.166	0.0029	0.027	YY	Y	0.415	95% Adjusted Gamma UCL
Mercury	34/37	92%	0.01–0.01	0.0063–0.0514	0.0231	0.014	NA	Y	0.0251	95% KM (BCA) UCL

Note: All units are mg/kg.

Table 6.3 Proportion of Species Caught as Percentage of Total Recreational Catch

Year	Wave	Atlantic Croaker	Red Drum	Southern Kingfish	Spot Croaker	Spotted Seatrout	Striped Mullet
2001	1	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
2001	2	1.84%	19.14%	14.14%	0.17%	35.06%	0.00%
2001	3	0.00%	0.00%	42.36%	0.00%	20.08%	0.00%
2001	4	0.34%	6.38%	13.18%	0.12%	39.93%	0.00%
2001	5	0.05%	37.40%	19.05%	0.04%	30.22%	0.00%
2001	6	0.00%	26.15%	5.60%	0.00%	45.40%	0.00%
2002	1	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
2002	2	0.43%	15.66%	15.80%	0.00%	33.57%	0.00%
2002	3	0.00%	2.13%	13.13%	0.00%	31.02%	0.00%

(Continued)

Table 6.3 (Continued)

Year	Wave	Atlantic Croaker	Red Drum	Southern Kingfish	Spot Croaker	Spotted Seatrout	Striped Mullet
2002	4	0.07%	19.93%	26.61%	0.00%	34.27%	0.51%
2002	5	0.63%	31.13%	12.23%	0.06%	43.52%	0.00%
2002	6	0.00%	25.03%	0.86%	0.00%	59.72%	0.00%
2003	1	0.00%	25.64%	9.27%	0.00%	52.03%	0.00%
2003	2	0.40%	30.53%	44.89%	0.00%	17.44%	0.00%
2003	3	5.84%	7.70%	10.26%	0.12%	21.77%	22.10%
2003	4	11.35%	8.06%	10.72%	0.00%	19.18%	0.54%
2003	5	1.58%	37.60%	8.05%	0.00%	39.01%	0.00%
2003	6	0.31%	12.35%	3.51%	0.01%	81.13%	0.05%
2004	1	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
2004	2	0.00%	12.20%	44.42%	0.00%	22.59%	0.00%
2004	3	2.44%	11.23%	24.19%	0.00%	20.43%	0.00%
2004	4	0.61%	2.22%	36.92%	0.00%	43.15%	0.00%
2004	5	0.00%	33.55%	20.59%	0.15%	21.61%	0.00%
2004	6	0.00%	25.64%	9.27%	0.00%	52.03%	0.00%
2005	1	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
2005	2	0.00%	1.03%	81.62%	0.00%	3.75%	0.00%
2005	3	0.00%	3.05%	29.72%	0.00%	30.45%	0.00%
2005	4	1.84%	19.14%	14.14%	0.17%	35.06%	0.00%
2005	5	0.00%	43.54%	8.10%	0.07%	38.90%	0.00%
2005	6	0.00%	40.51%	3.04%	0.20%	44.62%	0.00%
Mean		0.96%	17.14%	17.99%	0.04%	31.59%	0.80%
Median		0.00%	14.01%	12.68%	0.00%	32.29%	0.00%

A recent study by the National Academies of Sciences revealed that the MRFSS was considerably flawed in its execution and the data generated are inaccurate and biased.<sup>60</sup> There were several criticisms by the NAS: (1) sampling and statistical issues, such as failure to include anglers with access to private property and the use of different survey methods in different states; (2) lack of reliable human dimensions data, such as social, behavioral, attitudinal, and economic data; (3) lack of coordination between federal and state personnel, and “balkanization” of the survey methods and designs; and (4) improved communication and outreach with anglers.

Even if the MRFSS data were reliable, their use would entail an estimation of consumption from the harvest—with considerable uncertainty in the results.<sup>60,61</sup> If MRFSS data from a sufficiently large area are included, it is appropriate to use MRFSS data to obtain the relative abundance of species in the overall catch. The proportion of various species in the MRFSS data would reflect both the relative abundance of various species and angler success. Table 6.3 shows the average percentage of the various species of fish caught by coastal Georgia anglers between 2001 and 2005 developed from the MRFSS data. The MRFSS data are available from the NOAA Fisheries website ([www.st.nmfs.noaa.gov/st1/recreational/downloads.html](http://www.st.nmfs.noaa.gov/st1/recreational/downloads.html)) as SAS export files. However, data from 2004 and 2005 are no longer available, possibly because of the critique from the NAS.

Because the concentrations of COPCs are different in different species of fish, likely due to their feeding strategies, weighting the species-specific exposure point concentrations according to angler success and preferences is necessary for a more accurate exposure estimate. Inclusion of this information in the exposure calculation is made quite simple by the use of a fraction ingested (FI) term applied to individual fish species.<sup>3</sup>

#### **6.5.1.4.2 Fish Consumption Rates**

Site-specific information from the Brunswick area obtained by ATSDR and the Glynn County Health Department in 1997 was used to develop exposure assumptions for subsistence fish consumers.<sup>62</sup> The monthly frequency of self-caught fish meals was estimated using three categories: < 1/week, about 1/week, and > 1/week. These categories were considered to represent 3, 5, and 7 meals per month respectively. Fish meal sizes were obtained from Table 16–111 in EPA’s 2011 *Exposure Factors Handbook* (EFH 2011). Seven meals per month was multiplied by the 75th percentile meal size to represent the reasonable maximum exposure (RME) fish consumption rate; these values are 18, 30, and 31 g/d for children, adolescents, and adults respectively. The value of three meals per month was combined with the 50th percentile meal size for children, adolescents and adults to represent the central tendency fish consumption rate; these values are 5.8, 7.2, and 9.3 g/d for children, adolescents, and adults respectively.

#### **6.5.1.5 Toxicity Assessment**

The toxicity assessment for fish consumption will consider only two classes of chemicals—toxaphene, a pesticide consisting of a mix of over 600 different congeners, and polychlorinated biphenyls, used in 20th century in transformers.

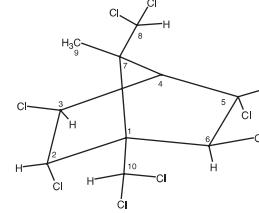
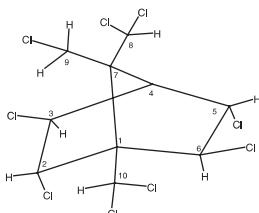
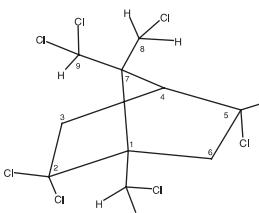
**Table 6.4** Exposure Assumptions

Receptor	Meal Size (Table 10-123, EFH 2011)		Meals per Month		Fish Consumption Rate (g/d)	
	RME	CTE	RME	CTE	RME	CTE
Child (2–5)	77	58	7	3	18	5.8
Adolescent (6–19)	127	72	7	3	30	7.2
Adult (20–60+)	134	93	7	3	31	9.3

Note: CTE = central tendency exposure.

#### 6.5.1.5.1 Toxaphene

Once in the environment, toxaphene undergoes weathering by both biotic and abiotic means, and a reduction in the number of congeners occurs. The three most persistent congeners observed in fish, marine mammals and humans are p26, p-50, and p-62. (Figure 6.2)<sup>50</sup> In the late 1990s, due to concern about human exposure to weathered toxaphene via fish consumption, the European Union commissioned the MATT study;

p-26	2-endo, 3-exo, 5-endo, 6-exo, 8,8,10,10 octachlorobornane or 2-exo, 3-endo, 5-exo, 6-endo, 8,8,10,10 octachlorobornane	
p-50	2-endo, 3-exo, 5-endo, 6-exo, 8,8,9,10,10 nonachlorobornane or 2-exo, 3-endo, 5-exo, 6-endo, 8,8,9,10,10 nonachlorobornane	
p-62	2,2,5,5,8,9,9,10,10 nonachlorobornane	

**Figure 6.2** Structures of the three persistent toxaphene congeners.

MATT stands for “Monitoring, Analysis and Toxicity of Toxaphene.”<sup>63</sup> EPA had previously developed an oral cancer slope factor for technical toxaphene of 1.1 per mg/kg/d based on liver tumor occurrence in mice. The toxicity assessment on IRIS was conducted prior to any focus on mode of action. In addition, weathering produces changes in composition of toxaphene, and the toxicity of weathered toxaphene was unknown.

Both technical toxaphene and weathered toxaphene produce rodent liver tumors via the same mode of action as phenobarbital—activation of the constitutive androstanone receptor and resulting induction of CYP enzymes leading to cytotoxicity with regenerative proliferation, a mode of action not relevant to humans.<sup>64,65</sup>

The MATT report misinterpreted this cancer slope factor as a “reference dose for carcinogenicity” and indicated that the US tolerable daily intake (TDI) value for a 60 kg individual would be 66 mg. The MATT derived a TDI of 0.41 mg/d for a 60 kg individual, equivalent to 0.007 mg/kg/d.<sup>66,67</sup>

In response to a request from a group of environmental activists living near the facility that produced toxaphene, EPA’s Office of the Inspector General issued a memo indicating that the EPA regional office needed a way to conduct a risk assessment of weathered toxaphene—all that was needed was a toxicity criterion.<sup>68</sup> At the urging of the project manager, one of the regional risk assessors teamed with Dr. Randy Manning, to whom the first edition of this book was dedicated, to develop a toxicity criterion from the experiments used in the MATT report. A reference dose with a value of 2E-05 mg/kg-d for Σ3PC was published soon thereafter.<sup>50</sup>

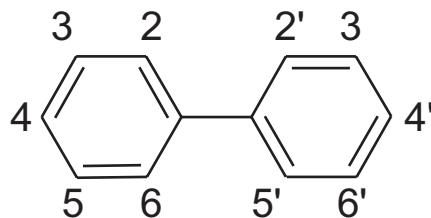
#### 6.5.1.5.2 *Aroclor 1268*

Polychlorinated biphenyls were produced for use as dielectric fluids during the 20th century. There are 209 different PCB congeners, depending on the position and level of chlorination (Figure 6.3). The various PCB congeners produce various effects at the cellular and biochemical level; whether PCBs produce health effects in humans remains both controversial and unconfirmed.<sup>69,70</sup>

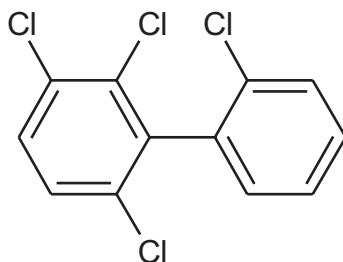
The congeners that produce the greatest toxicity are those in the middle range of chlorination, with four and five chlorines. Aroclor 1248 and Aroclor 1254, with 48% and 54% chlorine by weight respectively, are considered the most toxic of the PCB mixtures. Aroclor 1268 is 68% chlorine by weight and contains only a small percentage of congeners with less than six chlorines—hence, Aroclor 1268 has lower toxicity than the other Aroclor mixtures.<sup>70,88,51,52</sup>

The cancer slope factor for PCBs is based on liver tumors occurring in rodents dosed with PCBs.<sup>71</sup> The mode of action is similar to that of dioxin-like chemicals and is likely not applicable to humans.<sup>72</sup> For mixtures of high-risk, persistent congeners such as would occur in fish, the value is 2.0 per mg/kg/d. A cancer slope factor specific for Aroclor 1268 has been developed with a value of 0.27 per mg/kg/d.<sup>51</sup>

PCB mixtures have non-cancer effects, and reference doses exist in EPA’s IRIS database for Aroclor 1016 and Aroclor 1254. The RfD value for Aroclor 1016 is 7E-05 mg/kg/d, based on neurodevelopmental effects in monkeys. The RfD value for Aroclor 1254 is 2E-05 mg/kg/d, based on dermal effects. An RfD value for Aroclor 1268 has been developed based on comparison of congener composition



Chlorination positions on biphenyl for nomenclature of PCBs  
(a)



2,2',3,6-tetraCB or PCB-45  
(b)

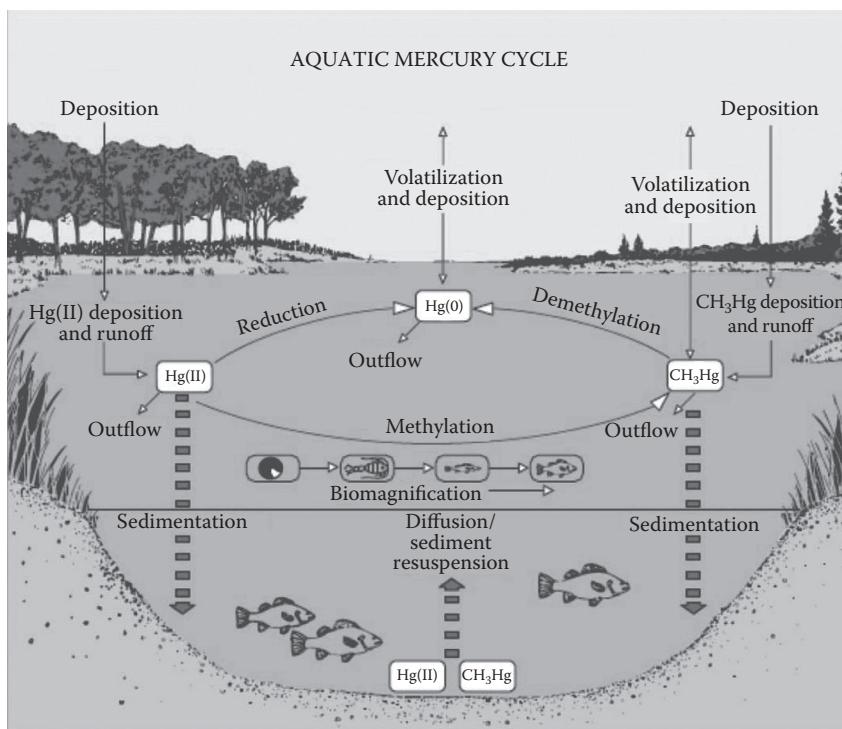
**Figure 6.3** PCB structure and nomenclature.

with both Aroclor 1016 and Aroclor 1254, with values of 1E-03 and 4E-04 mg/kg/d for the respective comparison Aroclor mixtures.<sup>52</sup>

#### 6.5.1.5.3 *Organic Mercury*

In fish, mercury exists as methylmercury (MeHg, or  $\text{CH}_3\text{Hg}^+$ ). Inorganic mercury is deposited from the air by rainfall in significant amounts and is transported in watersheds to water bodies. Methylmercury is formed in freshwater and estuarine ecosystems, primarily by sulfate-reducing bacteria in sediments. MeHg may become demethylated, and inorganic mercury may return to the atmosphere by volatilization.<sup>73,74</sup> A reservoir of mercury exists in the atmosphere and contributes to MeHg in fish and biota. Figure 6.4 provides a schematic diagram of mercury cycling.

Methylmercury produces neurodevelopmental effects, and unborn children represent a sensitive subpopulation. The RfD for methylmercury on EPA's IRIS database has a value of 1E-04 mg/kg/d and is based on longitudinal epidemiologic studies conducted in the Faroe Islands, the Seychelles, and New Zealand.<sup>75–77</sup> The dose–response analysis was conducted on the Faroese data using a one-compartment pharmacokinetic model.<sup>78</sup>



**Figure 6.4** Diagram of aquatic mercury cycling. Changing concentrations of mercury in the marsh due to methylation/deposition/volatilization enabled the use of the entire mercury and methylmercury datasets for calculation of the exposure point concentrations.

### 6.5.1.6 Risk Assessment Results

The RME cancer risk to the lifetime receptor was 3E-04. Of that, 1E-04 was attributable to Aroclor 1268 and 2E-04 attributable to toxaphene. The hazard indices for adults, adolescents and children were 2, 2, and 5 respectively. The CTE cancer risk to the lifetime receptor was 5E-05 and the CTE hazard indices were 0.6, 0.7, and 2 respectively for the adult, adolescent, and child receptors.

### 6.5.1.7 Uncertainty Characterization

One of the major uncertainties of the exposure assessment was the use of the MRFSS data, even just to assign percentages of the catch that were consumed. Other fish species were reported in the MRFSS—for example, Southern Flounder—but these species were not obtained during sampling and thus could not be analyzed for toxaphene. In addition, all the COPCs are lipophilic and bioaccumulative. Different cooking methods may remove some of these contaminants from fish. Last, the use

**Table 6.5a RME Risk Estimates for Adult Consumers of Fish**

Fish Species	EPC	FI	Cancer		Non-Cancer	
			mg/kg	%	mg/kg-day	mg/kg-day
<b>Atlantic Croaker</b>						
Aroclor 1268	1.044	0.96%	1.1E-06		2.6E-06	
Total Toxaphene	8.506				9.0E-06	
Toxaphene as Σ3PC	0.25					
Mercury	0.248					6.1E-07
<b>Red Drum</b>						
Aroclor 1268	0.164	17.14%	3.1E-06		7.2E-06	
Total Toxaphene	0.851				1.6E-05	
Toxaphene as Σ3PC	0.0244					
Mercury	0.287					1.3E-05
<b>Southern Kingfish</b>						
Aroclor 1268	0.649	17.99%	1.3E-05		3.0E-05	
Total Toxaphene	1.504				3.0E-05	
Toxaphene as Σ3PC	0.0483					
Mercury	0.452					2.1E-05
<b>Spot</b>						
Aroclor 1268	0.838	0.04%	3.7E-08		8.6E-08	
Total Toxaphene	11.88				5.2E-07	
Toxaphene as Σ3PC	0.623					
Mercury	0.12					1.2E-08
<b>Spotted Seatrout</b>						
Aroclor 1268	0.342	31.59%	1.2E-05		2.8E-05	
Total Toxaphene	1.855				6.5E-05	
Toxaphene as Σ3PC	0.0713					
Mercury	0.434					3.5E-05
<b>Striped Mullet</b>						
Aroclor 1268	2.737	0.81%	2.4E-06		5.7E-06	
Total Toxaphene	7.732				6.9E-06	
Toxaphene as Σ3PC	0.415					
Mercury	0.0251					5.2E-08
Total Intake from Fish			3.1E-05	1.3E-04	7.3E-05	6.9E-05
CSF/RfD			2	1.1	7E-05	7E-05
Risk/Hazard			6.3E-05	1.4E-04	1.0	1.0

**Table 6.5b RME Risk Estimates for Adolescent Consumers of Fish**

Fish Species	EPC	FI	Cancer		Non-Cancer	
			Aroclor 1268	Toxaphene	Aroclor 1268	Mercury
	mg/kg	percent	mg/kg-day	mg/kg-day	mg/kg-day	mg/kg-day
<b>Atlantic Croaker</b>						
Aroclor 1268	1.044	0.96%	3.0E-07		2.3E-06	
Total Toxaphene	8.506			2.3E-06		
Toxaphene as Σ3PC	0.25					
Mercury	0.248				5.4E-07	6.1E-07
<b>Red Drum</b>						
Aroclor 1268	0.164	17.14%	1.1E-06		8.6E-06	
Total Toxaphene	0.851			4.1E-06		
Toxaphene as Σ3PC	0.0244					
Mercury	0.287				1.1E-05	1.3E-05
<b>Southern Kingfish</b>						
Aroclor 1268	0.649	17.99%	3.4E-06		2.7E-05	
Total Toxaphene	1.504			7.6E-06		
Toxaphene as Σ3PC	0.0483					
Mercury	0.452				1.8E-05	2.1E-05
<b>Spot</b>						
Aroclor 1268	0.838	0.04%	2.1E-08		1.7E-07	
Total Toxaphene	11.88			1.3E-07		
Toxaphene as Σ3PC	0.623					
Mercury	0.12				1.0E-08	1.2E-08
<b>Spotted Seatrout</b>						
Aroclor 1268	0.342	31.59%	6.1E-06		4.7E-05	
Total Toxaphene	1.855			1.6E-05		
Toxaphene as Σ3PC	0.0713					
Mercury	0.434				3.0E-05	3.5E-05
<b>Striped Mullet</b>						
Aroclor 1268	2.737	0.81%	4.5E-07		3.5E-06	
Total Toxaphene	7.732					
Toxaphene as Σ3PC	0.415					
Mercury	0.0251				4.4E-08	5.2E-08
Total Intake from Fish			1.1E-05	3.0E-05	8.9E-05	5.9E-05
CSF/RfD			2	1.1	7E-05	7E-05
Risk/Hazard			2.3E-05	3.4E-05	1.3	0.8

**Table 6.5c RME Risk Estimates for Child Consumers of Fish**

Fish Species	EPC	FI	Cancer		Non-Cancer	
			mg/kg	percent	mg/kg-day	mg/kg-day
<b>Atlantic Croaker</b>						
Aroclor 1268	1.044	0.96%	4.5E-07		6.3E-06	
Total Toxaphene	8.506				3.4E-06	
Toxaphene as Σ3PC	0.25					
Mercury	0.248					1.5E-06 6.1E-07
<b>Red Drum</b>						
Aroclor 1268	0.164	17.14%	1.7E-06		2.3E-05	
Total Toxaphene	0.851				6.1E-06	
Toxaphene as Σ3PC	0.0244					
Mercury	0.287					2.9E-05 1.3E-05
<b>Southern Kingfish</b>						
Aroclor 1268	0.649	17.99%	5.1E-06		7.2E-05	
Total Toxaphene	1.504				1.1E-05	
Toxaphene as Σ3PC	0.0483					
Mercury	0.452					4.7E-05 2.1E-05
<b>Spot</b>						
Aroclor 1268	0.838	0.04%	3.2E-08		4.5E-07	
Total Toxaphene	11.88				2.0E-07	
Toxaphene as Σ3PC	0.623					
Mercury	0.12					2.8E-08 1.2E-08
<b>Spotted Seatrout</b>						
Aroclor 1268	0.342	31.59%	5.5E-06		7.7E-05	
Total Toxaphene	1.855				1.5E-05	
Toxaphene as Σ3PC	0.0713					
Mercury	0.434					4.8E-05 3.5E-05
<b>Striped Mullet</b>						
Aroclor 1268	2.737	0.81%	6.8E-07		9.5E-06	
Total Toxaphene	7.732					
Toxaphene as Σ3PC	0.415					
Mercury	0.0251					1.2E-07 5.2E-08
Total Intake from Fish			1.3E-05	3.6E-05	1.9E-04	1.3E-04
CSF/RfD			2	1.1	7.E-05	7.E-05
Risk/Hazard			2.7E-05	3.9E-05	2.7	1.8

of the site-specific fish consumption survey data along with the MRFSS data on species proportion of the catch raises the question of resource utilization.<sup>59</sup> The implicit assumption is that the proportion of fish caught represents the proportion of fish consumed. For example, Striped Mullet represented 0.8% of the catch and Spot Croaker represented 0.04%. Did fish consumers actually eat these small, bony fish?

The question of resource utilization is likely the largest uncertainty in the exposure assessment. The site-specific fish consumption study did not ask what species of fish were consumed. The implicit assumption of using the MRFSS data is that the entire catch is consumed.

Trophic level weighting has been used to develop fish consumption guidelines for MeHg.<sup>79</sup> Fish at trophic level 2 (TL2) consist of herbivores, planktivores, and detritivores; fish at trophic level 3 (TL3) consist of secondary piscine omnivores with diets that include other fish and invertebrates, and fish at trophic level 4 (TL4) are high-level carnivores, generally top predators that are exclusively or almost exclusively piscivorous. Trophic level weighting factors are used for the MeHg levels observed at the various trophic levels for the purpose of fish consumption advisories. Application of EPA's trophic level weighting scheme for methylmercury yielded an overall fish concentration of 0.168 mg/kg for methylmercury. This is lower than the criterion value of 0.3 mg/kg at which fish consumption advisories would be put into place.<sup>80</sup>

The toxicity of Aroclor 1268 and toxaphene also contribute to the uncertainty. The alternative toxicity values suggest that these substances are much less toxic than indicated by the toxicity criteria on IRIS—by several orders of magnitude. Table 6.6

**Table 6.6 RME Intakes, Showing Alternative Toxicity Criteria, Risks and Hazards**

	Cancer		Non-Cancer	
	Aroclor 1268	Toxaphene as Σ3PC	Aroclor 1268	Mercury
	mg/kg-day	mg/kg-day	mg/kg-day	mg/kg-day
<b>Adult</b>				
Total Intake from Fish	3.1E-05	7.3E-05	1.1E-05	6.9E-05
CSF/RfD	0.27	1.E-03	2.E-05	1.E-04
Risk/Hazard	8.5E-06	0.1	0.5	0.7
<b>Adolescent</b>				
Total Intake from Fish	1.1E-05	8.9E-05	8.3E-06	5.9E-05
CSF/RfD	0.27	1.E-03	2.E-05	1.E-04
Risk/Hazard	3.1E-06	0.1	0.4	0.6
<b>Child</b>				
Total Intake from Fish	1.3E-05	1.9E-04	1.7E-05	1.3E-04
CSF/RfD	0.27	1.E-03	2.E-05	1.E-04
Risk/Hazard	3.6E-06	0.2	0.9	1.3

shows the RME cancer risks and hazard indices using these alternate toxicity values. For toxaphene, the cancer result is actually a hazard quotient because the alternate toxicity criterion assumed a threshold for the cancer endpoint.

#### **6.5.1.8 Risk Assessment and Risk Management**

In preparation for a public meeting with the active community environmental group near the site, the risk manager sought information from the risk assessor. The issues about which she sought clarification were the differences between the toxicity criteria in the IRIS database and the alternate criteria in the scientific literature. She was also concerned about the hazard from methylmercury. The risk assessor suggested that she present the differences in the risk assessment and the trophic level weighted intakes and a very brief discussion of the reasons for the differences in the toxicity evaluations. She asked if the removal of the sediments containing the largest amounts of toxaphene had had any effect on the fish concentrations. The risk assessor indicated that there had been a notable reduction.<sup>53</sup>

“I’ll attend the meeting as backup,” he offered. She took him up on the offer.

At the meeting, the principal of the local elementary school offered to serve as a facilitator. They accepted his offer. At the meeting, there was no discussion of either toxaphene or Aroclor 1268—the interest of those attending the meeting was mercury. The risk assessor fielded a question from the head of the local environmental group.

“Why are the fish advisory levels that are considered safe higher than the levels that show a risk from mercury?”, asked this man. “How does that possibly make sense?”

“Sir,” responded the risk assessor, “that’s a really good question. I wondered that myself when I noticed it. Here’s why—when fish tissue concentrations are used for fish advisories, the outcome is a change in peoples’ fish consumption behavior. However, when fish tissue concentrations are used in a risk assessment, the outcome is a cleanup level in sediment, and high confidence is needed that this sediment cleanup level will result in fish concentrations that are not a health concern. So the risk assessment takes into account the uncertainty of relating environmental levels of mercury in sediment and other environmental media to mercury levels in fish tissue levels.”

“Wow,” said the man, “I never thought of that. We’re actually getting more bang for the buck in terms of health protection from the risk assessment than we would from any fish advisory.”

“That’s exactly right,” chimed in the project manager. The risk assessor looked around the room and saw many heads nodding. Before the project manager could continue, a number of the attendees gathered their belongings and left the meeting.

#### **6.5.2 Arsenic at a Former Gold Mine Proposed as a National Historic Site**

Gold mining and milling at the site began after an 1899 discovery of gold, and continued until approximately 1941, with the heaviest use in the 1930s.

The initial discovery of gold at the site in 1899 spurred a series of claims that were allowed to lapse after somewhat small yields of gold. Discovery of a rich vein of ore in 1925 prompted the formation of a private mining corporation in 1929. Mining activities continued through the 1930s, and the scale of mining operations was expanded to extract gold from 54 tons of ore a day. The minerals in the ore consisted mainly of pyrite, magnetite, and pyrrhotite, minerals containing arsenic and other heavy metals.

Mining was conducted by open underhand chiseling methods employed to break ore out of the ore shoots. The mined rock was carried by an aerial tram system to a nearby mill. Gold was extracted by mercury amalgamation and cyanide leaching. After gold and other valuable metals were extracted at the mill, mill tailings, which are the “waste” left over after extraction, were deposited over an area approximately 9 acres near the north fork of Trout Creek. The total depth of tailings generally varies from 0 to 2 feet.

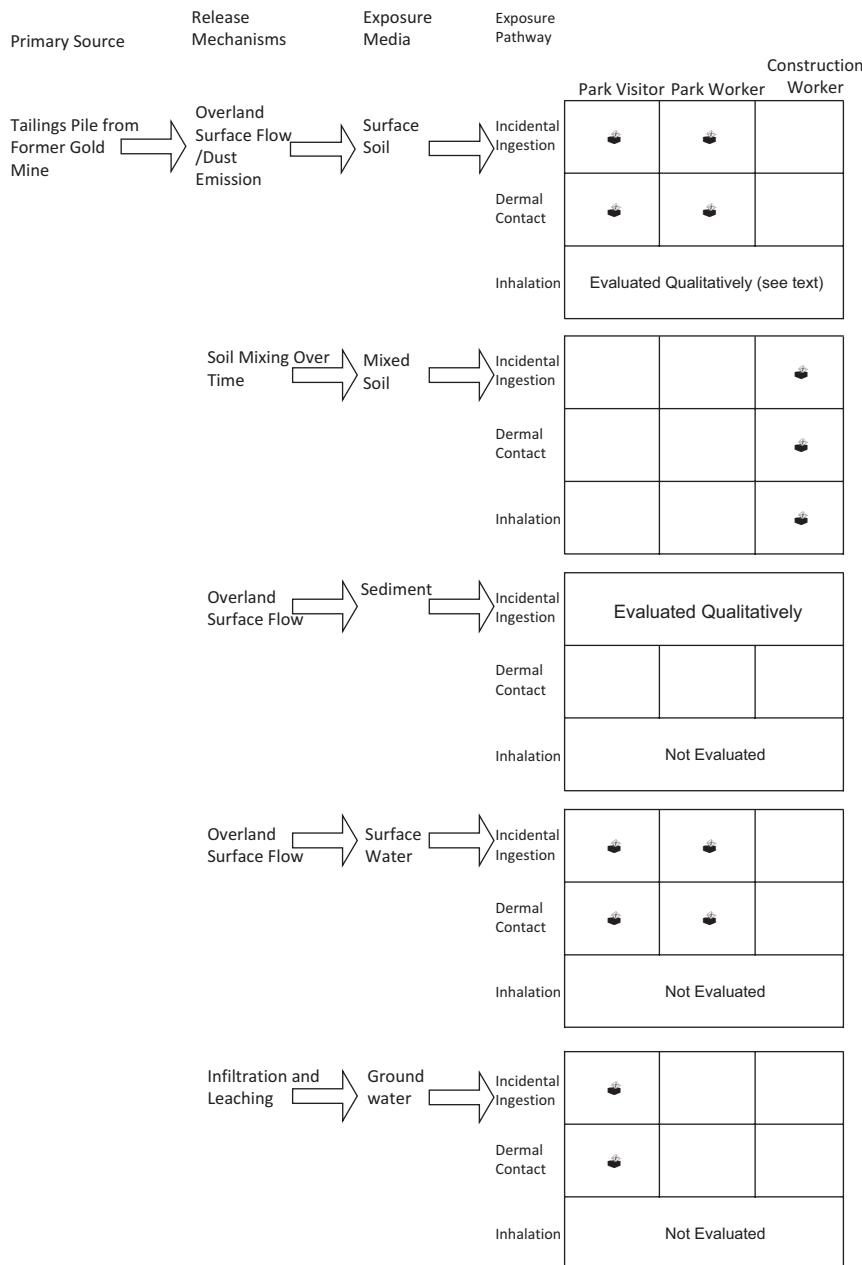
The tailings were deposited in their current locations due to the failure of a tailings dam. The iron-rich surface of the tailings has oxidized and appears as a bright orange and red packed crust, with some localized grey areas of unoxidized pyrite in areas of greater disturbance. A layer of hardpan is present on the surface of the tailings and extends in depth to between 1 and 6 inches below the surface of the tailings. The hardpan is not easily mobilized due to its physical structure, and the tailings do not support vegetation—except where they have been covered by soil or other organic matter. The tailings contain high levels of metals and are acidic in water. Sporadic mining and extraction attempts occurred throughout the 1980s; several partially empty, rusted drums of tailings are located on the site as a result of an attempt to pack and transport the tailings off-site to a separate mill.

The site is being developed as an historic park, therefore the following receptors are considered in this risk assessment:

- adult park visitor;
- child park visitor;
- adult park worker;
- construction/excavation worker.

#### **6.5.2.1 Conceptual Site Model for the Gold Mine Site**

The conceptual site model provides the framework of the risk assessment and is shown in Figure 6.5. It characterizes the primary and secondary potential sources and release mechanisms and identifies the primary exposure points, receptors, and exposure routes. Receptors include humans who contact environmental media at the site. This risk assessment focuses on potential human exposure to COPCs detected in soil, surface water, sediment, and groundwater at and adjacent to the site. Exposure points are places or “points” where exposure could potentially occur, and exposure routes include the basic pathways through which COPCs may potentially be taken up by the receptor.



**Figure 6.5** Conceptual site model for the former gold mine site showing sources of contamination, release mechanisms, receptors, and exposure routes. The bullets show complete exposure pathways considered in the quantitative risk assessment.

Inhalation of fugitive dust was considered, but not addressed quantitatively for the park visitors and workers. The reason is that all areas at the site were heavily vegetated except for the 9 acre tailings pile. However, as noted, the tailings pile was covered with a layer of hardpan that effectively prevents the generation of fugitive dust. Hence, inhalation of dust as an exposure pathway at the site was considered negligible for park visitors and park workers.

For the construction worker, vehicle traffic on contaminated unpaved roads typically accounts for the majority of emissions, with wind erosion, excavation soil dumping, dozing, grading, and filling operations contributing lesser emissions.<sup>81</sup> EPA's Supplemental Soil Screening Guidance provides a value of  $4.4\text{E+08}$  mg<sup>3</sup>/kg; this was used as the RME value of construction-related particulate emission factor. A value representative of dust emissions in non-construction scenarios of  $1.32\text{E+09}$  m<sup>3</sup>/kg was used as the central tendency exposure value. Multiplying this value by a soil concentration expressed in mg/kg provides the air concentration of a given chemical.

Exposure to surface water was considered to occur by dermal contact only. Purposeful ingestion would likely not occur due to the potential for *Giardia* in water. Park visitors are made aware of this in an orientation session and cautioned not to drink from streams. Incidental ingestion would likely not occur because the water is too cold for swimming or even wading, remaining most of the year below 60 °F.

In general, sediment exposure is thought to be minimal—most sediment on the skin washes off as a receptor moves through the water. For this reason, sediment was not evaluated quantitatively. The site is located in the northern US and even in the summer, the water temperature in Trout Creek, a small stream draining the site, remains below 60 °F. Hence, it is unlikely that prolonged exposure to either surface water or sediment would occur. However, for surface water, park visitors were assumed to put their hands in the surface water during two daily events, thus some dermal contact might occur.

Groundwater was not included in the conceptual site model, but was evaluated based on a hypothetical domestic use. While this exposure scenario is not realistic for the site, it provides a protective risk evaluation.

#### **6.5.2.2 Exposure Units (EUs)**

An exposure unit is defined as the geographic area within which a receptor comes in contact with a contaminated medium during the exposure duration. The EU is defined based on the receptor, exposure medium, and the nature of contact.<sup>23</sup> The current and future receptors at the site include park personnel, park visitors, and construction workers. These are atypical receptors, and the entire area around the site was considered the EU. While concentrations of metals are somewhat higher in samples from the tailings pile, many of the metals appear to be elevated in both soil and background samples.

### 6.5.2.3 Data Analysis and Selection of COPCs

Screening levels were obtained from EPA's most recent Regional Screening Level (RSL) Tables.<sup>82</sup> COPC screening was performed with a cancer risk of 1E-06 and a HQ value of 0.1. A value lower than 1 for the HQ is used to account for exposure to multiple chemicals.

Data were selected to represent both the site and exposure units appropriate to the medium considered. As the north fork of Trout Creek flows through the site, the creek goes underground and then re-emerges as springs. The portion of the creek near the site is dry for part of the year. Hence, sediment in these locations is considered as surface soil, and sampling results from the dry creek area were included as surface soil. The park workers and adult and child park visitors were assumed to be exposed to surface soil.

Surface water as potential dermal exposure media for workers and visitors were assumed to occur in the north fork of Trout Creek, between its emergence as springs between the mine site and the tailings pile and the confluence with the south fork of Trout Creek.

A construction/excavation worker would be exposed to a mixture of surface and subsurface soil. Groundwater was evaluated as if it could be a source of water for domestic use. The site and background datasets are provided in Tables 6.7–6.13.

The selection of COPCs generally uses four screening steps:

1. elimination of five inorganic constituents (calcium, chloride, magnesium, potassium, and sodium) that are considered essential human nutrients;
2. elimination of constituents for which the maximum detect did not exceed the screening benchmarks based on a cancer risk of 1E-06 and an HQ value of 0.1 (benchmarks were obtained from EPA's Regional Screening Level Table, November 2012 version);
3. elimination of constituents which were detected in fewer than 5% of the relevant samples;
4. elimination of constituents that were shown to be higher than the background sample using the Wilcoxon-Mann-Whitney test.<sup>32</sup>

EPA's ProUCL software v. 4.1 was used for the statistical comparison in step 4 and for calculation of the values for the 95% upper confidence limit of the mean that is recommended for use as the exposure point concentration.<sup>83,84</sup> ProUCL is a mature software package and provides recommendations for which UCL value to use. Guidance documents for ProUCL provide details of the statistical methods and UCL calculation methods.<sup>85–87</sup>

The results of COPC screening for various media are shown in Tables 6.14–6.17. Table 6.14 shows the selection of COPCs in surface soil. Residential soil screening levels were used. The COPCs in surface soil are Arsenic, Cadmium, Lead, Mercury, Silver and Zinc. Table 6.15 shows the selection of COPCs in mixed surface and subsurface soil. Commercial/industrial screening levels were used. The COPCs are arsenic, lead, manganese, and silver. Table 6.16 shows the selection of COPCs in surface water. Residential tap water screening levels were used. The COPCs in surface

Table 6.7 Surface Soil Sampling Results for Metals at the Former Gold Mine Site

Al	Sb	As	Ba	Be	Cd	Cr	Co	Cu	Fe	Pb	Mn	Hg	Ni	Se	Ag	Tl	Sn	Va	Zn
	389		1.6	14	16.8	601	84500	2960	220	3.3	12.2	3.2	26.6		34	292			
61.5		0.72	10.9	6.7	385	63500	627	171	0.39	7.7	1.1	7				23.6	81.6		
972		7.6	8.1	34.6	872	200000	717	1560	0.54	6.6	2.1	16.1				14.3	765		
3460		32.2	6	149	436	267000	443	661	1.2	17.4	8.4	13.3				11.8	2450		
224		1.8	3.1	8.6	173	37600	335	254	0.16	4.8	1.2	6.5				22.3	189		
6.1		0.46	7.7	185	55.1	22300	22	16200	0.079	42.7	5.3	0.66				35.8	44.6		
504		0.16	4.7	3.3	48.4	72800	300	112	0.98	3.8	3.2	6.2				35.3	118		
20.6		0.16	4.7	5.3	40.4	12900	31.5	256	0.018	6.7	5	0.5				32.8	40.1		
1.9	510	300	<1	9	14	110	340	25	140	7300	12	2				<5	57	1000	
3.7	430	200	<1	<2	50	8	540	9.3	1900	380	12	44				<5	70	140	
8	NA	57	420	3	<2	33	16	83	5.5	720	920	0.026	20	0.45	0.4		<5	92	160
1.5	NA	2100	230	<1	<2	18	13	53	25	75	3400	0.06	8	0.4	0.1	7	40	340	
2960	<4.0	49	37.6	0.07	0.71	1.6	6.41	12.9	18500	6.81	1350	<0.02	4.2	<0.2	0.38	<0.25	17.7	72.3	
1	3	760	27	<1	5	6	44	2500	14	820	2000	0.11	14	3	23		<5	110	1100
1.1	3	670	23	<1	8	5	39	3200	16	770	2100	0.12	13	3	24		<5	120	1300
6.8	<1	71	500	<1	<2	22	7	72	5.3	22	690	<0.005	18	0.8	<2		24	140	65
0.91	3	510	12	<1	<2	5	48	1400	13	700	3000	0.25	14	3.2	15		<5	90	890
1460	<40	1780	6.82	<0.50	11.3	<5.0	19	267	157000	1040	270	0.74	<10	7.49	24.8	0.94		16.5	1600
2710	<40	1190	2.5	<0.50	8.2	<5.0	70.4	146	125000	163	265	0.806	11	5.77	7.4	0.57		18.4	942
1610	<20	948	8.14	<0.25	7.22	<2.5	9.4	111	67300	939	187	2.47	<5.0	9.34	19.8	2.83		17.3	661
200	500	50	2	50	20	200	7000	20	500	100	30	1000				20	20	500	

(Continued)

Table 6.7 (Continued)

Al	Sb	As	Ba	Be	Cd	Cr	Co	Cu	Fe	Pb	Mn	Hg	Ni	Se	Ag	Tl	Sn	Va	Zn
200	1500	50	2	50	20	200	5000	50	700	500	30	100	20	20	30	500			
200	500	70	2	50	30	20	15000	7	100	500	15	700	20	100	500				
200	700	100	2	50	100	70	2000	10	100	200	20	10	20	50	500				
0.46	<15	960	13	<2	6	8	77	1700	21	1300	400	0.7	10	3.5	45	<10	9	390	
0.84	<15	1100	39	<2	11	16	33	1700	13	910	1100	0.27	7	1.3	26	<10	20	810	
1.7	<15	960	110	<2	<4	21	36	1300	14	5000	240	1.5	6	3.4	110	<10	28	300	
0.35	<15	435	18	<2	<4	5	12	795	9.8	6100	150	0.505	<4	1.95	48.5	<10	9	150	
1	<15	870	15	<2	10	13	41	3400	15	890	1400	0.15	8	0.9	27	<10	18	720	
1.4	17	1500	23	<2	9	9	20	300	13	880	400	1.1	<4	3.3	14	<10	26	980	
1560	<20	1170	3.64	<0.25	5.32	3.2	<5.0	1710	96200	1330	147	0.442	<5.0	3.43	36.7	<0.25	14.8	225	
411	<8.0	205	4.76	<0.10	1.5	3.6	4.6	1420	42700	4190	65.4	3.87	10.8	10.6	73.8	4.78	5.89	139	
1930	<20	6.92	19.5	<0.25	<10	74	<5.0	86.3	4720	38.3	145	0.317	6.7	<0.4	<1.5	<0.25	5.59	35.5	
1760	<40	449	32.1	<0.5	6.5	117	21	2000	329000	2470	449	0.944	242	<0.60	35.5	<1.0	26	2320	
9660	<4.0	56.8	47.5	0.16	1.26	91.8	8.31	146	20500	483	611	3	57.3	<0.4	10.1	<0.25	30.1	165	

Notes: A number preceded by “<” indicates the chemical was not detected and the number is the analytical reporting limit from the laboratory. Units are mg/kg soil. Chemical symbols were used to save space, and represent the various metals as follows: Al = aluminum; Sb = antimony; As = arsenic; Ba = barium; Be = beryllium; Cd = cadmium; Cr = chromium; Co = cobalt; Cu = copper; Fe = iron; Pb = lead; Mn = manganese; Hg = mercury; Ni = nickel; Se = selenium; Ag = silver; Tl = thallium; Sn = tin; Va = vanadium; Zn = zinc.

Table 6.8 Background Concentrations of Surface Soil at the Former Gold Mine Site

Al	Sb	As	Ba	Be	Cd	Cr	Co	Cu	Fe	Pb	Mn	Hg	Ni	Se	Ag	Tl	Sn	Va	Zn
11000	<4.0	9.32	190	0.32	0.21	23.5	11	37.8	23500	7.38	443	0.0692	26.3	0.45	0.34	<0.25	54.1	57.2	
0.09	<15	3100	7	<2	4	9	20	560	45	12	230	<0.02	<4	<4	<10	21	25		
0.03	<15	31	<2	<2	<4	<2	130	4400	47	77	140	<0.02	<4	0.6	11	<10	<4	140	
0.97	<15	500	9	<2	<4	87	<2	300	14	1600	110	0.03	6	0.7	25	<10	72	130	
4.5	<15	<20	97	<2	6	90	59	12000	26	<8	6100	<0.02	12	7	37	95	900		
1.6	<15	1200	6	<2	95	12	33	4100	29	2900	2900	0.12	12	1.4	16	<10	52	7300	
1860	<40	21.1	24.5	<0.50	8.6	6.9	19	3430	211000	44	1070	0.14	<10	28.7	109	<0.75	23.5	2200	
	4			0.098	5.1	5.1	22	11800	2.6	213	0.015	7.5	<5	1		37.7	28.4		
58.2		0.21	110	7.7	141	27000	5	1190	0.046	50.1	<5.3	0.81				14.9	36.8		
24.7		1.7	67.5	11.5	122	27300	2.3	1280	0.034	36	<5.3	0.32				28	363		
55.5		1.9	26.5	5.6	533	19400	83.4	525	0.064	15.8	5.1	1.7				14.5	140		
1.3		<1	12.9	3.9	17.8	9270	1.1	150	0.017	10	<5.1	<1				31.8	23.1		
130		1.3	33.8	10.4	527	30400	68.2	762	0.085	19.3	<5.2	2.1				17.3	132		

Notes: A number preceded by “<” indicates the chemical was not detected and the number is the analytical reporting limit from the laboratory. Units are mg/kg soil.

Table 6.9a Mixed Surface and Subsurface Soil Sampling Results for Metals at the Former Gold Mine Site, Part 1

Al	Sb	As	Ba	Be	Cd	Cr	Co	Cu	Fe	Pb	Mn	Hg	Ni	Se	Ag	Tl	Sn	Va	Zn	
389		1.6	14	16.8	601	84500	2960	220	3.3	12.2	3.2	26.6			34	292				
61.5		0.72	10.9	6.7	385	63500	627	171	0.39	7.7	1.1	7			23.6	81.6				
972		7.6	8.1	34.6	872	200000	717	1560	0.54	6.6	2.1	16.1			14.3	765				
3460		32.2	6	149	436	267000	443	661	1.2	17.4	8.4	13.3			11.8	2450				
224		1.8	3.1	8.6	173	37600	335	254	0.16	4.8	1.2	6.5			22.3	189				
6.1		0.46	7.7	185	55.1	22300	22	16200	0.079	42.7	5.3	0.66			35.8	44.6				
504		0.16	4.7	3.3	48.4	72800	300	112	0.98	3.8	3.2	6.2			35.3	118				
20.6		0.16	4.7	5.3	40.4	12900	31.5	256	0.018	6.7	5	0.5			32.8	40.1				
1.9	510	300	<1	9	14	110	340	25	140	7300	12	2			<5	57	1000			
3.7	430	200	<1	<2	50	8	540	9.3	1900	380	12	44			<5	70	140			
8	57	420	3	<2	33	16	83	5.5	720	920	0.026	20	0.45	0.4		<5	92	160		
1.5	2100	230	<1	<2	18	13	53	25	75	3400	0.06	8	0.4	0.1	7	40	340			
2960	<4.0	49	37.6	0.068	0.71	1.6	6.41	12.9	18500	6.81	1350	<0.02	4.2	<0.2	0.38	<0.25	17.7	72.3		
1	3	760	27	<1	5	6	44	2500	14	820	2000	0.11	14	3	23		<5	110	1100	
1.1	3	670	23	<1	8	5	39	3200	16	770	2100	0.12	13	3	24		<5	120	1300	
6.8	<1	71	500	<1	<2	22	7	72	5.3	22	690	<0.005	18	0.8	<2		24	140	65	
0.91	3	510	12	<1	<2	5	48	1400	13	700	3000	0.25	14	3.2	15		<5	90	890	
1460	<40	1780	6.82	<0.50	11.3	<5.0	19	267	157000	1040	270	0.74	<10	74.9	24.8	0.94		16.5	1600	
2710	<40	1190	2.5	<0.50	8.2	<5.0	70.4	146	125000	163	265	0.806	11	5.77	7.4	0.57		18.4	942	
1610	<20	948	8.14	<0.25	7222	<2.5	9.4	111	67300	939	187	2.47	<5.0	9.34	19.8	2.83		17.3	661	
200	500	50	2	50	20	200	7000	20	500	100	100	30	1000		20	20	500			

(Continued)

Table 6.9a (Continued)

Al	Sb	As	Ba	Be	Cd	Cr	Co	Cu	Fe	Pb	Mn	Hg	Ni	Se	Ag	Tl	Sn	Va	Zn
200	1500	50	2	50	20	200	5000	50	700	500	30	100	20	30	20	30	500	500	
200	500	70	2	50	30	20	15000	7	100	500	15	700	20	100	20	100	500	500	
200	700	100	2	50	100	70	2000	10	100	200	20	10	20	50	20	50	500	500	
0.46	<15	960	13	<2	6	8	77	1700	21	1300	400	0.7	10	3.5	45	<10	9	390	
0.84	<15	1100	39	<2	11	16	33	1700	13	910	1100	0.27	7	1.3	26	<10	20	810	
1.7	<15	960	110	<2	<4	21	36	1300	14	5000	240	1.5	6	3.4	110	<10	28	300	
0.35	<15	435	18	<2	<4	5	12	795	9.8	6100	150	0.505	<4	1.95	48.5	<10	9	150	
1	<15	870	15	<2	10	13	41	3400	15	890	1400	0.15	8	0.9	27	<10	18	720	
1.4	17	1500	23	<2	9	9	20	300	13	880	400	1.1	<4	3.3	14	<10	26	980	
0.74	<15	1000	<2	<2	58	10	110	4800	19	40	2100	0.02	16	0.9	<4	<10	<4	2900	
0.38	<15	2000	5	<2	50	6	69	2800	23	570	1100	0.38	9	1.9	15	<10	5	2400	
0.35	<15	970	15	<2	4	<2	130	1200	29	1500	150	1.2	12	4.1	35	<10	<4	200	
1.1	<15	760	26	<2	7	6	6	180	5.7	710	190	0.56	<4	2	12	<10	22	420	
2210	<20	739	20.2	<0.25	3.3	4	<5.0	722	94200	825	98.5	0.241	<5.0	2.47	20.8	<0.25	19.1	152	

Note: A number preceded by ‘<’ indicates the chemical was not detected and the number is the analytical reporting limit from the laboratory.

Table 6.9b Mixed Surface and Subsurface Soil Sampling Results for Metals at the Former Gold Mine Site, Part 2

Al	Sb	As	Ba	Be	Cd	Cr	Co	Cu	Fe	Pb	Mn	Hg	Ni	Se	Ag	Tl	Sn	Va	Zn
3780	<20	960	59.1	<0.25	3.4	7.6	7	228	106000	57	71.8	0.105	<5.0	1.6	2.2	<0.25	39	107	
2590	<40	1295	9.63	<0.50	11.65	70.05	20.5	308	142500	807.5	216.5	0.9735	49.35	4.525	18.05	0.6	16.2	2015	
		622							78900										
		845							88900										
		702							83000										
		210							48000										
		389							52400										
		396							51600										
		208							66500										
		21.7							24300										
		3.91							10000										
		1670							69800										
		96.4							50300										
		1560	<20	1170	3.64	<0.25	5.32	3.2	<5.0	1710	96200	1330	147	0.442	<5.0	3.43	36.7	<0.25	14.8
		411	<8.0	205	4.76	<0.10	1.5	3.6	4.6	1420	42700	4190	65.4	3.87	10.8	10.6	73.8	4.78	225
		1930	<20	6.92	19.5	<0.25	<1.0	7.4	<5.0	86.3	4720	38.3	145	0.317	6.7	<0.4	<1.5	<0.25	5.59
		1760	<40	449	32.1	<0.5	6.5	117	21	2000	329000	2470	449	0.944	242	<0.05	35.5	<1.0	35.5
		9660	<4.0	56.8	47.5	0.16	1.26	91.8	8.31	146	20500	483	611	3	57.3	<0.4	10.1	<0.25	26
																		165	

Notes: A number preceded by “<” indicates the chemical was not detected and the number is the analytical reporting limit from the laboratory. Units are mg/kg soil.

Table 6.10 Background Mixed Surface and Subsurface Soil Sampling Results at the Former Gold Mine Site

Al	Sb	As	Ba	Be	Cd	Cr	Co	Cu	Fe	Pb	Mn	Hg	Ni	Se	Ag	Sn	Tl	Va	Zn
11000	<4.0	9.32	190	0.32	0.21	23.5	11	37.8	23500	7.38	443	0.0692	26.3	0.45	0.34	<0.25	54.1	57.2	
0.09	<15	3100	7	<2	4	9	20	560	45	12	230	<0.02	<4	<4	<10	21	25		
0.03	<15	31	<2	<2	<4	<2	130	4400	47	77	140	<0.02	<4	0.6	11	<10	<4	140	
0.97	<15	500	9	<2	<4	87	<2	300	14	1600	110	0.03	6	0.7	25	<10	72	130	
4.5	<15	<20	97	<2	6	90	59	12000	26	<8	6100	<0.02	12	7	37	95	900		
1.6	<15	1200	6	<2	95	12	33	4100	29	2900	2900	0.12	12	1.4	16	<10	52	7300	
1860	<40	21.1	24.5	<0.50	8.6	6.9	19	3430	211000	44	1070	0.14	<10	28.7	109	<0.75	23.5	2200	
	4			0.098	5.1	5.1	22	11800	2.6	213	0.015	7.5	<5	1		37.7	28.4		
58.2				0.21	110	7.7	141	27000	5	1190	0.046	50.1	<5.3	0.81		14.9	36.8		
24.7				1.7	67.5	11.5	122	27300	2.3	1280	0.034	36	<5.3	0.32		28	363		
55.5				1.9	26.5	5.6	533	19400	83.4	525	0.064	15.8	5.1	1.7		14.5	140		
1.3				<1	12.9	3.9	178	9270	1.1	150	0.017	10	<5.1	<1		31.8	23.1		
130				1.3	33.8	10.4	527	30400	68.2	762	0.085	19.3	<5.2	2.1		17.3	132		
12100	<4.0	6.64	238	0.35	0.21	23.4	12.4	43.1	25400	5.36	509	0.153	27.4	0.44	0.34	<0.25	61.2	60.3	
2.1	<15	50	5	<2	7	76	59	5800	26	11	5200	<0.02	9	1.1	<4	49	43	820	
0.14	<15	59	5	<2	5	5	31	160	49	<8	470	<0.02	4	2.4	<4	<10	7	20	
0.07	<15	23	20	<2	<4	<2	2	97	1.1	<8	38	0.03	<4	0.1	<4	<10	5	53	
0.02	<15	<20	4	<2	<4	<2	24	1700	43	51	100	<0.02	<4	0.7	35	<10	<4	40	
0.13	<15	98	5	<2	<4	<2	24	3000	21	450	37	0.03	<4	1.8	41	<10	4	57	

Notes: A number preceded by "<" indicates the chemical was not detected and the number is the analytical reporting limit from the laboratory. Units are mg/kg soil.

Table 6.11 Surface Water Sampling Results at the Former Gold Mine Site

Al	Sb	As	Ba	Be	Cd	Cr	Co	Cu	Fe	Pb	Mn	Hg	Ni	Se	Ag	Sn	Tl	Va	Zn	
0.12	2.4	<5	<10	23	<10	<10	<10	<10	<10	<50	<0.05	0.021	<10	<5	<0.05	<0.1	<1	<10	<10	
0.06	1.8	6	<10	12	<10	<10	<10	<10	<10	280	<0.05	0.016	<10	<5	<0.05	<0.1	2	<10	<10	
0.05	2	<5	<10	13	<10	<10	<10	<10	<10	120	<50	0.021	<10	0.5	<0.01	<0.05	<0.05	<10	<10	
<0.02	2	<5	<10	<10	<10	<10	<10	<10	<10	310	<50	0.019	<10	<0.2	<0.01	<0.05	<0.05	<10	<10	
0.1	5.6	19	<10	26	<10	<10	<10	<10	<10	28	2500	<50	0.024	<10	0.7	<0.01	<0.05	0.06	<10	150
1.06	<10			<1	<1			3.66	314	<1		0.032	2.23				172	<10		
3.6	4.3							81.1	<0.5			0.018					3.4	<4.0		
1.4	21.8								67	<0.5		0.016					<3.0	<4.0		
4.5		<0.33		<1		0.85		<50				0.016					4.1	4.7		
11.2		<0.33		0.25		1.4		120			0.018						<20	11.5		
6		<0.33		0.094		2.1		65.3			0.016						0.44	5.1		
4.3		<0.33		0.074		1.3		<50									3.1	2.9		
31.4		<0.33		<1		0.88		<50									1.3	2.6		
4.4		<0.33		<1		1.1		32.3									<20	4		
10.7		<0.33		0.28		1.2		297									0.53	3.5		

Notes: A number preceded by “<” indicates the chemical was not detected and the number is the analytical reporting limit from the laboratory. Units are µg/L.

Table 6.12 Background Surface Water Sampling Results at the Former Gold Mine Site

Al	Sb	As	Ba	Be	Cd	Cr	Co	Cu	Fe	Pb	Mn	Hg	Ni	Se	Ag	Sn	Tl	Va	Zn
<40	0.4	4.4	18	<1	190	<1	<2	<2	<4	30	<5	0.023	<4	<0.1	<0.4	<0.5	<2	<2	
<40	<0.2	<0.8	3	<1	<50	<1	<2	<2	<4	<20	<5	0.021	<4	<0.1	<0.4	<0.5	3	<2	
<40	<0.2	<0.8	12	<1	<50	<1	<2	<2	<4	10	<5	0.013	<4	<0.1	<0.4	<0.5	<2	<2	
45	0.35	3.3	4	<1	<50	<1	<2	3.5	19.5	1050	<5	0.013	<4	<0.1	<0.4	<0.5	2	<2	
<40	<0.2	1	12	<1	<50	<1	<2	<2	7	60	<5	<4	<0.1	<0.4	<0.5	<2	<2	<2	
<40	<0.2	<0.8	18	<1	<50	<1	<2	<2	5	60	<5	<4	<0.1	<0.4	<0.5	<2	<2	<2	
<40	0.56	<0.8	9	<1	<50	<1	<2	<2	5	30	<5	<4	<0.1	<0.4	<0.5	<2	<2	<2	
<40	<0.2	<0.8	5	<1	<50	<1	<2	<2	<4	200	<5	<4	<0.1	<0.4	<0.5	<2	<2	<2	
<40	<0.2	0.8	5	<1	<50	<1	<2	<2	<4	<20	<5	<4	<0.1	<0.4	<0.5	3	<2	<2	
120	0.07	<0.5	22	<10	67	<10	<10	<10	<10	170	<50	<10	<5	<0.05	<0.1	<1	<10	<10	
56	<0.02	0.4	<5	<10	<10	<10	<10	<10	<10	100	<50	<10	0.3	<0.01	<0.05	<0.05	<10	<10	
17	<0.02	1	7.7	<10	<10	<10	<10	<10	<10	420	<50	<10	0.4	<0.01	<0.05	<0.05	<10	<10	
71	0.03	2	5.1	<10	11	<10	<10	<10	<10	60	<50	<10	0.8	<0.01	<0.05	<0.05	<10	<10	
56.5	<0.02	0.75	<5	<10	<10	<10	<10	<10	<10	<50	<50	<10	0.4	<0.01	<0.05	<0.05	<10	<10	
250	<0.02	0.7	24	<10	64	<10	<10	<10	<10	420	<50	<10	0.8	<0.01	<0.05	<0.05	<10	<10	
32.6	1.1				<0.33		<1	1.2	<50								2.8	5.4	
19.6	1.8				<0.33		<1	0.96	<50								2.3	4.7	
<50	2.5				<0.33		<1	1.1	<50								2.4	3.1	
229	8				0.24		0.36	8.8	390								1.7	33	
<50	4.1				<0.33		<1	1	<50								2.8	6.3	

Notes: A number preceded by “<” indicates the chemical was not detected and the number is the analytical reporting limit from the laboratory. Units are  $\mu\text{g/L}$ .

Table 6.13 Groundwater Sampling Results at the Former Gold Mine Site

As	Ba	Cd	Cr	Cu	Fe	Pb	Hg	Ni	Se	Ag	Va	Zn
0.0015	0.014	<0.001	0.0037	0.0041	0.22	<0.001	<0.0002	0.0044	0.00025	0.0019	0.0013	0.007
0.0077	0.065	<0.001	0.0098	0.0088	10	0.0026	<0.0002	0.0069	<0.005	0.00084	0.0082	0.029
0.0046	0.033	<0.001	0.0029	0.0007	6.8	<0.001	<0.0002	0.0021	<0.005	0.00062	<0.02	0.0041
0.00059	0.016	<0.001	<0.002	0.004	0.38	0.00028	<0.0002	0.0021	0.0013	<0.001	0.0018	0.0036
0.00195	0.017	<0.001	<0.002	0.00305	1.045	0.00047	<0.0002	0.00101	<0.005	<0.001	0.00105	0.00345
0.0048	0.014	<0.001	0.0019	0.0078	1.5	0.0013	<0.0002	0.0023	<0.005	0.00038	0.0043	0.0099
0.0037	0.18	<0.001	0.0015	0.004	0.56	0.00023	<0.0002	0.0017	<0.005	0.00053	0.0055	0.0044
0.0025	0.028	0.0037	0.0074	0.0074	0.72	0.0003	<0.0002	0.0091	0.0083	0.0037	0.0024	0.038

Note: Units are  $\mu\text{g/L}$ .

water are beryllium and iron. Table 6.17 shows the selection of COPCs in groundwater. No background data were available. Residential tap water screening levels were used. The COPCs are also beryllium and iron.

#### **6.5.2.4 Exposure Assessment**

An exposure assessment was conducted as part of the health risk assessment to evaluate the potential exposure pathways at the site. An exposure pathway is defined by the following four elements: (1) a source and mechanism of constituent release to the environment, (2) an environmental transport medium for the released constituent, (3) a point of potential contact with the contaminated medium (the exposure point), and (4) an exposure route at the exposure point. These pathways are shown in the conceptual site model (Figure 6.5). The purpose of the exposure assessment is to estimate the way a population may potentially be exposed to constituents at a site. Typically, exposure assessment involves projecting concentrations along potential pathways between sources and receptors. The projection usually is accomplished using site-specific data and, when necessary, mathematical modeling. Exposure can occur only when the potential exists for a receptor to experience direct contact with an environmental medium containing released constituents or if a mechanism exists for released constituents to be transported to a receptor. Without exposure, there is no risk; therefore, the exposure assessment is a critical component of the risk assessment.

#### **6.5.2.5 Exposure Assumptions**

To provide some understanding of the range of exposures and consequent risks, scenarios based on both RME and CTE were evaluated. Standard default values for assessing risk that generally lead to the RME risk estimates were used.<sup>58,59,88–90</sup>

The values for soil adherence factors were obtained from Exhibit 3-3 in EPA's *Risk Assessment Guidance for Superfund, Volume 1: Human Health Evaluation Manual (Part E, Supplemental Guidance for Dermal Risk Assessment) Final*.<sup>4</sup> The values for drinking water ingestion from EPA's 2011 *Exposure Factors Handbook*.<sup>59</sup> The values for soil ingestion rate from EPA's *Standard Default Exposure Assumptions*.<sup>88,90</sup>

For dermal contact with surface water, the values for skin surface area representing arms, forearms, and lower legs for both adults and children were obtained from Exhibit CI in EPA's *Risk Assessment Guidance for Superfund, Part E, Supplemental Guidance for Dermal Risk Assessment*.<sup>4</sup> For park workers and construction workers, just the hands and forearms were assumed to contact soil, and just the hands for surface water contact.

The concept of reasonable maximum exposure was envisioned to provide an estimate of the highest reasonable exposure possible to an individual. Such an individual is defined as the RME receptor, and is considered to be at the 90th percentile of the exposure distribution or higher. The National Contingency Plan indicates that site decisions should be based on the RME receptor, and RME exposure assumptions are shown for all four receptors in Table 6.18.<sup>91</sup> EPA has indicated that the RME

Table 6.14 Selection of Chemicals of Potential Concern for Surface Soil at the Former Gold Mine Site

Chemical	N	#D	Freq. of Detect	Min. ND	Max. ND	Min. Detect	Max. Detect	Mean of Detects	SD	RSLs	Background Comparison		COPC (Y/N)	UCL95 EPC	Method
											Cancer	NC			
<b>Surface Soil (mg/kg) Park Visitors and Workers</b>															
Aluminum	23	23	100%	—	—	0.35	9660	1047	2114	—	7700	≤BG	N	—	—
Antimony	23	8	35%	4	40	3	200	103.3	103.5	—	3.1	≤BG	N	—	—
Arsenic	35	35	100%	—	—	6.1	3460	732.1	714.5	0.39	2.2	—	Y	1034	95% Approx. Gamma
Barium	27	27	100%	—	—	2.5	500	87.5	130.7	—	1500	—	N	—	—
Beryllium	27	8	30%	0.1	2	0.07	3	1.65	1.01	1400	16	—	N	—	—
Cadmium	35	28	80%	1	4	0.15	50	12.38	15.82	1800	7	—	Y	36.6	99% KM (Chebychev)
Chromium	35	32	91%	5	5	1.6	117	21.21	28.82	—	12000	—	N	—	—
Cobalt	35	33	94%	5	5	3.3	200	46.74	57.6	370	2.3	≤BG	N	—	—
Copper	35	35	100%	—	—	12.9	15000	1568	2798	—	310	≤BG	N	—	—
Iron	35	35	100%	—	—	5.3	329000	463337	80366	—	5500	≤BG	N	—	—
Lead	35	35	100%	—	—	6.81	6100	1078	1435	—	400	—	Y	1363	Mean for IEUBK or ALM*
Manganese	35	35	100%	—	—	65.4	16200	1363	2925	—	180	≤BG	N	—	—
Mercury	29	27	92%	0.005	0.02	0.018	3.87	0.891	1.06	—	1	—	Y	1678	95% KM (Chebychev)

(Continued)

Table 6.14 (Continued)

Chemical	N	#D	Freq. of Detect	Min. ND	Max. ND	Min. Detect	Max. Detect	Mean of Detects	SD Detects	RSLs		Background Comparison	COPC (Y/N)	UCL95 EPC	Method
										Cancer	NC				
<b>Surface Soil (mg/kg) Park Visitors and Workers</b>															
Nickel	35	30	85%	4	10	3.8	242	22.36	43.12	1300	150	≤BG	N	—	—
Selenium	29	24	86%	0.2	0.6	0.4	10.6	3.653	2.803	—	39	—	N	—	—
Silver	35	33	94%	1.5	2	0.1	1000	74.98	205.1	—	39	—	Y	407	99% KM (Chebychev)
Thallium	9	4	44%	0.25	1	0.57	4.78	2.28	1.938	—	0.078	≤BG	N	—	—
Tin	18	6	33%	5	10	7	24	18.5	5.857	—	4700	—	N	—	—
Vanadium	35	35	100%	—	—	5.59	140	39.75	35.36	—	39	≤BG	N	—	—
Zinc	35	35	100%	—	—	35.5	2450	585.3	603.2	—	2300	—	Y	797.6	95% Approx. Gamma

Note: \*Integrated Exposure Uptake Biokinetic Model for Lead and Adult Lead Model. See [www.epa.gov/superfund/health/contaminants/lead/pbbrisk.htm](http://www.epa.gov/superfund/health/contaminants/lead/pbbrisk.htm).

Table 6.15 Selection of Chemicals of Potential Concern for Mixed Surface and Subsurface Soil at the Former Gold Mine Site

Chemical	N	#D	Freq. of Detect	Mixed Surface and Subsurface Soil (mg/kg) Construction/Excavation Worker						COPC (Y/N)	UCL95 EPC	Method
				Min. ND	Max. ND	Min. Detect	Max. Detect	Mean of Detects	SD			
										Cancer	NC	
Aluminum	30	30	100%	—	—	0.35	9660	1089	1981	—	99000	—
Antimony	30	8	27%	1	40	3	200	103.3	103.5	—	41	≤BG
Arsenic	53	53	100%	—	—	3.91	3460	726.7	659	1.6	26	—
Barium	34	33	97%	2	2	2.5	500	75.68	120.8	—	19000	—
Beryllium	34	7	21%	0.1	2	0.068	3	1.604	1.082	6900	200	—
Cadmium	42	34	81%	1	4	0.16	58	14.18	18.41	9300	80	—
Chromium	42	38	91%	2	5	1.6	117	20.59	28.08	—	150000	—
Cobalt	42	39	93%	5	5	3.3	200	48.33	56.53	1900	30	≤BG
Copper	42	42	100%	—	—	12.9	15000	1551	2633	—	4100	≤BG
Iron	53	53	100%	—	—	5.3	329000	48836	69338	—	72000	≤BG
Lead	42	42	100%	—	—	6.81	6100	1006	1331	—	800	—
Manganese	42	42	100%	—	—	65.4	16200	1229	2697	—	2300	—
Mercury	36	34	94%	0.005	0.02	0.018	3.87	0.81	0.973	—	4.3	—

(Continued)

Table 6.15 (Continued)

Chemical	N	#D	Freq. of Detect	Min. ND	Max. ND	Min. Detect	Max. Detect	Mean of Detects	SD Detects	RSLs		Background Comparison	COPC (Y/N)	UCL <sub>95</sub> EPC	Method
										Cancer	NC				
<b>Mixed Surface and Subsurface Soil (mg/kg) Construction/Excavation Worker</b>															
Nickel	42	35	83%	4	10	3.8	242	21.75	40.33	64000	2000	—	—	—	N
Selenium	36	32	89%	0.05	0.4	0.4	10.6	3.4	2.581	—	510	—	—	—	N
Silver	42	39	93%	1.5	4	0.1	1000	66.09	189.5	—	510	—	—	Y	238.1 95% KM (Chebychev)
Thallium	12	5	42%	0.25	1	0.57	4.78	1.944	1.839	—	0.61	≤BG	—	Y	—
Tin	22	6	27%	5	10	7	24	18.5	5.857	—	61000	—	—	—	N
Vanadium	42	40	95%	4	4	5	140	37.31	33.88	—	520	—	—	—	N
Zinc	42	42	100%	—	—	35.5	2900	682.8	753.2	—	31000	—	—	—	N

Note: \*Adult Lead Model. See <http://www.epa.gov/superfund/health/contaminants/lead/pbriisk.htm>.

Table 6.16 Selection of Chemicals of Potential Concern for Surface Water at the Former Gold Mine Site

Chemical	N	#D	Freq. of Detect	Min. ND	Max. ND	Mean Detect	Max. Detect	Mean of Defects	Surface Water (µg/L) Park Visitors and Workers		COPC (Y/N)	UCL95 EPC	Method	
									SD Detects	RSLs Cancer	Background Comparison NC			
Aluminum	5	4	80%	0.02	0.05	0.12	0.0825	0.033	1600	—	N	N		
Antimony	8	8	100%	—	—	1.06	5.6	2.483	1.469	6.0*	N	N		
Arsenic	15	11	73%	5	10	4.3	31.4	11.24	9.066	0.045	0.47	≤BG		
Barium	4	0	0%	10	10	—	—	—	290	—	N	N		
Beryllium	5	4	80%	10	10	12	26	18.5	7.047	1.6	23.86	95% KM (t) UCL		
Cadmium	13	0	0%	0.33	10	—	—	—	—	—	N	N		
Chromium	6	0	0%	1	10	—	—	—	—	—	N	N		
Cobalt	13	4	31%	1	10	0.074	0.28	0.175	0.106	0.106	0.47	N	N	
Copper	13	9	69%	10	10	0.85	28	4.499	8.856	62	N	N		
Iron	15	11	74%	50	50	32.3	2500	380.6	711.5	1100	1304	97.5% KM (Chebychev)	N	
Lead	8	0	0%	0.5	50	—	—	—	—	—	15*	N		
Manganese	2	0	0%	0.05	0.05	—	—	—	—	—	32	N		
Mercury	11	11	100%	—	—	0.016	0.032	0.0197	0.0048	0.0048	0.43†	N	N	
Nickel	6	1	17%	10	10	2.23	2.23	2.23	—	—	30	N	N	
Selenium	5	2	40%	0.2	5	0.5	0.7	0.6	0.141	0.141	7.8	N	N	
Silver	5	0	0%	0.01	0.05	—	—	—	—	—	7.1	N	N	
Thallium	5	2	40%	0.05	1	0.06	2	1.03	1.372	0.016	≤BG	N	N	
Tin	5	0	0%	0.05	0.1	—	—	—	—	—	930	N	N	
Vanadium	15	7	47%	3	20	0.44	17.2	4.296	5.871	7.8	≤BG	N	N	
Zinc	15	8	53%	4	10	2.6	150	23.04	51.38	470	N	N		

Note: An asterisk denotes the federal maximum contaminant level (MCL) used if lower than the concentration at HQ = 0.1.

† as mercuric chloride or other mercury salts.

Table 6.17 Selection of Chemicals of Potential Concern for Groundwater at the Former Gold Mine Site

Chemical	N	#D	Freq. of Detect	Min. ND	Max. ND	Min. Detect	Max. Detect	Groundwater (µg/L) Potential Residents		SD Detects	RSLs	Cancer	NC	COPC (Y/N)	UCL95 EPC	Method
								Mean of Detects	SD Detects							
Arsenic	8	8	100%	—	—	0.59	7.7	3.418	2.28	0.045	0.47	Y	4.945	95% Student's-t		
Barium	8	8	100%	—	—	14	180	45.88	56.82	290	N					
Cadmium	8	1	12%	1	1	3.7	3.7	—	—	5.0*	N					
Chromium	8	2	75%	2	2	1.5	9.8	4.533	3.33	100*	N					
Copper	8	8	100%	—	—	0.7	8.8	4.981	2.755	62	N					
Iron	8	8	100%	—	—	220	10000	2653	3670	1100	Y	7341	95% Approx. Gamma			
Lead	8	6	75%	1	1	0.23	2.6	0.863	0.94	15*	N					
Mercury	8	0	0%	0.2	0.2	—	—	—	—	0.43†	N					
Nickel	8	8	100%	—	—	1.01	9.1	3.701	2.884	30	N					
Selenium	8	3	38%	5	5	1.3	8.3	4.033	3.743	7.8	Y	4.638	95% KM(t)			
Silver	8	6	75%	1	1	0.38	3.7	1.328	1.283	7.1	N					
Vanadium	8	7	88%	20	20	1.005	8.2	3.501	2.642	7.8	Y	5.393	95% KM(t)			
Zinc	8	8	100%	—	—	3.45	38	12.43	13.4	470	N					

Note: An asterisk denotes the MCL used if lower than the concentration at HQ = 0.1

† as mercuric chloride or other mercury salts.

**Table 6.18 Exposure Assumptions Used in the Risk Assessment of the Former Gold Mine Site**

Parameter	Abbreviations	Units	Child Park Visitor	Adult Park Visitor	Park Worker	Construction Worker
			RME Value	CTE Value	RME Value	CTE Value
Body Weight	BW	kg	15	15	70	70
Averaging Time—C	AT-C	days	25550	25550	25550	25550
Averaging Time—NC	AT-NC	days	ED* 365	ED* 365	ED* 365	ED* 365
Exposure Frequency	EF	days/yr	24	7	7	7
Exposure Duration	ED	years	6	2	30	2
Drinking Water Ingestion	IRW	L/d	1	0.5	2	1
Incidental Water Ingestion	IRWI	L/event			Not evaluated quantitatively (see Figure 6.1)	
Inhalation rate	IN	m <sup>3</sup> /day			Not evaluated	
Soil Ingestion rate	IR	mg/day	200	50	100	20
	SA	cm <sup>2</sup>	1400	1400	4500	4500
Skin Surface Area—hands, forearms and lower legs for soil contact	SAW	cm <sup>2</sup>	400	400	900	900
Skin surface Area—hands for surface water contact	SAF	mg/cm <sup>2</sup>	0.4	0.04	0.3	0.02
Sol Adherence Factor	RBA	percent	31%	4.1%	31%	4.1%
Relative bioavailability (As)	PEF	m <sup>3</sup> /kg			31% 1.32E09	
Particulate Emission Factor	ET	Hr			0.3 4.1% 1.32E09	
Exposure Time					8	8

Note: PEF = particulate emission factor.

approach is incomplete by presenting only a point estimate of risk with no indication of where it falls within the risk distribution and that central tendency exposure risk estimates should also be presented.<sup>19,92</sup>

#### 6.5.2.6 Exposure Pathways and Receptors

The most likely route of potential human exposure to constituents detected is through direct contact with soil. The potential for exposure to fugitive dust generated at the site is low due to the presence of hardpan covering the tailings pile, snow in the winter, and vegetative cover in the summer. Notwithstanding, this pathway was considered quantitatively for construction workers.

The exposure dose for oral and dermal exposure to soil or sediment was estimated for both carcinogens and non-carcinogens as follows:

$$\text{ADD (mg/kg-day)} = \text{C}_{\text{soil}} \times \text{IR}_{\text{soil}} \times \text{EF} \times \text{ED} \times \text{CF} / \text{BW} \times \text{AT} + \text{C}_{\text{soil}} \times \text{CF} \times \text{SAF} \times \text{ABS}_{\text{dermal}} \times \text{EF} \times \text{ED} \times \text{SSA} / \text{BW} \times \text{AT} \quad (6.3)$$

where:

ADD = average daily dose (mg/kg/d)

$\text{C}_{\text{soil}}$  = concentration in soil (mg/kg)

$\text{IR}_{\text{soil}}$  = soil ingestion rate (mg/day)

EF = exposure frequency (days/yr)

ED = exposure duration (yr)

BW = body weight (kg)

CF = conversion factor (kg/mg)

SAF = soil adherence factor (mg/cm<sup>2</sup>)

$\text{ABS}_{\text{dermal}}$  = dermal absorption (chemical-specific)

SSA = skin surface area (cm<sup>2</sup>)

PEF = particulate emission factor (m<sup>3</sup>/kg)

For the construction/excavation worker, the exposure concentration for inhalation exposure was estimated as:

$$\text{EC}_{\text{inhalation}} = \text{C}_{\text{soil}} \times (1/\text{PEF}) \times \text{ET} \times \text{EF} \times \text{ED} / (\text{AT} \times 24 \text{ hr/day}) \quad (6.4)$$

Equation 6.5 provides an exposure concentration in air that can be used with inhalation reference concentrations in units of mg/m<sup>3</sup> or inhalation unit risks in units of per  $\mu\text{g}/\text{m}^3$ .

$$\text{Risk} = \text{EC}_{\text{inhalation}} \times 1000 \times \text{IUR} \quad (6.5)$$

$$\text{Hazard Quotient} = \text{EC}_{\text{inhalation}} / \text{RfC} \quad (6.6)$$

Equations 6.5 and 6.6 are respectively used to estimate inhalation risk and inhalation hazard. Both IUR values and RfC values need to represent continuous

exposure as a time-weighted average of exposure in the study used to derive the toxicity factor.<sup>51</sup> Because the values for soil concentration were in mg/kg, EC<sub>inhalation</sub> was multiplied by 1000 to convert to  $\mu\text{g}/\text{m}^3$  for assessing carcinogenic risk. The value of the particulate emission factor, was the default value recommended by EPA.<sup>5</sup>

The intake or dose equation shown above is provided on three separate lines to show the separation of ingestion, dermal, and inhalation routes for soil contact. For both carcinogens and non-carcinogens, Equation 6.3 was applied to adults and children separately.

Regarding inhalation, the metals at the site are not volatile and exposure to fugitive dust generation will be very low. During the winter, the climate and snow cover will prevent any exposure to dust. During the summer, the extensive vegetation and the presence of the hardpan covering on the tailings pile will mitigate the generation of dust. Equations 6.4, 6.5, and 6.6 were developed to be able to use a toxicity criterion expressed as an inhalation unit risk value rather than an inhalation slope factor. The application of unit risks to different life stages (i.e., children and adults) requires understanding of whether the chemical acts by a potentially mutagenic mode of action. This mode of action is highly unlikely for arsenic.<sup>93</sup> A full discussion of this issue is presented in EPA's *Risk Assessment Guidance for Superfund, Part F: Supplemental Guidance for Inhalation Risk Assessment Final*.<sup>5</sup>

#### **6.5.2.7 Bioavailability of Arsenic**

Recently, EPA recommended a default relative bioavailability (RBA) value of 60% for arsenic in soil.<sup>94</sup> What RBA measures is the difference in both bioaccessibility and gastrointestinal (GI) absorption. Bioaccessibility is the proportion of the arsenic that dissolves in the gut lumen, and GI absorption is the proportion of dissolved arsenic that moves from the gut lumen to the bloodstream. In bioavailability studies of arsenic in juvenile swine and monkeys, RBA values ranged from 4.1% to 78%, with an arithmetic mean of  $31 \pm 16\%$ .<sup>95</sup> In more recent studies on mice, soils containing arsenopyrite slag similar to the mine tailings at the site showed the lowest bioavailability—around 7%, similar to that observed in monkeys.<sup>96</sup> In addition, *in vivo* bioavailability was found to correlate well with bioaccessibility measured *in vitro*.<sup>96</sup> As noted, bioaccessibility is essentially the solubility in the gastrointestinal tract. The *in vitro* bioaccessibility measurements are considerably less costly than *in vivo* studies.

A site-specific value for bioavailability for the former gold mine site can be estimated using a comparison between results obtained from the soil leaching calculator at EPA's website ([http://epa-prgs.ornl.gov/cgi-bin/chemicals/csl\\_search](http://epa-prgs.ornl.gov/cgi-bin/chemicals/csl_search)) and actual soil and groundwater concentrations at the site. The calculator provides a default value of soil concentration protective of groundwater at the MCL of 10  $\mu\text{g}/\text{L}$ . This value is 0.292 mg/kg. These values represent the potential ability of rainwater to dissolve arsenic in soil.

At the site, the arithmetic mean value for arsenic in mixed surface and subsurface soils at the site is 726.7 mg/kg and in groundwater is 3.4 µg/L (Tables 5-8 and 5-10). Comparing the soil/groundwater concentration ratio from the calculator and the site indicates there is a five-order of magnitude difference in these estimates of arsenic solubility. Based on this comparison, the bioavailability of arsenic would be 0.001%. Hence, the RME value used in the risk calculation was 31%, the average from EPA's database, and the CTE value was 4.1%, representing a low but still observable value.<sup>95</sup>

#### **6.5.2.8 Toxicity Assessment**

This section discusses the two general categories of toxic effects (non-carcinogenic and carcinogenic) evaluated in risk assessments and the toxicity values used to calculate potential risks. Toxicity values for potential non-carcinogenic and carcinogenic effects are determined from available databases. For this risk assessment, toxicity values were first obtained from either EPA's IRIS database or the Risk Assessment Information System (RAIS) at <http://rais.ornl.gov>.

Whenever possible, route-specific toxicity values have been used. However, toxicity values for dermal exposures have not yet been developed by EPA; therefore, the oral toxicity values were used to derive adjusted toxicity values for use in assessing dermal exposure. The adjusted toxicity values represent the theoretical toxicity of the orally absorbed dose of the constituent based on the oral toxicity value and the assumed or measured gastrointestinal absorption (ABS<sub>o</sub>) in the study underlying the no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL):

$$RfD_a = RfD_o \times ABS_o \quad (6.7)$$

$$CSF_a = CSF_o / ABS_o \quad (6.8)$$

Toxicity values were generally obtained from the RAIS at <http://rais.ornl.gov>. This is a joint venture between EPA and the Department of Energy. The hierarchy of sources of toxicity values recommended by EPA was used to obtain toxicity criterion.<sup>97</sup> Table 6.19 shows the toxicity criteria and absorption factors used.

Notes:

- (a) Dermal RfD = Oral RfD × GI Absorption.
- (b) Dermal CSF = Oral CSF/Oral Absorption.

RfD, reference dose; CSF, cancer slope factor; IRIS, Integrated Risk Information System (EPA database of toxicity criteria); PPRTV, provisional peer-reviewed toxicity value (EPA values not on IRIS); CALEPA, California Environmental Protection Agency.

Table 6.19 Toxicity Criteria and Absorption Factors

COPC	Non-Cancer Effects				Cancer Effects				Absorption Factors				
	Oral RfD (mg/kg-d)	Source	Dermal RfD (a) (mg/kg-d)	Inhalation RfC (mg/m <sup>3</sup> )	Source	Oral CSF (mg/kg-d) <sup>-1</sup>	Source	Dermal CSF (b) (mg/kg/d) <sup>-1</sup>	Inhalation IUR (mg/m <sup>3</sup> ) <sup>-1</sup>	Source	GI Absorption (unitless)	Dermal Absorption (unitless)	Skin Permeability Kp (cm/hr)
Arsenic, Inorganic	0.0003	IRIS	0.0003	1.5E-05	CALEPA	1.5	IRIS	1.5	0.0043	IRIS	1	0.03	0.001
Beryllium	0.002	IRIS	1.4E-05	2.0E-05	IRIS	—	—	—	0.0024	IRIS	0.007	—	0.001
Cadmium (Diet)	0.001	IRIS	2.5E-05	2.0E-05	CALEPA	—	—	—	0.0018	IRIS	0.025	0.001	0.001
Cadmium (Water)	0.0005	IRIS	2.5E-05	2.0E-05	CALEPA	—	—	—	0.0018	IRIS	0.05	0.001	0.001
Iron	0.7	PPRTV	0.7	—	—	—	—	—	—	—	1	—	0.001
Manganese (Diet)	0.14	IRIS	0.14	5.0E-05	IRIS	—	—	—	—	—	1	—	0.001
Manganese (Water)	0.024	IRIS	0.00096	5.0E-05	IRIS	—	—	—	—	—	0.04	—	0.001
Mercury (elemental)	—	—	—	0.0003	IRIS	—	—	—	—	—	1	—	0.001
Mercury, Inorganic Salts	0.0003	IRIS	2.1E-05	—	—	—	—	—	—	—	0.07	—	0.001
Selenium	0.005	IRIS	0.005	0.02	CALEPA	—	—	—	—	—	1	—	0.001
Silver	0.005	IRIS	0.0002	—	—	—	—	—	—	—	0.04	—	0.0006
Vanadium	0.005	IRIS	0.005	—	—	—	—	—	—	—	1	—	0.001
Zinc	0.3	IRIS	0.3	—	—	—	—	—	—	—	1	—	0.0006

### 6.5.2.9 Risk Assessment Results

The reasonable maximum and central tendency exposure risk estimates for the various receptors were:

Receptor	Cancer Risk	Hazard Index
Adult Park Visitor	RME = 6E-06; CTE = 1E-08	RME = 0.2; CTE = 0.004
Child Park Visitor	RME = 2E-04; CTE = 1E-07	RME = 1; CTE = 0.2
Park Worker	RME = 2E-04; CTE = 3E-06	RME = 1; CTE = 0.1
Construction	RME = 6E-06; CTE = 8E-08	RME = 1; CTE = 0.02

The major contributors to hazard indices were arsenic and silver. The critical toxic effects of arsenic are hyperpigmentation, keratosis, and possible vascular complication; hence, the vascular system is the target of the non-cancer effects of arsenic. The critical toxic effect of silver is argyria, a medically benign but permanent bluish-gray discoloration of the skin. Although the deposition of silver is permanent, it is not associated with any adverse health effects. Hence, the HI could be segregated, and when arsenic only was included, all HIs were less than unity. The quantitative results of the risk assessment are provided in Tables 6.20–6.25.

#### 6.5.2.9.1 Risk from Lead Exposure to Children

Because exposure to lead occurs from multiple media, the Integrated Exposure/Uptake/Biokinetic (IEUBK) model is used to assess the risks of lead to children.<sup>98</sup> The endpoint in the IEUBK model is the proportion of a hypothetical population of children six years old and under with blood lead concentrations greater than 10 µg/dL. The regulatory target is to have 95% or more of the hypothetical population with blood lead concentrations less than 10 µg/dL.

Lead exposure to children aged 6 years or less from the site was assessed as a time-weighted average between the site and their home.<sup>99</sup> The IEUBK model was executed using default values for all inputs except two. Children were assumed to visit the site for 24/365 days out of the year (Table 6.18). The outdoor soil lead concentration was 277 mg/kg, based on a weighted average between 200 mg/kg, the default value used in the model, and 1363 mg/kg, the average in surface soil at the site. A second source of lead in the “Multiple Source Analysis” option used was “Second Home Dust.” The default value of the conversion factor for soil lead to indoor dust lead is 0.7, and the second home dust concentration used was  $0.7 \times 1363$  mg/kg, or 954 mg/kg. Exposure to this second source would occur 24/365 days, or 6.6% of the time. The average is used because all sources of uncertainty and variability—including that in the exposure point concentration—are included in the geometric standard deviation included in the current implementation of the IEUBK model.<sup>99</sup>

Table 6.20 Quantitative Characterization of Risk and Hazard for Park Visitors (RME)

Chemical	Surface Soil EPC (mg/kg)	Oral Intake (mg/kg/d)	DA <sub>event</sub> (mg/cm <sup>3</sup> )	Dermal Intake (mg/kg/d)	Dermal Absorption (ABS <sub>d</sub> ) (unitless)	GI Absorption (ABS <sub>GI</sub> ) (unitless)	Oral Bioavailability (unitless)	Toxicity Values CSF <sub>oral</sub>	Oral Risk CSF <sub>dermal</sub>	Dermal Risk	Total Risk
Adult Cancer Risks											
Arsenic	1034	8.33E-06	9.31E-06	3.37E-06	0.03	0.95	31%	1.5	1.6	3.87E-06	6E-06
Child's Cancer Risk											
Arsenic	1034	3.89E-04	1.24E-05	3.26E-05	0.03	0.95	31%	1.5	1.6	1.81E-04	2E-04
Summation of Adult and Child RME Cancer Risks = 2E-04											
Chemical	Surface Soil EPC (mg/kg)	Oral Intake (mg/kg/d)	DA <sub>event</sub> (mg/cm <sup>3</sup> )	Dermal Intake (mg/kg/d)	Dermal Absorption (ABS <sub>d</sub> ) (unitless)	GI Absorption (ABS <sub>GI</sub> ) (unitless)	Oral Bioavailability (unitless)	Toxicity Values RfD <sub>oral</sub>	Oral HQ RfD <sub>dermal</sub>	Dermal HQ	Total HI HQ
Adult RME Non-Cancer Hazard from Soil											
Arsenic	1034	9.71E-05	9.31E-06	3.93E-05	0.03	0.95	31%	3.00E-04	2.90E-04	1.00E-01	4.20E-02
Cadmium	36.6	3.44E-06	1.10E-08	4.64E-08	0.001	0.025	100%	0.001	2.50E-05	3.44E-03	1.86E-03
Lead	1363							Assessed with the Adult Lead Model			
Mercury	1.68	1.58E-07	5.03E-09	2.13E-08	0.01	0.07	100%	0.0003	2.10E-05	5.25E-04	1.01E-03
Silver	407	3.82E-05	1.22E-06	5.16E-06	0.01	0.04	100%	0.005	0.0002	7.65E-03	2.58E-02

(Continued)

Table 6.20 (Continued)

Table 6.21 Quantitative Characterization of Risk and Hazard for Park Visitors (CTE)

Chemical	Surface Soil EPC (mg/kg)	Oral Intake (mg/kg/d)	$DA_{event}$ (mg/cm <sup>3</sup> )	Dermal Intake (mg/kg/d)	GI Absorption (ABS <sub>GI</sub> ) (unitless)	Bioavailability (unitless)	Oral Bioavailability (ABS <sub>GI</sub> ) (unitless)	Toxicity Values	Oral Risk/HI	Dermal Risk/HI	Total Risk/HI
<i>Adult CTE Cancer Risks</i>											
Arsenic	1034	1.6E-07	6.9E-05	2.4E-06	0.03	0.95	4.1%	1.5	1.6	1.0E-09	1.6E-07
<i>Child CTE Cancer Risk</i>											
Arsenic	1034	1.89E-06	3.9E-05	2.0E-06	0.03	0.95	4.1%	1.5	1.6	1.2E-07	1.3E-07
<i>CTE Lifetime Receptor Summation of Adult and Child CTE Cancer Risks = 4E-07</i>											
Chemical	Surface Soil EPC (mg/kg)	Oral Intake (mg/kg/d)	$DA_{event}$ (mg/cm <sup>3</sup> )	Dermal Intake (mg/kg/d)	GI Absorption (ABS <sub>GI</sub> ) (unitless)	Bioavailability (unitless)	Oral Bioavailability (unitless)	Toxicity Values	Oral HQ	Dermal HQ	Total HQ
<i>Adult CTE Non-Cancer Hazard from Surface Soil</i>											
Arsenic	1034	5.67E-06	2.17E-06	2.68E-06	1	0.95	4.1%	3E-04	2.9E-04	4E-04	0.001
Cadmium	36.6	2.01E-07	2.56E-09	3.16E-09	0.03	0.025	100%	0.001	2.5E-05	2.0E-04	0.0003
Lead	1363							Assessed with the Adult Lead Model			
Mercury	1.68	9.21E-09	1.18E-09	1.45E-09	1	0.07	100%	0.0003	2.1E-05	3.1E-05	6.9E-06
Silver	407	2.23E-06	2.85E-07	3.51E-07	1	0.04	100%	0.005	0.0002	4.5E-04	1.8E-03
Zinc	798	4.37E-06	5.59E-07	6.89E-07	1	1	100%	0.3	0.3	1.5E-05	2.3E-06

(Continued)

Table 6.21 (Continued)

		Adult CTE Non-Cancer Hazard from Surface Water				Child CTE Non-Cancer Hazard				Total CTE Hazard for Adult Park Visitor = 0.03				Total CTE Hazard for Child Park Visitor = 0.2			
		Beryllium	Iron	3.82E-06 2.09E-04	2.10E-09 1.14E-07	1	1	0.007	100% 100%	1.4E-05 0.7	0.003 0.7	0.003 1.6E-07	0.003 2E-07	Total CTE Hazard for Child Park Visitor = 0.2			
Arsenic	1034	6.6E-05	4.14E-05	740E-05	1	0.95	4.1%	3E-04	2.9E-04	0.2	0.007	0.02					
Cadmium	36.6	2.3E-06	4.39E-08	7.86E-08	0.03	0.025	100%	0.001	2.5E-05	0.002	0.0004	0.005					
Lead	1363						Assessed with the IUBK Model										
Mercury	1.68	1.1E-07	6.72E-08	1.20E-07	1	0.07	100%	0.0003	2.1E-05	0.0004	6E-06	0.006					
Silver	407	2.6E-05	1.63E-05	2.91E-05	1	0.04	100%	0.005	0.0002	0.004	0.0001	0.2					
Zinc	798	5.1E-05	3.19E-05	5.71E-05	1	1	100%	0.3	0.3	0.0002	2E-07	4E-04					
Beryllium	23.9		1.91E-06	1.05E-09	1	0.007	100%		1.4E-05		7E-05	7E-05					
Iron	1304		1.04E-04	5.72E-08	1	1	100%		0.7		8E-08	8E-08					

**Table 6.22 Quantitative Characterization of Risk and Hazard for Park Workers (RME)**

**Table 6.23 Quantitative Characterization of Risk and Hazard for Park Workers (CTE)**

**Table 6.24 Quantitative Risk and Hazard Characterization for Construction/Excavation Workers (RME)**

Table 6.25 Quantitative Risk and Hazard Characterization for Construction/Excavation Workers (CTE)

A total of 98.3% of the hypothetical population of children modeled this way had blood lead concentrations less than 10  $\mu\text{g}/\text{dL}$ . Hence, lead concentrations in soil at the site are below levels of regulatory concern for children.

#### *6.5.2.9.2 Risk to Adults from Lead Exposure*

EPA's Adult Lead Model was used along with a lead soil concentration of 1363 mg/kg. This value was the higher of the two average concentrations from either surface soil and mixed soil, and thus would be protective of any receptors evaluated. The model spreadsheet and guidance can be obtained at [www.epa.gov/superfund/health/contaminants/lead/products.htm#alm](http://www.epa.gov/superfund/health/contaminants/lead/products.htm#alm). Updated values of the geometric mean blood lead concentration in women of child-bearing age and the geometric standard deviation were used in the model.<sup>63,64</sup> There was a 98.8% probability that fetal blood lead concentration would be less than the target of 10  $\mu\text{g}/\text{dL}$ . Hence, lead concentrations in soil at the site are not of concern for adults.

As with children, all sources of uncertainty and variability are considered by EPA to be addressed in the geometric standard deviation.<sup>100,101</sup>

#### ***6.5.2.10 Characterization of Uncertainty***

The risk estimates presented here are conservative estimates of potential risks associated with potential exposure to constituents detected in media at the former gold mine site. Uncertainty is inherent in the risk assessment process, and a brief discussion of these uncertainties is presented in this section. Each of the three basic building blocks for risk assessment (monitoring data, exposure scenarios, and toxicity values) and for the exposure assessment (parameters, models, and scenarios) contribute to the overall uncertainty.

Samples collected during site investigations were intended to characterize the nature and extent of potential contamination at the site. Subsequently, most of the samples were collected from locations selected in a directed manner to accomplish this goal. Sampling locations selected in this way provide considerable information about the site, but tend to be concentrated in areas of higher levels of contamination. Therefore, data from sampling locations selected in this manner tend to overestimate constituent concentrations representative of the potential exposure area. The samples were obtained to support contaminant characterization and, ultimately, remediation, and not to estimate human exposure. Hence, this risk assessment is based on the assumption that the available monitoring data adequately describe the occurrence of constituents in media at the site.

Environmental sampling itself introduces uncertainty. This source of uncertainty can be reduced through a well-designed sampling plan, use of appropriate sampling techniques, and implementation of laboratory data validation and quality assurance/quality control. The most likely source of uncertainty regarding concentration is the possible mismatch between the assumptions about receptor behavior.

The toxicity values and other toxicological information used in this report are likewise associated with significant uncertainty. In addition, humans are different than laboratory animals. In addition, the effects shown by the animals in the

high-dose studies are often very different than effects reported by humans in parallel epidemiology studies. As indicated, arsenic is the risk driver for both the child visitor and the park service worker, both exposure scenarios with hazard indices above 1. The reference dose for arsenic was estimated from human data on circulatory effects.

#### *6.5.2.10.1 Range of Uncertainty Based on Bioavailability*

As an exercise, risk estimates were calculated using arsenic bioavailability estimates of 1% and 100% for those receptors showing risk or hazard above regulatory thresholds. For the Park Service Worker, the range of cumulative risk estimates based on this bioavailability range is 4E-06–3E-04 and the range of cumulative hazard indices is 1–5. For the Child Visitor, the range of cumulative hazard indices is 0.9–4. Because the arsenic at the site is very likely in the form of arsenopyrite, 1% is more likely as an accurate value of the bioavailability of arsenic at the site. Hence, if this value of 1% were used rather than 19%, then all receptors in all use scenarios would have risk or hazard estimates below regulatory criteria.

#### *6.5.2.10.2 Comparison to Risks from Background Concentrations in Environmental Media*

As an additional exercise, exposure point concentrations were calculated for arsenic and cobalt from background surface soil samples. Arsenic and cobalt show the highest HQs in surface soil. The background samples used are shown in Table 20. It should also be noted that the background locations are described as “iron-rich” or as “pyrite.” Hence, it is likely that the arsenic in the general area of the former gold mine site exists as arsenopyrite and has very low bioaccessibility.

Exposure point concentrations were calculated for COPCs in surface soil. The 95% UCL concentrations for arsenic, cadmium and zinc were higher than site concentrations. It is left as an exercise at the end of the chapter for the reader to calculate risks from background soil for all receptors.

#### **6.5.2.11 Conclusions from the Gold Mine Risk Assessment**

The Child Park Visitor and the Park Service Worker were the only receptors showing unacceptable risks. The medium of concern is surface soil. Target organ separation according to the *Risk Assessment Guidance for Superfund, Volume 1: Human Health Evaluation Manual, Part A* indicated that only the Park Service Worker would experience non-cancer risks from arsenic above levels of concern:

Receptor	HI (Total)	HI (by Target Organ)
Child Park Visitor	1.7	0.8
Park Service Worker	2.3	1.3

Because the arsenic at the site appears to be predominantly in the form of arsenopyrite, which has a very low bioaccessibility, it is likely that these risks are overestimated and risks at the site are very likely below regulatory criteria.

### 6.5.2.12 Risk Characterization and Risk Management

When the results of the risk assessment were presented to the project manager, she immediately noted that for the child visitor and the park worker, there was a huge difference in RME and CTE cancer risk estimates from arsenic. The explanation was given that the largest contributors to this difference were the RME and CTE bioavailability estimates, which were approximately an order of magnitude apart. The risk assessor had come to this meeting prepared, and showed his spreadsheet calculations with the overhead projector. The project manager asked what the RME cancer risk would be for 4.1% bioavailability, and the risk assessor performed this calculation by changing a single value in the spreadsheet.\* The risk dropped to 4E-05, now well within the target risk range of  $10^{-6}$  to  $10^{-4}$ .<sup>48</sup>

The project manager asked about the reason for the low bioavailability value. The risk assessor was able to show her the high values of arsenic in soil and the low values in surface water and groundwater. He noted that the same low bioavailability values had been measured for other gold mine soils, and was likely due to poor solubility of the arsenic. The risk assessor explained that the knowledge base about arsenic bioavailability included historical knowledge of metals bioavailability at mining sites, guidance from EPA, and two laboratory animal studies—all indicated that arsenic in mining soils had very low bioavailability. The risk assessor also noted that a relatively inexpensive validated *in vitro* assay for bioavailability was available.<sup>95</sup>

“Makes sense to me,” was the project manager’s comment. She then asked if 4.1% was appropriate to use for the RME calculation. The risk assessor said that such use likely was appropriate. Her last question was about the solubility, and the risk assessor was able to explain his estimation of the five-order of magnitude difference in solubility that was shown earlier in this chapter.

“Based on that,” said the project manager, “4.1% is probably an overestimate of the bioavailability.” The risk assessor agreed.

“I can sell this,” she said. “The park workers were complaining because of their perception of the arsenic risk. They wouldn’t get out of their trucks anywhere near the tailings pile. Bunch o’ whiners!”

“The animals don’t seem to mind it,” said the risk assessor. “There’s a photo in the ecological risk assessment of a Ground Squirrel on the tailings pile.” (See Figure 6.6.) “Some of them have built burrows in the tailings. The arsenic levels in those tailings is over 7500 parts per million, and it sure doesn’t seem to have hurt the animals.

“Can I get the photo?” asked the project manager. “I can show it at the next meeting. Maybe it’ll stop those slackers from whining.”

“In my day,” said the risk assessor, “we would have called them goldbricks, which seems kind of fitting for the gold mine.”

\* These spreadsheets are available at [www.crcpress.com/9780367250973](http://www.crcpress.com/9780367250973). For an exercise at the end of the chapter, you will repeat this calculation.



**Figure 6.6** Ground Squirrel near the burrow on the tailings pile.

## 6.6 RISK ASSESSMENTS BASED ON EPIDEMIOLOGIC DATA

The risk evaluations presented in this section are brief. The purpose of these is to demonstrate other ways of thinking about environmental risk, following the words of the architect Mies van der Rohe: “Less is more.” The figures illustrating these two risk evaluations were created with the R statistical computing language, and the data used and code for analyzing the data and creating the plots are also shown. The intention is to help those who don’t yet know R to become a little more familiar with this widely used tool. For the second example, you will need to install Stan, a state-of-the-art platform for statistical computation, and Rstan, the interface to R. The links are provided at the end of Chapter 3.

### 6.6.1 Arsenic in Drinking Water and Lung Cancer

Arsenic is a naturally occurring metal widely distributed in soil and rock. Arsenic compounds have been used for years as pesticides, wood preservatives, and as alloy material for automobile batteries and electronic parts. During Victorian times, arsenic trioxide, or “white arsenic,” was used as a cosmetic. At that time and others in history, arsenic compounds were used to treat parasitic infections and syphilis. Dating from the late 1800s, arsenic trioxide in the form of Fowler’s solution was used to treat leukemia and psoriasis. In 2000, the US Food and Drug Administration approved arsenic trioxide for treatment of acute promyelocytic leukemia.<sup>102</sup>

Hippocrates, Aristotle, and Paracelsus are reported to have used arsenic as a medicine. Nero used arsenic to murder his stepbrother Britannicus and clear his path to become Emperor of Rome.<sup>103</sup> Arsenic has been used as a poison and a medicine dating back to 2000 bce.<sup>104</sup> The Emperor Napoleon may have been poisoned with

arsenic in his wine. The toxicity of arsenic is common knowledge—this storied metalloid has been the murder weapon of choice in both real life and fiction.<sup>104</sup>

Arsenic has long been associated with a range of health endpoints. This observation suggests that the toxicity of arsenic may well be due to disruption of basic cellular processes common to many types of cells.

Arsenic may exist in either the +3 or +5 valence state. The binding of trivalent arsenic compounds to critical sulfhydryl groups is a likely event in the mode of action in both humans and rodents.<sup>105</sup> Trivalent arsenicals may either be administered, produced metabolically, or occur naturally in water. In 2005, EPA's Office of Pesticides concluded that the mode of action of arsenic for bladder cancer supported a nonlinear default approach and that a RfD/TDI was an appropriate TRV rather than a slope factor.<sup>105</sup>

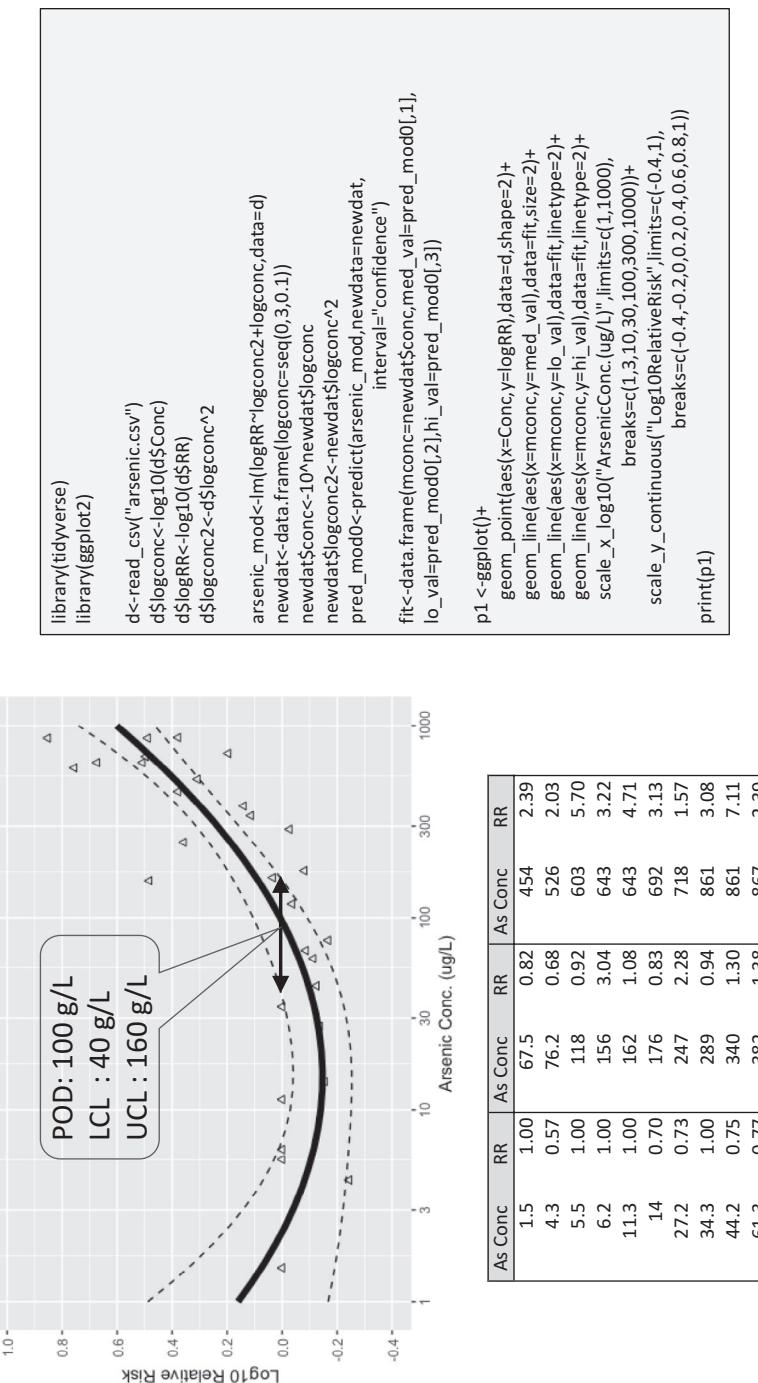
Life on earth evolved in an oxygen-rich atmosphere, and oxygen is vital for life. In response, life on earth has evolved with a host of antioxidant molecules and the enzymes to produce them. The most abundant of such molecules is glutathione (GSH), which is a target of arsenic toxicity at the molecular level.<sup>106</sup>

One of the key cellular pathways that depends on sulfhydryl groups is the activation of the antioxidant response mediated by the transcription factor nuclear factor E2-related factor 2, or Nrf2. The induction of the enzyme heme oxygenase-1 is a marker for Nrf2 activation. Arsenic disrupts the Nrf2 pathway and cellular antioxidant response.<sup>107</sup> In human primary lung epithelial cells exposed to either arsenite as  $\text{As}_2\text{O}_3$  or a mixture of trivalent arsenic compounds, heme oxygenase-1 enzyme activity was increased in a concentration-dependent fashion and activation of gene expression in pathways associated with cell adhesion, cytoskeleton remodeling, development and morphogenetic changes, control of the cell cycle, and inflammatory responses.<sup>108</sup>

The involvement of arsenic in these basic cellular processes suggests that possibly beneficial affects appear at very low doses of arsenic, whereas higher doses would be toxic—in short, an example of hormesis. Hormesis was observed in the relationship between lung cancer incidence and relative risk for cancer in a meta-analysis of six epidemiologic studies over the concentration range of 1–1000  $\mu\text{g/L}$  arsenic in drinking water.<sup>109</sup>

The plot of log relative risk versus log arsenic concentration of the combined studies was fit well with a second-order polynomial that dropped below the x-axis (Figure 6.7). The R code needed to create this figure is also shown. Arsenic has been observed to act as a “threshold carcinogen” for many years, and this dose response for lung cancer is consistent with those observations.<sup>93,110,111</sup>

The distribution obtained from the three values at the x-axis crossings does not exactly correspond to a benchmark dose; nonetheless, they are considered to comprise a distribution for a point of departure (POD). The lower confidence limit (LCL) of the POD is 40  $\mu\text{g/L}$ . If one wishes to consider arsenic in drinking water, the concentrations in the source being considered can be directly compared to this value or to the central value of the POD at 100  $\mu\text{g/L}$ . For example, if the water concentration in a municipal water supply were 5  $\mu\text{g/L}$ , the margin of exposure (MOE) at the POD would be 20, and the MOE at the LCL would be 8.



**Figure 6.7** Plot of arsenic data from Lamm et al. (2015) along with the 95% confidence interval. The crossings of the x-axis were used to develop a distribution for the BMD. The data are provided in the table and need to be entered as a two-column comma-separated variable (csv) file readable by Excel. For those who know R or wish to learn, the code to create the figure (without the callout) is also shown.

**Source:** Lamm SH, Ferdosi H, Dissen EK, Li J, Ahn J. (2015) A systematic review and meta-regression analysis of lung cancer risk and inorganic arsenic in drinking water. *Int J Environ Res Public Health* 12:15498–15515.

To obtain an RfD, one would first have to consider whether to add in dietary arsenic. The major source of arsenic in food occurs in fish. The populations considered in Lamm et al. (2015)<sup>109</sup> generally do not consume fish as might a population in a coastal area, and dietary arsenic would likely not contribute much to the total daily dose above 40 µg/L. A simple conversion for obtain a dose corresponding to the LCL would be to assume a water consumption rate of 2 L/d and a body mass of 70 kg. The resulting dose would be  $40 \times 2/70 = 1.14 \text{ }\mu\text{g/kg/d}$ . EPA chose 3 as a default value for the UF for human variability, and we will use that here. The resulting RfD would have a value of 3E-04 mg/kg/d, an identical value to the RfD EPA derived for dermal and vascular effects. The similarity in these two dose-response evaluations is consistent with the earlier discussion of the mode of action of arsenic that may underlie all of its toxic effects.

The analysis presented here is really quite simple, and is consistent with a very recent analysis that concluded the threshold level of arsenic in drinking water for the lung cancer, bladder cancer, and dermal keratosis was about 100 µg/L.<sup>112</sup>

## 6.6.2 Dioxin Exposure and the Risk of Congenital Hypothyroidism

The herbicide Agent Orange was used extensively in Vietnam as a defoliant. Agent Orange contained 2,4,5-trichlorophenoxyacetic acid and a contaminant generated during manufacture, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, or TCDD. TCDD is highly persistent in the environment, and many parts of Vietnam remain contaminated.<sup>113</sup> Da Nang is the largest city in central Vietnam, and was the location of a US airbase during the Vietnam conflict in the 1970s. The chair of the People's Committee of Da Nang City was made aware of EPA's current toxicity criterion for TCDD based on the possibility of congenital hypothyroidism in infants due to reduced maternal thyroid-stimulating hormone (TSH).

A large international consulting company stepped up and offered to conduct a *pro bono* evaluation. Because the project entailed no billable hours, the management assigned a young risk analyst named Jennifer to the project. She had been hired just a month before.

Jennifer began by searching PubMed, the database of scientific publications from the National Library of Medicine ([www.ncbi.nlm.nih.gov/pubmed](http://www.ncbi.nlm.nih.gov/pubmed)). She found a paper reporting TCDD serum levels from 69 Vietnamese adults aged 20–40 years living in Da Nang, and she used this sample to represent women of child-bearing age. The distribution was well fit by a lognormal distribution with a geometric mean of 3.2 pg/g lipid and a geometric standard deviation of 3.13. The maximum value was 120 pg/g lipid.<sup>114</sup> The units of pg/g lipid were confusing at first, but Jennifer continued reading, and learned that because of the lipophilic nature of dioxin-like chemicals, they are associated with blood lipids, and serum results are expressed as per weight of total blood lipids.<sup>115</sup>

From EPA's IRIS website, she obtained the scientific reports underpinning the Agency's assessment for TCDD.<sup>116</sup> In the executive summary, she found that EPA

chose a neonatal blood of TSH of 5  $\mu\text{U}/\text{ml}$  identified as the response associated with a LOAEL value.

During her college years, Jennifer had considered medicine as a career, and she worked as an aide in a neonatal intensive care unit for a year after graduation. She knew that 5  $\mu\text{U}/\text{ml}$  TSH was a screening level for re-testing, and definitely not a LOAEL. She was also well aware that congenital hypothyroidism led irrevocably to mental retardation and other neurological impairments—a serious endpoint indeed!

She recalled the neonatal care specialist she worked with recounting that just after birth, the pituitary releases periodic spikes of TSH often over 100  $\mu\text{U}/\text{ml}$  to “kick-start” the baby’s thyroid.<sup>117</sup> Waiting until 72 hours to obtain a heel stick for testing was enough time for TSH to return to baseline levels. “You know what a circus it is in here,” the doctor had told Jennifer. “The nurses do the heel sticks when they have the time.”

Jennifer also knew that maternal iodine deficiency could also affect thyroid hormone production in babies and also their TSH levels by feedback through the HPT axis. Since dioxin potentially affected TSH, she wanted to know the risk of congenital hypothyroidism at various levels of neonatal TSH. Again from a PubMed search, she found a paper reporting results on over 160,000 infants; none of the infants with TSH levels below 28  $\mu\text{U}/\text{ml}$  were confirmed to be hypothyroid.<sup>118</sup> She realized she had identified a NOAEL.

EPA had obtained the data used to develop the toxicity criterion from a 2008 paper by Baccarelli et al. reporting results from 51 mother/child pairs exposed to TCDD following a 1976 explosion at an herbicide manufacturing plant in Seveso, Italy and examined between 1994 and 2005.<sup>119</sup> The paper provided a graph of individual results of maternal TCDD levels and neonatal TSH for the 51 pairs. Jennifer carefully copied the graph and digitized the data. She fit a linear equation using Bayesian regression and developed a posterior prediction for the maternal dioxin serum levels corresponding to the NOAEL of 28  $\mu\text{U}/\text{ml}$  neonatal TSH. The plot she made along with the R-code for the regression model is shown in Figure 6.8.

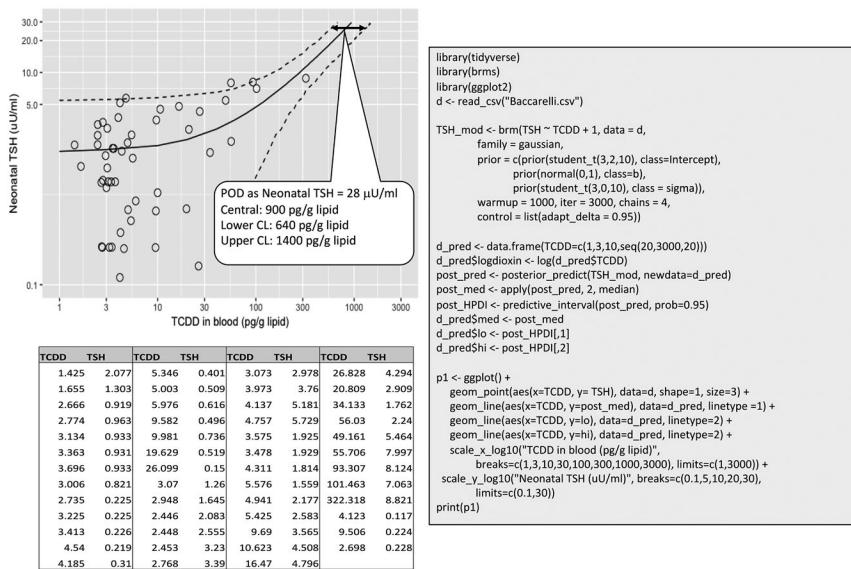
The 95% lower confidence limit of the dioxin levels corresponding to 28  $\mu\text{U}/\text{ml}$  neonatal TSH was 640 pg/g lipid, and the highest value in the Da Nang data was 120 pg/g lipid.

Jennifer’s supervisor liked PowerPoint shows, so she created one to present her results. Her supervisor listened carefully.

“But what about the reports of developmental problems in Vietnamese kids in the literature?” he asked when she was finished.<sup>120</sup>

Jennifer had prepped for this question. She had located a recent paper showing that rural Vietnamese women had insufficient iodine intake, and explained to her boss that, rather than TCDD, iodine deficiency was a more likely cause of any neurodevelopmental effects in the Vietnamese population.<sup>121</sup>

Jennifer’s supervisor nodded, and after a moment, he spoke. “There’s a meeting with the Da Nang officials in Paris in about three weeks. Could you present this work there? If you haven’t been, the food there is the best in the world.”



**Figure 6.8** Plot of data from Baccarelli et al. (2008) showing the Bayesian linear fit to the data. The data used and the R-code using the package “brms” from Paul Buerkner are shown below and to the right of the plot. The fit is curved on a log-log plot. The data are provided in the table, and need to be entered as a two-column comma-separated variable (csv) file readable by Excel. For those who know R or wish to learn, the code to create the figure (without the callout) is also shown.

**Source:** Baccarelli A, Giacomini SM, Corbetta C et al. (2008) Neonatal thyroid function in Seveso 25 years after maternal exposure to dioxin. *PLoS Med.* 5:e161.07-PLME-RA-2317 [pii]. doi:10.1371/journal.pmed.0050161.

## 6.7 HOLISTIC APPROACHES AND THE NEED FOR CAUTION

Dear reader, no doubt you have remarked to yourself just how full of detail, how “down in the weeds,” individual risk evaluations can be. Knowledge of and ability to work with details is a necessary skill for any risk analyst. Cultivation of the ability to view a situation “from 10,000 feet” is also a valuable and necessary skill.

The fundamental implicit relationship underpinning any risk evaluation is causality. The nine considerations for causation first put forward by Sir Austin Bradford Hill for causation were discussed earlier. The consideration of coherence enables the risk analyst to step back and ask: “What else could it be?”

Both LeMasters et al. (2006) and the International Agency for Research on Cancer (IARC, 2010) conducted meta-analyses of prostate cancer incidence in firefighters and concluded that these public servants experienced a 30% greater incidence of prostate cancer.<sup>122,123</sup> One possible reason is the exposure to flame retardant chemicals that are associated with a variety of adverse health outcomes.<sup>124,125</sup> You should already be thinking about causation.

Current efforts in prostate cancer epidemiology have focused on genetic makeup. Single-nucleotide polymorphisms can identify men at elevated risk for prostate cancer.<sup>126–128</sup> The genetic association is strong, and appears to outweigh other causal factors. Consistent with this evidence is the fact that no epidemiologic studies have linked prostate cancer to flame retardant exposure.

Obesity has been associated with mortality from prostate cancer in several large cohort studies,<sup>129</sup> and firefighters have among the highest rates of obesity of any male occupations, the job-related physical activity notwithstanding.<sup>130,131</sup> Prevalence of overweight and obesity (body mass index  $\geq 25$ ) ranged from 73% to 88% in career firefighters, greater than the prevalence of these conditions in the general population, which is about 2/3.<sup>132</sup> This epidemiologic evidence suggests that the consistently observed increased incidence of prostate cancer in firefighters likely occurs as a result of the increased prevalence of overweight and obesity compared with the general population, along with an unlucky contribution from genetics.

In this example, both unlucky genetics and the prevalence of overweight among firefighters seem reasonable answers to the question of “What else could it be?”

### 6.7.1 What Is a Holistic Risk Assessment?

In general, integrated risk assessment refers to the inclusion of both human health and environmental risk in one assessment. A holistic risk assessment is a systems approach using different data types and a variety of stressors, including socio-economic, lifestyle, belief, etc., to address health risks arising from multiple interacting factors.<sup>133</sup>

The technological revolution that continues has the potential to change the environment more radically and extensively than in the past. Increasing globalization and connectedness spread these effects to populations at a distant remove from the origin of any given hazard. A host of causal factors contribute to these systemic risks. In response, government policies have become more expansive, and may, with the best of intentions, attempt to manage these systemic risks that are embedded in environmental, social, political, and economic systems.<sup>134</sup>

The complexity of these systemic risks in the 21st century is enormous. The National Academies of Sciences considers them “wicked problems”: they are difficult to define, unstable, socially complex, without a clear solution, and beyond the understanding of any one discipline or the purview of any single organization.<sup>135</sup> Even worse, the effect of any attempt at management may actual worsen the situation because of interlocking feedback loops and unknown hysteresis.

Such problems call for a problem formulation well beyond anything yet performed. In addition to the question about causation at the start of this section, a risk analyst needs to ask: “What am I missing?”

The science of risk analysis is still discovering exactly what goes into a holistic risk assessment. Each one may be different, depending on the needs and wishes of the stakeholders in the decision.<sup>136,137</sup>

A relatively simple means of addressing the overall/cumulative/integrated risk from the many chemicals in commerce to which all are exposed would be to include

consideration of exposure early as a mechanism for triaging those chemicals. The hazard-only approach for selection of chemicals or even other stressors within a holistic risk assessment rubric can result in unintended consequences. A number of highly regrettable chemical substitutions have been made in household and personal care products. Consideration of exposure over the product lifecycle and possibly beyond, the performance of the product for its intended use, and hazard will likely result in better choices.<sup>138</sup> An example of this method was conducted to decide upon the solvent used in an indoor residential wall paint. Margins of exposure between NOAEL and LOAEL values and exposure estimates for the five candidate solvents using a target MOA of 100 for NOAELs and 1000 for LOAELs were used as a screen. Three solvents survived this screen and were then considered based on their performance characteristics.<sup>139</sup>

### **6.7.1.1 Endogenous Exposures: A Problem to Be Formulated**

The occurrence of formaldehyde in breath from endogenous generation within the body was discussed in Chapter 2. An adequate problem formulation for EPA's 2009 formaldehyde assessment would have included the consideration of endogenously produced formaldehyde as an ongoing background exposure. As a species, *Homo sapiens* cannot escape the effects, deleterious or beneficial, of endogenously produced chemicals. Reactive oxygen species from endogenous sources modify about 20,000 bases of DNA within a single cell each day.<sup>140</sup> Christopher Wild of IARC brought forward the concept of the exposome and indicated that exposures should include not only chemicals entering the body from air, water, food, medicines, or other sources, but also internally generated toxicants produced by the gut flora, inflammation, oxidative stress, lipid peroxidation, and other natural biological processes.<sup>141,142</sup>

Ethylene oxide is classified by the IARC as carcinogenic to humans and produced endogenously in the liver from endogenously produced ethylene in circulating blood and from the microbiome.<sup>143,144</sup> Alkylating agents such as methylnitrosourea (MNU) and methylmethane sulfonate (MMS) react with DNA by methylating guanine or thymine bases and induce mutations. S-adenosylmethionine (SAM) is produced within the body from the amino acid methionine, and is sometimes taken as an over-the-counter dietary supplement for osteoarthritis and depression. SAM is the major source of endogenous DNA methylation, and may contribute to the background mutation rate.<sup>145</sup> Acetaldehyde is a metabolic product of ethyl alcohol, and is also endogenously produced as a by-product of cellular metabolism. Experiments in cell cultures using with carbon-13-labeled acetaldehyde indicate that at low exogenous exposures, adduct formation from endogenous adducts dominates; this situation reverses at high exposure, however.<sup>146</sup> Formaldehyde reacts with DNA in a similar fashion to acetaldehyde, and distinguishing exogenous from endogenous DNA adducts requires the use of formaldehyde labeled with both carbon-13 and deuterium, or heavy hydrogen.<sup>141</sup>

Obviously, the presence of endogenous exposures that contribute to cancer risk raises the problem of determining attributable risk.<sup>147</sup> A bottom-up approach for

inclusion of including endogenous exposures as a lower bound when calculating a slope factor is one way of dealing with this, should regulatory agencies persist in using the LNT for TRV derivation for cancer endpoints.<sup>148,149</sup> Another approach is the derivation of endogenous equivalent values using the correlation between external exposure and an internal biomarker. This approach proved to be a pragmatic way to provide context for estimating and managing risks from ethylene oxide exposures.<sup>150</sup>

## 6.8 CONCLUSIONS

When conducting any risk evaluation, the risk analyst should continually be questioning the results, wondering about other causes, and worrying about what factors are not being considered. Taking such a position of curiosity requires humility, and will likely improve the analysis. You can't know the "unknown unknowns," but that shouldn't prevent you from thinking of possibilities.

## 6.9 EXERCISES FOR THOUGHT AND DISCUSSION

### 6.9.1 Working with ProUCL

Go to EPA's website at [www.epa.gov](http://www.epa.gov) and enter the term "ProUCL" in the search box. Download the software and documentation, and check that the statistics and UCL values in the tables are correct. The tables in this chapter provide all the data.

### 6.9.2 The Use of Alternate Toxicity Criteria

The fish consumption and gold mine examples in this chapter use alternative criteria for bioavailability and toxicity respectively. Develop convincing arguments both for and against the use of such non-standard approaches. Set up a role-playing scenario in which one group, representing the regulated entity, attempts to convince others, representing the regulatory agency, that the use of new science is appropriate.

The other two shorter examples, essentially derivations of estimates of toxicity for 2,3,7,8-TCDD and arsenic, depend on the use of statistics to obtain confidence limits around the POD. Continuing role-playing with arguments for and against using the LCL and the central value.

From your library, obtain a copy of Shaw et al.'s 2005 paper "Treating and drinking well water in the presence of health risks from arsenic contamination: results from a U.S. hot spot" (doi:10.1111/j.1539-6924.2005.00698.x). This paper provides sampling results for arsenic from private wells in Churchill County, Nevada. Its Table 1 provides the average and quartile values of arsenic concentration in tap water. Conduct a margin of exposure assessment with the arsenic TRV for lung cancer derived earlier in this chapter.

### 6.9.3 Calculation of Fish Advisories

Take a look at both of the EPA documents in the references (numbers 74, 79 and 80) that relate to fish advisory levels for methylmercury. Using the data in Tables 6.1a, b, and c, reproduce the risk assessor's calculation to determine whether fish advisory levels are needed.

## REFERENCES

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## CHAPTER 7

# Ecological Risk Assessment

A man is ethical only when life, as such, is sacred to him, that of plants and animals as that of his fellow men, and when he devotes himself helpfully to all life that is in need of help.

**Albert Schweitzer**

The only way to save a rhinoceros is to save the environment in which it lives, because there's a mutual dependency between it and millions of other species of both animals and plants.

**David Attenborough**

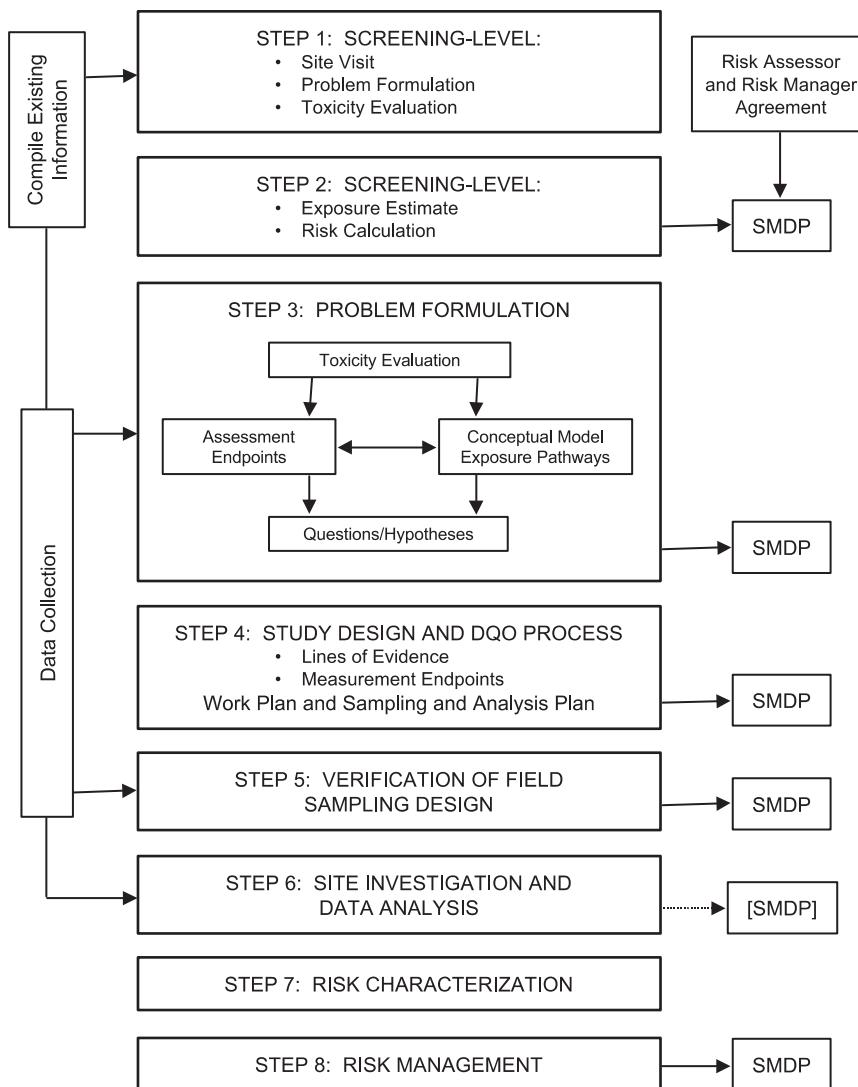
Ecological risk assessment addresses the parts of National Environmental Policy Act (NEPA) that require protection of the environment. Thus far, in this textbook, human health has been the sole focus. This chapter is devoted to ecological risk assessment—protection of biota in the wild and entire ecosystems.

Ecological risk assessment led the way in problem formulation, as discussed in Chapter 2, but is often given only cursory attention by decision-makers. Concern for protection of natural areas, wild populations and similar resources was envisioned explicitly in NEPA (see Figure 1.1 in Chapter 1).<sup>1</sup>

Adverse ecological effects may result from exposure to one or more stressors. The lion's share of ecological risk assessment activity is predictive: often, data are combined with uncertain assumptions to predict the effect of stressors on ecological receptors, both at the individual and population levels. In those cases where data are collected to answer particular questions or test specific hypotheses as part of the ecological risk assessment, this uncertainty can be reduced by careful planning.

Ecological risk assessment has been developed with a focus on problem formulation, and thus seems to follow the scientific method to a greater extent than does human health risk assessment. The reason for this is that the endpoints are less clear. What does “a significant effect on a population” mean? Can the population withstand a reduction of 10%? 20%?

One can think of ecological risk assessment in two parts: the first part is theoretical and predictive. The second part consists of data gathering or experimentation that seeks to provide evidence regarding any hypotheses developed in the first part.



**Figure 7.1** Eight-step process used in ecological risk assessment. The acronym SMDP means scientific management decision point.

Ecological risk assessments are anthropocentric, in that they are designed to address and inform specific risk management decisions from a human perspective—the values to be protected are those valued by society, as pointed out in Chapter 1.

In the 1991 report of a colloquium to develop a set of inference guidelines for ecological risk assessment following the suggestion of the “Red Book,” EPA admitted that the development of standard methods for ecological risk assessment had lagged behind that for human health. The reason given was that ecological risk assessments

address a variety of endpoints at different levels of biological organization—from individuals to communities to ecosystems—and choosing these endpoints presented a challenge.

This single chapter can do no more than provide an introduction to the field of ecological risk assessment. There are as many nuances and complexities in ecological risk assessment as in human health risk assessment. For those writing ecological risk assessments, familiarity with EPA guidance (discussed below) is a necessary starting point.

Dr. Glen Suter is one of the foremost scientists in the field of ecological risk assessment. He worked as a staff scientist at the Oak Ridge National Laboratory (ORNL) until 1998, and then joined EPA. Dr. Suter has written a recent textbook, *Ecological Risk Assessment*, also published by Taylor & Francis. As noted, this single chapter is not intended to be comprehensive, and those serious about wanting to learn more are encouraged to consult Dr. Suter's book.<sup>2</sup>

## 7.1 EPA GUIDANCE FOR ECOLOGICAL RISK ASSESSMENT

As part of the response to the recommendation by the National Academy of Sciences “Red Book” to develop inference guidelines for risk assessment, EPA’s Risk Assessment Forum held discussions in 1990 for the purpose of developing such guidelines specifically for ecological risk assessment.<sup>3</sup> These discussions resulted in a framework document that underwent peer review and was published by EPA in 1992.<sup>4</sup>

The framework document was fairly general, and started with the existing paradigm for human health risk assessment. The proposed framework consisted of three major phases: (1) problem formulation, (2) analysis, and (3) risk characterization.

The framework also recognized the need for ecological risk assessment to consider effects at the population, community, or ecosystem levels. The framework introduced flexibility in the choice of endpoints, noting that “no single set of ecological values to be protected that can be generally applied,” and recommended that these values be selected based on both science and policy considerations.

In 1989, EPA’s Superfund program released *Risk Assessment Guidance for Superfund, Volume II: Environmental Evaluation Manual, Interim Final* as a companion to *Risk Assessment Guidance for Superfund, Volume 1* for human health.<sup>5</sup> Although this document provided a thoughtful discussion of ecological risk issues, what was lacking was a prescriptive explanation of how to conduct and present an ecological risk assessment. The risk assessment community would have to wait until 1997 for such a document.

The first guidance document issued by EPA’s Risk Assessment Forum was the *Framework for Ecological Risk Assessment*.<sup>4</sup> In 1995, the Risk Assessment Forum published draft *Proposed Guidelines for Ecological Risk Assessment*. These were peer-reviewed and finalized in 1998.<sup>6,7</sup>

Concurrently, within the Superfund program, a much-needed revision of the 1989 guidance was being developed. This revision was published in 1997 as *Ecological*

*Risk Assessment Guidance for Superfund: Process for Designing and Conducting Ecological Risk Assessments—Interim Final.* This guidance is commonly referred to as the “Process Document.”<sup>8</sup>

The Process Document issued by the Superfund program differs in the number of steps and prescriptiveness of the process from the framework document and the 1998 *Guidelines for Ecological Risk Assessment*, also issued by the Risk Assessment Forum.<sup>7</sup> Regardless of these differences, the Process Document is generally consistent with the framework and the guidelines.<sup>8</sup>

The process described consisted of eight steps (see Figure 7.1). In practice, the majority of ecological risk assessments conclude following Step 3. The flexibility of this process is not shown in the diagram. In practice, Step 3 has evolved to include a consideration of all available information, and most often, comparison to background concentrations or risks and food chain modeling provide sufficient information to stop the process. Step 3 has been separated into parts A and B. A screening level ecological risk assessment (SLERA) includes steps 1, 2, and 3A; a baseline ecological risk assessment (BERA) includes Steps 1–7, and usually involves site-specific data gathering.

To fill in gaps in the guidance, EPA’s Superfund program has occasionally issued ECO Update Bulletins. These can be found by searching EPA’s website for “ECO+update+bulletins” using the search box at the upper right of EPA’s main webpage at [www.epa.gov/](http://www.epa.gov/), and provide a range of guidance on specific issues. Essentially what has happened is that rather than rewriting guidance documents, ecological risk assessors within the Superfund program have chosen to issue these periodic updates.

EPA’s Office of Pesticide Programs has much less guidance, and relies more heavily on the Framework and Guidelines from the Risk Assessment Forum. The Pesticide program has issued specific guidance on endangered and threatened species.<sup>9</sup> In addition, there are a number of concerns about the use and permitting of rodenticides in the Office of Pesticide Programs.<sup>10</sup>

There are a number of new terms specific to ecological risk assessment. A selection of these are defined in Box 7.1.

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### BOX 7.1 DEFINITION OF SELECTED TERMS FOR ECOLOGICAL RISK ASSESSMENT

**Abiotic:** Characterized by the absence of life. Abiotic materials or conditions include non-living environmental media (e.g., water, sediment) or light, temperature, humidity or other factors.

**Area Use Factor:** The ratio of an organism’s foraging range to the area of contamination at the site. A value of 100% is the most protective.

**Assessment Endpoint:** An explicit expression of the environmental or ecological value being investigated or sought to be protected by the risk assessment.

*Benthic Community:* the community of sediment-dwelling organisms at the bottom of a water body.

*Bioaccumulation:* A process by which chemicals are taken up by an organism due to exposure. Generally, bioaccumulative chemicals tend to increase in concentration moving up the food chain.

*Biomagnification:* The result of bioaccumulation by which tissue concentrations of chemicals at a higher trophic level exceed those in organisms at a lower trophic level.

*Community:* A group of populations of different species living at a specified location and time.

*Biotic:* Characterized as living. Biotic refers to the protists, plants, animals and communities that comprise ecosystems.

*Conceptual Model:* A series of working hypotheses of how contaminants or other stressors might affect ecosystems or communities. These hypotheses describe the relationships between exposure scenarios and assessment endpoints, and between assessment endpoints and measurement endpoints.

*Chemical of Potential Ecological Concern (COPEC):* A substance with the potential to affect ecological receptors adversely due to its concentration, distribution, and mode of toxicity.

*Ecosystem:* The biotic community and abiotic environment at a specific time and place, including the chemical, physical and biological interactions.

*Food Chain Transfer:* The process by which higher-trophic-level organisms substances are exposed to substances occurring in the tissues of lower-trophic-level prey organisms.

*Hazard Index:* The sum of e-hazard quotients for multiple substances and/or multiple exposure pathways.

*Hazard Quotient:* ratio of an exposure level to a substance to a toxicity reference value selected for the risk assessment for that substance (e.g., LOAEL or NOAEL).

*Home Range:* area to which an organism lives.

*Lowest Observed Adverse Effect Level (LOAEL):* The lowest level of a stressor evaluated in a toxicity test or biological field survey that has a statistically significant adverse effect on the exposed organisms compared with unexposed organisms.

*Measurement Endpoint:* A measurable characteristic reflecting the assessment endpoint.

*No Observed Adverse Effect Level (NOAEL):* The highest level of a stressor evaluated in a toxicity test or biological field survey that causes no statistically significant difference in effect compared with controls.

*Scientific/Management Decision Point (SMDP):* The point during the risk assessment process when stakeholder discussions occur to decide

whether available information is sufficient to support risk management or whether additional information is needed.

*Toxicity Reference Value:* A numerical value expressing the exposure–response relationship in an ERA. It can be a NOAEL, LOAEL, or benchmark dose.

*Trophic Level:* A classification of species within a community based on feeding or predator/prey relationships.

**Source:** EPA (1997) *Ecological Risk Assessment Guidance for Superfund: Process for Designing and Conducting Ecological Risk Assessments—Interim Final.*

## 7.2 THE EIGHT STEPS OUTLINED IN THE PROCESS DOCUMENT

Here, each of the eight steps in the ecological risk assessment processes detailed in EPA's Process Document will be considered. This process is used by a large number of regulatory agencies, and is the general method for proceeding. Most state agencies require a screening level ecological risk assessment (SLERA), which consists of the first three steps of the process.

Recently, the EPA Region 4 office in Atlanta provided an update to their 1995 ecological risk guidance. The new guidance provides screening values for environmental media developed with newer computational tools. This document also provides a useful summary of the ecological risk process.<sup>11</sup>

### 7.2.1 Step 1: Screening Level Problem Formulation and Ecological Effects Evaluation

This first step is supposed to address five distinct issues:

- environmental setting and known contaminants;
- fate and transport mechanisms;
- mechanisms of ecotoxicity and categories of receptors
- exposure pathways;
- screening endpoints for ecological risk.

In many SLERAs, the first four issues are discussed in narrative and the SLERA focuses on screening chemical concentrations measured in various environmental media. These considerations are used to develop a preliminary site conceptual model of how contaminants occur at the site and how they might affect the ecosystem at both individual and population levels.

### **7.2.1.1 Sources of Ecological Screening Values**

Ecological screening benchmarks exist for biota, soil, and sediment. Criteria exist for surface water. Criteria are acceptable regulatory values, whereas benchmarks are intended for use as screening values. Air and groundwater are excluded because these are not usually considered in ecological risk assessment. A comprehensive source for these values is the Risk Assessment Information System at <http://rais.ornl.gov>, maintained by the Oak Ridge National Laboratory (ORNL). Dr. Glen Suter, mentioned above, authored many of the documents that provide commonly used screening benchmarks.<sup>12-17</sup>

### **7.2.1.2 Ecological Screening Benchmarks for Surface Water**

The list of National Ambient Water Quality Criteria (NAWQC) provides values for surface water. These criteria are generally protective, but may not be applicable at every site. These criteria are based on three specific endpoints: human health, aquatic life, and organoleptic effects in humans such as smell and taste. These criteria are updated periodically, and are currently available at [www.epa.gov/wqc/national-recommended-water-quality-criteria-aquatic-life-criteria-table#altable](http://www.epa.gov/wqc/national-recommended-water-quality-criteria-aquatic-life-criteria-table#altable). The values based on aquatic life should be used in ecological risk assessment.

### **7.2.1.3 Ecological Screening Benchmarks for Soil**

The first attempt at developing soil screening criteria for ecological risk assessment was begun in the 1980s by the Dutch government.<sup>18</sup> Ecological screening values for soil may be based on protection of endpoints in plants, soil invertebrates, and the soil ecosystem or vertebrates. The next attempt at a systematic collection of chemical-specific screening values was conducted at ORNL. For plants, soil benchmarks were determined based on a literature review and were based on laboratory experiments.<sup>13</sup> For invertebrates and soil bacteria, three specific endpoints were examined: toxicity to earthworms, toxicity to soil microbes and heterotrophic processes in the soil, and toxicity to invertebrates other than earthworms.<sup>12</sup> Earthworm toxicity was assessed from laboratory experiments reported in the scientific literature; toxicity to heterotrophic microbes was assessed based on changes in the activities of various microbial enzymes, respiration, or the ability to fix nitrogen. Toxicity to invertebrates other than earthworms was assessed from laboratory experiments on mollusks, arthropods, or nematodes. Soil values were also developed for birds and mammals.<sup>15</sup>

In 1998, Gary Friday of the Westinghouse Savannah River Company compiled ecologically based soil screening values from a variety of sources, including ORNL documents, US Fish and Wildlife benchmarks, the Dutch values, and values from the Canadian Council of Ministers of the Environment.<sup>19</sup> Over time, various sets of soil screening values have been assembled by different regulatory agencies in state governments, with considerable overlap.

In 2003, EPA developed ecological soil screening levels (Eco-SSLs) for 24 chemicals. Eco-SSLs are concentrations of contaminants in soil protective of ecological receptors that contact or live in soil, or ingest biota living in soil. Four groups of receptors are considered: plants, soil invertebrates, birds, and mammals. The set of 24 chemicals are comprised of metals and bioaccumulative organic chemicals.<sup>20</sup>

#### **7.2.1.4 Ecological Screening Benchmarks for Sediment**

The development and use of sediment screening benchmarks are controversial. Generally, sediment benchmarks are based on three methods: laboratory bioassays, field studies, and models of equilibrium partitioning.

The first method is laboratory bioassays conducted on contaminated sediments collected in the field or background sediments spiked in the laboratory with single chemicals or mixtures. The endpoint is generally mortality of a sediment-dwelling organism. Most often, the amphipod *Hyalella azteca* is used as the test organism. Other organisms used are the midge *Chironomus tentans* or the mayfly *Hexagenia* spp. Questions have been raised about whether these laboratory tests are applicable to field populations.<sup>21</sup>

The second method, field surveys, attempts to estimate the highest concentration of a particular contaminant that can be tolerated by 95% of the benthos. This screening level concentration (SLC) approach uses field data from sites with different concentrations of contaminants in sediments and on the co-occurrence of benthic infaunal species in these sediments. At least ten species and ten different locations are required for each chemical. The frequency distribution of the concentrations of a contaminant at all sites where a given species is present is calculated, and the 90th percentile of this distribution is used as the SLC for that species. When these species-specific SLC values are developed for at least ten species, the 5th percentile of the resulting distribution is thought to represent the concentration that 95% of the species can tolerate. This 5th percentile value becomes the SLC. This method assumes that the chemical concentration data used cover the full tolerance range of each species. Hence, a range of at least two orders of magnitude is needed for some validity. The concentration range is not always reported, and the full tolerance range of most species remains unknown.<sup>22</sup>

The third method, equilibrium partitioning, is based on the idea that because sediment-dwelling benthic organisms contact the interstitial pore water in sediment, concentrations in pore water will reflect the most relevant exposure metric. This equilibrium partitioning approach estimates the concentration of a chemical in pore water based on the concentration in bulk sediment. For non-ionic organic chemicals, the partition coefficient is roughly equal to the organic carbon partition coefficient multiplied by the fraction of organic carbon in sediment.<sup>22</sup> For metals, the equilibrium partitioning approach is more difficult, and may not be possible because of a variety of factors; hence, for metals, measurement of the bioavailable pool of metal in sediment requires simultaneous measurement of acid-volatile sulfides.<sup>23–25</sup>

Clearly, there are areas of great uncertainty associated with all three approaches. The bulk of the work to integrate these three approaches has been conducted by

Dr. Don MacDonald, a private consultant in Nanaimo on the island of Vancouver in British Columbia. The National Oceanic and Atmospheric Administration has adopted many of MacDonald's recommendations.<sup>26-28</sup> The state of Florida also depends on an evaluation by MacDonald for marine and estuarine sediment quality benchmarks.<sup>29</sup>

EPA's Regional Office in Chicago (Region 5) provides a compilation of sediment screening benchmarks on a single webpage.<sup>30</sup>

### **7.2.1.5 Natural Resource Trustees**

Communication with natural resource trustees and the decision to conduct a natural resource damage assessment may commence during Step 1 of the ecological risk assessment process.

The National Oil and Hazardous Substances Pollution Contingency Plan (40 CFR 300) and the Comprehensive Environmental Response, Compensation and Liability Act require that a natural resource damage assessment (NRDA) be conducted as part of most hazardous waste site evaluations. Natural resource trustees include other federal agencies such as the National Oceanic and Atmospheric Administration and the US Fish and Wildlife Service, state officials, usually designated by the governor, and representatives from Native American tribes.

The requirements for completing an NRDA for the various trustees are slightly different. Risk assessors working on these will need to consult with both project managers and attorneys to make sure these requirements are met.

### **7.2.2 Step 2: Screening Level Exposure Estimate and Risk Calculation**

This step is analogous to chemical of potential concern (COPC) screening in human health risk assessment. The acronym COPEC, meaning "chemicals of potential ecological concern," has come into common usage. In this step, COPECs are determined by comparing the maximum detected level of a chemical in an environmental medium with the screening benchmark. If the maximum detect is greater than the benchmark, the chemical is considered a COPEC. The Process Document indicates that highly conservative exposure factors should be used. The other part of the step is the calculation of a screening level hazard index as the ratio of the maximum detected concentration and the screening benchmark.

Obviously, this calculation will likely produce a gross overestimate of risk. In addition, because of uncertainty in the screening benchmarks, a number of these screening benchmarks are below naturally occurring background concentrations in soil. EPA's 2005 update to the Guidance for Developing Ecological Soil Screening Levels indicates:

It is EPA's policy to not screen against background levels. Background concentrations, the speciation of metals, and the effects of conservative modeling assumptions are generally taken into account in the initial steps of the baseline risk assessment.<sup>20</sup>

The upshot of this policy is that preliminary estimates of ecological risk are often reversed once background comparison is performed. However, the ecological risk assessment process does not include this comparison until Step 3. These reversals are often difficult to communicate to stakeholders who may not be familiar with the process.

Regarding Step 2, the Process Document indicates that risk is estimated by comparing maximum concentrations detected with the ecotoxicity screening benchmarks collected in Step 1. This results in a set of hazard quotients for the chemicals detected at the site. The Process Document also prescribes a scientific management decision point (SMDP) at the conclusion of Step 2. At the conclusion of Step 2, the risk manager and risk assessment team will decide that either the screening level ecological risk assessment is adequate to determine that ecological threats are negligible, or whether the process should continue to a more detailed ecological risk assessment.

This prescription for an SMDP following Step 2 proved problematic. If an SMDP consisted of an informal conversation between a risk assessor and a project manager, there would, of course, be no delay in the process. However, if the SMDP required the presence of stakeholders to attend in person, a situation involving airplane travel and other expenses, the difficulty that arose was that the information developed in Steps 1 and 2 was insufficient to decide whether the process should go forward.

### **7.2.3 Step 3: Baseline Risk Assessment Problem Formulation**

Although a preliminary problem formulation had been developed in Step 1, the baseline problem formulation used all other available information to develop more refined estimates of risk. The problem with putting this activity off until after the first SMDP was that the information needed to decide whether to proceed had not been developed. Step 3 included the following activities:

- refinement of COPEC selection;
- review of information on contaminant fate and transport, exposure pathways, and ecosystems potentially at risk;
- comparison of site and background concentrations;
- selection of assessment endpoints and refined estimation of exposure, likely using food chain modeling;
- development of a refined conceptual model and problem formulation with working hypotheses or questions that would be addressed by further site investigation.

In 2000, the Department of Defense could not obtain funding for activities related to ecological risk assessment at military bases further into the future than the next SMDP. In response to this, regional toxicologists split Step 3 into two parts—3a and 3b. In Step 3a, information from the first four items in the list above would be addressed. The SLERA would consist of a report or technical memorandum detailing the results of Steps 1, 2 and 3a. An SMDP would then be conducted and would have sufficient information to make the decision whether to proceed. Step 3b would

then include only the last item in the list, and would occur only if the decision to move forward had been made in the SMDP.<sup>31</sup>

### **7.2.3.1 Step 3a**

Once Step 3 had been split into two parts, development of the SLERA consisting of Steps 1, 2, and 3a allowed ecological risk activities at many sites to be concluded much more quickly. Any available information that had bearing on the ecological risk at the site and did not require additional data gathering could be included. Such information often consisted of a background comparison, assessment of bioavailability, and food chain modeling. For ecological risk assessment where significant work and resources might be involved if the assessment progressed, background comparison was almost always conducted—even though doing so was inconsistent with EPA's guidance on the use of background.<sup>32</sup>

### **7.2.3.2 Step 3b**

Based on the information developed in Steps 1, 2, and 3a and presented in the SLERA, a refined problem formulation should include a detailed conceptual model and hypothesis regarding how the contaminants at the site are negatively impacting the ecosystem. This hypothesis should provide testable predictions that can be confirmed, if true, based on data that can be gathered at the site. Problem formulation will include consideration and refinement of the site conceptual model, exposure pathways, and selection of assessment endpoints and measurement endpoints. The exposure pathways must be linked to the assessment endpoints.

A strong line of evidence that ecological effects observed at the site are indeed site-related can be obtained by sampling along a biological gradient. For example, at a site where the occurrence of polycyclic aromatic hydrocarbons (PAHs) in sediment has been hypothesized to be toxic to benthic invertebrates, co-located sample points at which both sediment samples for laboratory PAH analysis and measures of number and diversity of benthic invertebrates (as a measure of the health of this ecological community) are obtained.

The most useful time for the SMDP is after the SLERA has been completed. At this time, risk assessors, decision-makers and other stakeholders can discuss possible paths forward. The measurement endpoints need to reflect testable hypotheses; the choice of these hypotheses is based on the assessment endpoints, and needs agreement between all involved in these endpoints.

An excellent example of refined problem formulation is available in the literature. EPA worked with Dr. Don MacDonald (mentioned above) on the ecological risk assessment for the Calcasieu Estuary near Lake Charles, Louisiana. In 1937, the Calcasieu ship channel allowed Lake Charles to become a deepwater port and enabled rapid industrial development. Because of this development, a portion of the estuary sediment became contaminated by industrial waste water discharges, municipal wastewater discharge, spills associated with shipping activities, and likely other processes. The

SLERA was completed in 1999, and identified metals, PAHs, polychlorinated biphenyls (PCBs), pesticides, polychlorinated dibenzo-p-dioxins/polychlorinated dibenzofurans (PCDDs/PCDFs) chlorophenols, chlorinated benzenes, chlorinated ethanes, phthalates, cyanide, and acetone as COPECs. The refined problem formulation identified sediments, surface water, and the surface microlayer at the air–water interface as relevant exposure media. A number of COPECs were bioaccumulative, and others were directly toxic. The contaminants and relevant ecological receptors are shown in Table 7.1.

**Table 7.1 Receptors and Contaminants Considered in the Calcasieu Estuary**

Type of Toxicity	Receptors	Aquatic		Terrestrial	
		Contact	Ingestion	Contact	Ingestion
Bioaccumulative	Mercury				
	PAHs				
	PCBs				
	Dioxins/Furans				
	Hexachlorobenzene	●	●		●
	Hexachlorobutadiene				
	Aldrin				
	Dieldrin				
	Copper				
	Chromium				
Directly Toxic in Sediment	Lead				
	Mercury				
	Nickel				
	Zinc				
	PAHs	●	●		●
	PCBs				
	HCB				
	HCBD				
	Carbon disulfide				
	Acetone				
Directly Toxic in Surface Water	Ammonia				
	Hydrogen sulfide				
	Copper				
	Mercury				
	1,2-dichloroethane	●			●
	Trichloroethane				

*Note:* The bullets indicate chemicals, habitats and exposure routes selected for further assessment.

### 7.2.4 Step 4: Study Design and Data Quality Objective Process

The products of Step 4 are the work plan (WP) and sampling and analysis plan (SAP) for data collection activities related to the measurement endpoints. The WP should describe the following:

- site conceptual model;
- exposure pathways;
- assessment endpoints;
- testable hypotheses;
- measurement endpoints;
- uncertainties and assumptions.

The SAP provides details of the actual data collection and analysis procedures, including sampling techniques, data reduction, statistical analyses, quality assurance, and quality control. EPA has developed guidance on data quality objectives to ensure data collection results in interpretable results.<sup>33-38</sup>

Once the WP and SAP are developed, an SMDP should occur to ensure that all involved parties agree on the measurement endpoints and methods of data collection and interpretation. Rewriting the WP and SAP is often much more efficient than mobilizing a field sampling team on two occasions.

### 7.2.5 Step 5: Field Verification of Sampling Design

Before mobilizing a field sampling team, verification of the SAP should be performed. Can the proposed samples actually be collected? Is the proposed sampling appropriate for the site, and can the sampling approach be implemented?

Often, in Step 4, as part of developing the WP and SAP, the ability and efficiency of the proposed data collection should be field-tested. The data quality objectives process provides a means of specifying the number of samples needed to obtain sufficient statistical power to support a chosen level of confidence.<sup>37,38</sup> Can a sufficient number of samples be obtained? For example, if the SAP indicates collection of soil invertebrates, usually earthworms, it is necessary to ensure that earthworms are indeed present at the site and can be obtained in sufficient quantity for the proposed laboratory testing. Another example might be sediment sampling in a lake or river. Is the water shallow enough that a team member in waders can collect the samples, or is a boat needed, along with a dredge or grab sampler? Is the water deep enough to require a winch to retrieve the sampler?<sup>39</sup>

Reference areas are used to determine possible ecological impacts from site-related contaminants. Reference areas represent “background” conditions, and should be selected to be as similar to the site as possible in all aspects except contamination. For example, should an ecological risk assessment be conducted at the former gold mine site discussed in Chapter 5, a reference creek might be found within the same drainage but topographically separated, and thus likely unaffected by former mining activities at the site. The reference areas for soil and sediment

comparisons should be evaluated for similarity in terms of slope, habitat, species potentially present, and other soil and sediment characteristics. The reference areas for surface water should be evaluated for similarity in terms of flow rates, substrate type, water depth, temperature, turbidity, oxygen levels, water hardness, pH, and possibly other water quality parameters.<sup>8</sup>

If fulfillment of the WP and SAP is not feasible, these will need to be rewritten. Hence, Step 5 may be an iterative process, and will require an SMDP to review any changes to the WP and SAP. As noted in the Process Document:

In the worst cases, changes in the measurement endpoints could be necessary, with corresponding changes to the risk hypotheses and sampling design. Any new measurement endpoints must be evaluated according to their utility for inferring changes in the assessment endpoints and their compatibility with the site conceptual model (from Steps 3 and 4). Loss of the relationship between measurement endpoints and the assessment endpoints, the risk questions or testable hypothesis, and the site conceptual model will result in a failure to meet study objectives.<sup>8</sup>

## **7.2.6 Step 6: Site Investigation and Analysis Phase**

This step should be straightforward, and follows the WP and SAP developed in Steps 4 and 5. Despite careful planning, unexpected conditions may arise in the field. For example, a spring flood may change the course of a river once the water subsides. How will the new river course affect the chosen sampling locations?

Sampling along a range of contaminant concentrations will likely provide much useful information. Changing site conditions may require decisions in the field to ensure the measurement endpoints reflect the assessment endpoints and the data obtained are sufficient to address the hypotheses put forward in problem formulation.

In the field, initial sampling may reveal unexpected aspects of the nature and extent of contamination or about biological effects along contamination gradients. At times, the WP and SAP may need field modification, but it is important to ensure that the study objectives, both in terms of data quality and measurement endpoints, is met.

Exposure of organisms, communities, or populations can be defined as the co-occurrence in time and place of these ecological components and one or more stressors.<sup>4</sup> Spatial patterns or distributions of the stressor(s) and ecological components may appear to predict effects on ecological components. Sampling for biological effects along a gradient of contamination is especially important for demonstrating relationships between the spatial patterns of exposure and effects.

The biological gradient of effects can often be used to develop a site-specific toxicity reference value (TRV). This site-specific value will incorporate not only the intrinsic toxicity of the chemical or stressor, but also aspects such as bioavailability. The site-specific TRV may be predictive of the spatial pattern of effects, and this would constitute a strong piece of evidence that the stressor was indeed producing effects at the site. Other evidence will likely emerge from the site investigation. This evidence should be evaluated for causal associations, potential confounding, and overall probative value.<sup>4</sup>

Site project managers or others in a risk management role may find such an exposure response analysis especially useful for the evaluation of various cleanup strategies. Because the plan for site investigation has already been determined in Steps 4 and 5, the hope is that the information developed in Step 6 can be integrated into a credible risk characterization in Step 7.

### **7.2.7 Step 7: Risk Characterization**

In Step 7, information developed in Step 6 on exposure and effects is integrated into a statement of risk regarding the assessment endpoints determined during problem formulation. Different studies or datasets can provide multiple lines of evidence to support the conclusions in Step 6. All these lines of evidence should be factored into the risk characterization.

The risk characterization ideally provides the risk manager with contaminant concentration levels in various abiotic media that provide a upper and lower bounds on the estimated threshold for adverse ecological effects. The upper bound would be developed using central tendency measures of exposure along with a TRV that represents a LOAEL value. The lower bound would be developed using more protective/conservative measures of exposure and a TRV that represents a NOAEL value. For higher-trophic level organisms considered in assessment endpoints, actual sampling of tissue concentrations may not be possible for practical or ethical reasons; hence, the study design will have specified how trophic transfer/food chain modeling could be used to back-calculate the abiotic concentration representing the bounds on the effect threshold.

Risk characterization should also consider the uncertainties attendant in the risk characterization using both fate-and-transport and food chain models.

## **7.3 SCREENING ECOLOGICAL RISK ASSESSMENT FOR A FORMER MANUFACTURED GAS PLANT IN A RAILROAD YARD**

Manufactured gas was used throughout most of the 19th century and the first half of the 20th century until the advent of natural gas production. The manufacturing process typically consisted of the gasification of combustible materials, almost always coal, but also wood and oil.

In the coal gasification process, coal gas was produced through the distillation of bituminous coal under anaerobic conditions. The gases produced were drawn off, and some of the vapors were converted to liquids. The remaining vapor was coal gas.

In the carburetted water gas process, coal gas was produced and passed into a carburetor, where oil was introduced into the vapor. This oil-gas mixture was superheated to thermally “crack” the oil. Carburetted water gas was thus a mixture of the gaseous products of coal and petroleum. Impurities were removed, and the gas was passed through a scrubber that brought the vapor into direct contact with water. This process increased the thermal content of the fuel, and the form of coal gas produced was known as water gas. One of the scrubbing methods consisted of application of

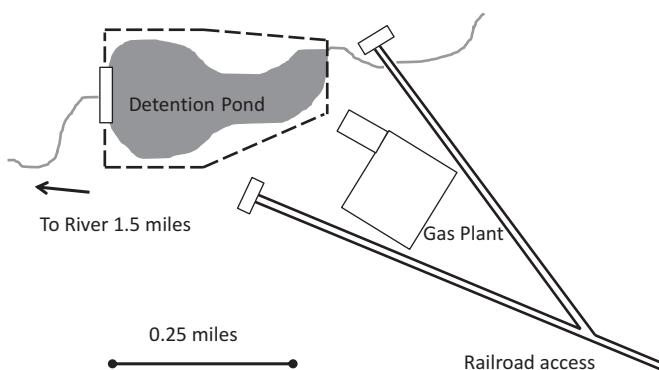
direct electrical current to precipitate the particles of coal tar. This electrical process required transformers and other components containing PCBs used as heat exchange and dielectric fluids. Often, railroads served manufactured gas plants to enable shipping of the gas to consumers.

In this example, outflow from a detention pond near a manufactured gas plant enters an unnamed stream that supports aquatic life (Figure 7.2). The stream flows about 1.5 river miles before its confluence with a river known internationally for its high-quality trout fishing. The contaminants at the former manufactured gas plant include metals from the spent coal, PAHs from the manufactured gas process, pesticides, polychlorinated biphenyls from transformers, and polychlorinated dioxins and furans occurring both as byproducts of gas production and as contaminants of PCB mixtures.

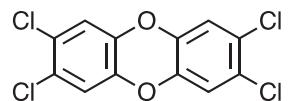
The detention pond is large enough to support a fish population, but conversations with the plant manager indicated the pond had never been stocked with fish and that he had not seen fish in it. The chain-link fence surrounding the pond was old, and around the dam there were gaps in the fence that could allow access by small terrestrial animals. Birds could, of course, access the pond from the air. The plant manager indicated the pond was dredged once a year to ensure it would have sufficient capacity to catch and hold run-off from the plant site. The dredge spoils were taken to a hazardous waste landfill about 400 miles away.

### 7.3.1 Ecological Risk Assessment of Polychlorinated Dibenzo Dioxins and Furans (PCDD/Fs)

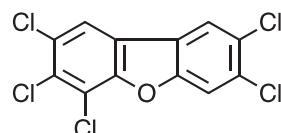
Most dioxins, furans, and dioxin-like compounds lack individual screening benchmarks. However, the congener-specific dioxin and furan data can be consolidated into a single measure called the toxic equivalence (TEQ) of the sample. The TEQ is calculated by multiplying the concentrations of each congener or congener containing chlorine at the 2,3,7, and 8 positions in a sample by a toxicity equivalence factor (TEF) and summing those products. The TEF normalizes the toxicity of those congeners to the toxicity of the 2,3,7,8-TCDD congener, generally considered to be



**Figure 7.2** Simplified map of the manufactured gas plant. The dashed line around the pond shows the approximate location of a chain link fence.



2,3,7,8-tetrachlorodibenzodioxin



2,3,4,7,8-pentachlorodibenzofuran

**Figure 7.3** Structures of two PCDD/F congeners.

the most toxic of the dioxin, furan, and dioxin-like compounds. A great deal of effort by internationally known scientists have gone into developing the TEF scheme for dioxin-like chemicals.<sup>40,41</sup> In effect, the TEQ indicates the concentration of 2,3,7,8-TCDD that would have the same toxicity as the mixture of dioxins and furans being evaluated. The TEFs used here reference the World Health Organization values for mammals, birds, and fish.<sup>42</sup> Figure 7.3 shows the structure of some PCDD/Fs.

### 7.3.2 Ecological Risk Assessment of Polycyclic Aromatic Hydrocarbons and Polychlorinated Biphenyls

PAHs consist of many different chemicals, likely at least 100. PAHs occur from incomplete combustion, such as vehicle exhaust. PAHs are the molecules in cigarette smoke considered carcinogenic. Asphalt contains PAHs, and they occur in sediment in most water bodies due to run-off. PAHs are a by-product of the manufactured gas process.

The bioavailability and toxicity of PAHs vary considerably. Higher-molecular weight PAHs are less water-soluble, and consequently have low bioavailability. Although lower-molecular weight PAHs have greater water solubility and are more bioavailable, they may be more subject to loss from evaporation and other weathering processes in the environment. The ecological effects of PAH mixtures can be approximated using estimates of total PAHs. This calculation is most often done by adding up concentrations of each PAH congener in a sample. The surrogate value for non-detect values is calculated as half the reporting limit for the sample.

PCB mixtures contain up to 209 different chemicals, called congeners. There are 209 possible combinations for one to ten chlorine atoms bound to biphenyl.<sup>43</sup> PCBs produce toxicity by a number of mechanisms. Twelve PCB congeners have dioxin-like properties. Often, these PCB congeners are sampled individually and added to the TEQ calculation discussed in the previous section.<sup>42</sup>

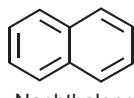
Manufacture of PCBs ceased in the late 1970s. The commercial mixtures of PCBs were used dielectric fluid in transformers and capacitors and were sold as mixtures known as Aroclors. Each Aroclor mixture differed in the weight percentage of chlorine present. In the environment, weathering by various biotic and abiotic processes alters the PCB congener composition from the original commercial products. Hence, sampling for Aroclors cannot provide accurate information about the PCB congener mixtures present in environmental media and biota.<sup>44</sup> Nevertheless, Aroclor analyses are often still used for environmental samples because of cost.

Similar to PAHs, the ecological effects of PAH mixtures can be approximated using estimates of total PCBs. This calculation is most often done by adding up concentrations of each congener in a sample. The surrogate value for non-detect values is calculated as half the reporting limit for the sample.

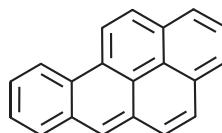
Figure 7.4 shows the structure of two polycyclic aromatic hydrocarbons and one of the PCB congeners.

### 7.3.3 Bioaccumulation of Contaminants

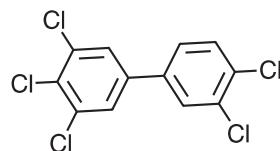
The composition of PCB mixtures alters during movement into the food chain.<sup>45</sup> Organisms acquire PCBs through contact with sediment or soil and through diet. Once the PCBs enter an organism, individual congeners are metabolized and excreted, or else stored in fat.



Naphthalene



Benzo-[a]-pyrene



3,3',4,4',5-pentachlorobiphenyl (PCB 126)

**Figure 7.4** Structure of two polycyclic aromatic hydrocarbons and one polychlorinated biphenyl.

Several factors tend to influence the bioaccumulation tendency of different congeners, including the number of chlorine substituents and their positions on the two phenyl rings. In general, the more chlorinated congeners exhibit a higher level of persistence in vertebrates and will concentrate to higher levels in tissues of predators than in the surrounding environmental media or prey organisms.

Much work has been done to understand differences in bioaccumulation between animal receptors at various trophic levels. The most direct and ecologically relevant approach to assessing bioaccumulation is to measure concentrations of contaminants in the tissue of organisms collected or exposed in the field.<sup>5</sup> Sampling of benthic organisms, which provides a much clearer understanding of the bioavailability of contaminants and extent of contamination, is often limited by the workload constraints of obtaining sufficient tissue biomass for analytical measurements.<sup>8</sup> Caging organisms, such as freshwater mussels, in the field is one approach to address this issue. Though providing a balance between experimental control and ecological relevance not offered with field collections or laboratory studies, *in situ* studies are still time-consuming, labor-intensive, and occasionally prone to vandalism, predation, or destruction.<sup>7,8</sup>

### 7.3.4 Site Visit

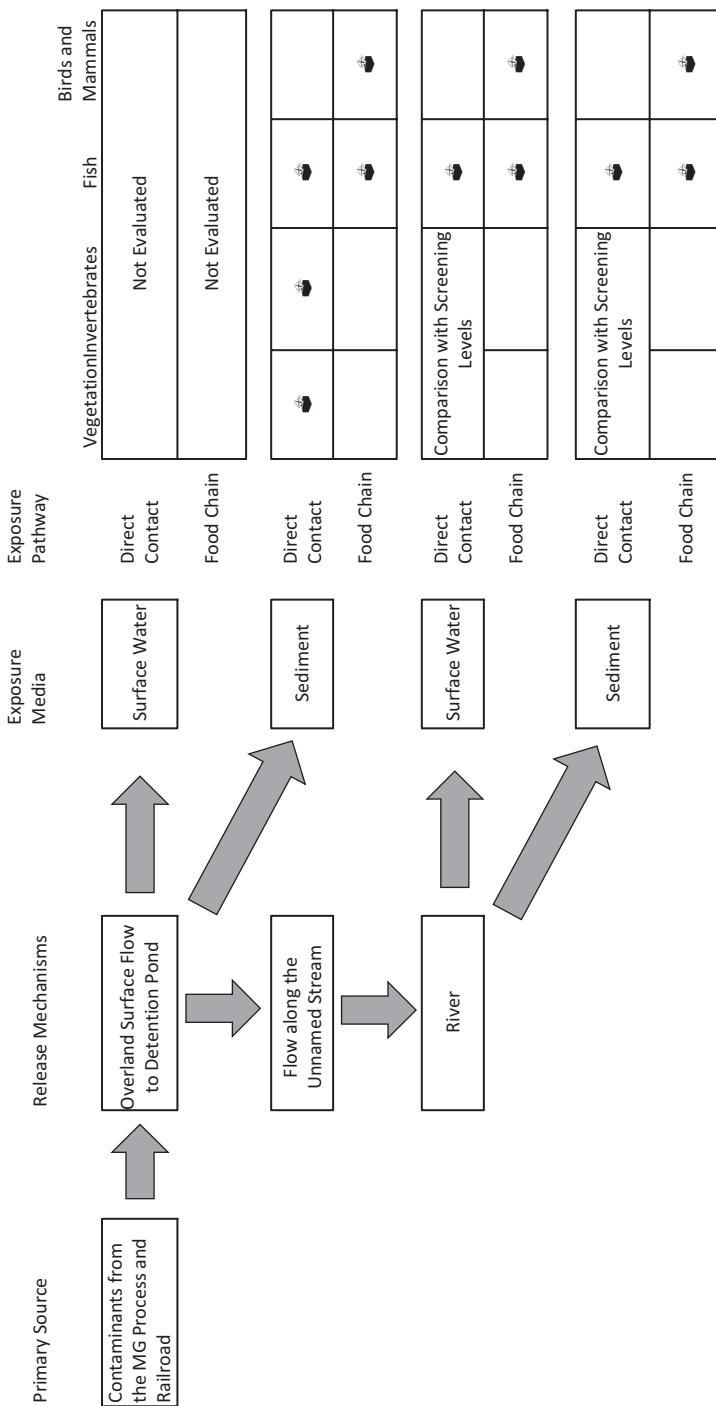
Within a mile of the pond, the unnamed stream exiting from the detention pond is not large enough to support fish—even after rain, the water is only 2 inches deep. Downstream, the unnamed stream joins a larger stream that flows into the river. The risk assessor had conducted a site visit and had walked the unnamed stream all the way from the pond outlet to the river. The hillside downstream of the detention pond was steep, but after 200 yards, the gradient became much flatter. In this flat section, the stream made many turns before its confluence with the larger tributary. Near the confluence, the unnamed stream widened to become a slow-moving pool. The risk assessor noted considerable sediment accumulation in the pool. He also noted the presence of a number of aquatic invertebrates, including mayflies, caddis flies and crayfish.

No fish were observed in the unnamed stream or the larger tributary, but when the risk assessor reached the river, he saw several anglers wading about 100 feet offshore. He watched for a few minutes, noting that one angler was consistently hooking and releasing trout. As he turned to leave, he noticed several mink tracks in the muddy bank. Looking up, he saw a Great Blue Heron rise from the trees 100 feet downstream and take to the air.

### 7.3.5 Scientific Management Decision Point #1

The risk assessor prepared a preliminary site visit report for the project manager. This report included the conceptual site model shown in Figure 7.5.

In follow-up discussions, the project manager noted that the pool in the unnamed stream would likely act as a sediment trap.



**Figure 7.5** Conceptual site model for the manufactured gas plant, detention pond, and river.

“That’s exactly right,” the risk assessor agreed. “That’s what I’m expecting samples to show.”

“I had samples taken from the pond and from the river near where the tributary comes in, none in the stream.”

“I doubt there’ll be much in the river,” said the risk assessor, “but we’ll see.”

“Samples should be here day after tomorrow. Do the screening for the river first.”

When the risk assessor received the sample results, he prepared a set of tables using a spreadsheet so he would have easy access to the data. Tables 7.2–7.13 show the results of his work. He reformatted these tables so that they could be easily imported into EPA’s ProUCL software to be able to calculate the needed statistics. Next, he prepared screening tables for COPECs, both in the detention pond and the river (Tables 7.14–7.26). When he showed the tables to the project manager, she noted that with the exception of PAHs and dioxins, the concentrations in river sediment were essentially no different than the concentrations in the detention pond.

“Aren’t the chemicals all background? No one uses those chlorinated pesticides any more. Haven’t they all been banned?” she asked.

“Maybe not,” he answered. “The metals in the river sediment are all COPECs in the pond, but have lower concentrations. I looked at the sampling locations in the river, and the samples were all taken in deposition area. It’s especially hard to say where the metals came from. PCB concentrations in the river and the pond are about the same—of course, spring run-off could have carried the PCBs downstream. The dioxin concentrations are about ten-fold lower in the river, so they could have been flushed as well. And you’re right about the legacy pesticides.”

He showed her the preliminary hazard characterization from Steps 1 and 2 conducted with measured concentrations in river sediment (Table 7.27).

“Nothing there but dioxins,” she said.

“Depends on the screening value you use. I figure there’s more concern for the river, so I used some of the values in the new Region 4 guidance. For the detention pond, I used a set of 1993 numbers from the EPA lab in Duluth, Minnesota. That’s the difference.”<sup>11,46</sup>

“So we really don’t know,” said the project manager.

“There’s another thing to think about,” said the risk assessor. “Part of the reason the river is such a good fishery is that it’s a tailwater. The water comes out the dam 20 miles upstream. It’s a constant 58 degrees Fahrenheit all year—ideal trout temperature. Much of what’s in the river sediment could have come from the lake sediment above the dam.”

“Do you agree that it makes no sense to try to clean up the pond?” asked the project manager.

“I agree,” said the risk assessor. “Maybe all we need to show is that it’s not likely to impact the river. I got a compilation of dioxin screening levels in my email yesterday.<sup>47</sup> I’ll send it to you and do a food chain model for a bird and a mammal, including all the metals, PAHs, PCBs, and dioxins. That should allay any doubt that the river is impacted. It’s easy enough to do a River Otter and a Great Blue Heron. I don’t know how to do the fish. Can we collect fish and get ‘em analyzed?”, he asked.

“Sure. But no more than ten. You know how expensive the analytical gets.”

**Table 7.2 Surface Water Sampling Results for Metals from the Detention Pond at the Manufactured Gas Plant**

	Al	Sb	As	Ba	Be	Cd	Cr	Co	Cu	Fe	Pb	Mn	Hg	Ni	Se	Ag	Tl	Va	Zn
SW-1	22	<5	<5	34	<10	<0.05	0.27	<0.01	<0.5	248	<0.05	42	<0.01	<1	<0.2	<0.05	<1	<10	<10
SW-2	<0.02	<5	<5	36	<10	0.14	0.28	<0.01	1.6	580	<0.05	74	<0.01	5.3	<0.2	0.40	<1	<10	<10
SW-3	30	<5	<5	36	<10	0.22	<0.05	<0.01	2.2	220	<0.05	69	<0.01	16.6	<0.2	0.43	<1	<10	<10
SW-4	42	<5	<5	37	<10	<0.05	2.90	<0.01	2.1	526	0.95	104	<0.01	33.8	<0.2	0.57	<1	<10	<10
SW-5	87	<5	<5	39	<10	0.29	0.49	<0.01	1.6	273	<0.05	83	<0.01	1.5	<0.2	<0.05	<1	<10	<10
SW-6	70	<5	<5	40	<10	0.36	0.61	<0.01	3.6	488	<0.05	83	<0.01	33.8	<0.2	<0.05	<1	<10	<10
SW-7	<0.02	<5	<5	41	<10	0.44	<0.05	<0.01	3.9	294	<0.05	42	<0.01	200	<0.2	<0.05	<1	<10	<10
SW-8	107	<5	<5	43	<10	0.53	0.74	<0.01	3.0	458	<0.05	42	<0.01	1.5	1.1	<0.05	<1	<10	<10
SW-9	55	<5	<5	44	<10	0.63	1.09	<0.01	2.5	313	27	42	<0.01	2.7	<0.2	0.43	<1	<10	4.5
SW-10	133	<5	<5	45	<10	2.90	0.90	<0.01	4.3	432	<0.05	63	<0.01	1.0	<0.2	0.57	<1	<10	<10
SW-11	165	<5	<5	47	<10	<0.05	1.33	<0.01	2.7	332	<0.05	100	<0.01	2.7	<0.2	<0.05	<1	<10	<10
SW-12	210	<5	<5	48	<10	1.83	<0.05	<0.01	2.8	350	<0.05	97	<0.01	1.7	<0.2	<0.05	<1	<10	<10
SW-13	276	<5	<5	67	<10	0.90	<0.01	<0.01	2.2	370	<0.05	91	<0.01	5.3	5.2	<0.05	<1	<10	2800
SW-14	402	<5	<5	52	<10	1.09	2.12	<0.01	3.4	409	<0.05	91	<0.01	6.5	<0.2	<0.05	<1	<10	<10
SW-15	<0.02	<5	<5	55	<10	0.75	1.65	<0.01	3.9	432	<0.05	55	<0.01	8.1	<0.2	0.43	<1	<10	<10
SW-16	840	<5	<5	67	<10	1.37	0.38	<0.01	5.0	700	<0.05	97	<0.01	1.7	<0.2	0.57	<1	<10	<10

Notes: A number preceded by “<” indicates the chemical was not detected and the number is the analytical reporting limit from the laboratory. Units are  $\mu\text{g/L}$ .

Table 7.3 Surface Water Sampling Results for Polycyclic Aromatic Hydrocarbons from the Detention Pond at the Manufactured Gas Plant

Analyte	SW-1	SW-2	SW-3	SW-4	SW-5	SW-6	SW-7	SW-8	SW-9	SW-10	SW-11	SW-12	SW-13	SW-14	SW-15	SW-16	SW-17	SW-18	SW-19	SW-20	SW-21
2-Chloronaphthalene	<5	<5	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	
1-Methylnaphthalene	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	
2-Methylnaphthalene	<0.5	210	<0.5	11	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.2	<0.2	
Acenaphthene	<0.2	<0.2	0.37	0.4	0.9	2.6	<0.2	0.25	1.8	160	100	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	
Acenaphthylene	10	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	
Anthracene	16	<0.8	<0.8	<0.8	<0.8	<0.8	<0.8	<0.8	<0.8	<0.8	<0.8	<0.8	<0.8	<0.8	<0.8	<0.8	<0.8	<0.8	<0.8	<0.8	
Benzol[a]anthracene	<0.05	0.09	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	
Benzol[a]pyrene	<0.1	0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	
Benzol[b]fluoranthene	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	
Benzol[g,h]perylene	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	
Benzol[k]fluoranthene	<0.1	<0.1	1.3	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	
Chrysene	<0.1	<0.1	0.2	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	
Dibenz[a,h]anthracene	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	
Fluoranthene	1.5	<0.07	<0.07	1.8	<0.07	<0.07	3	<0.07	<0.07	<0.07	<0.07	6	<0.07	<0.07	9	<0.07	<0.07	<0.07	<0.07	<0.07	
Fluorene	<0.5	4.4	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	
Indeno[1,2,3-c,d]Pyrene	<1	<1	<1	<1	<1	<1	<1	<1	<1	5	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	
Naphthalene	<0.2	<0.2	27	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	520	<0.2	<0.2	
Phenanthrene	<0.2	<0.2	5.5	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	
Pyrene	1.7	<0.08	<0.08	3.1	<0.08	<0.08	10	<0.08	<0.08	<0.08	<0.08	2.2	<0.08	<0.08	<0.08	<0.08	<0.08	<0.08	<0.08	<0.08	

Notes: A number preceded by “<” indicates the chemical was not detected and the number is the analytical reporting limit from the laboratory. Units are  $\mu\text{g/L}$ .

Table 7.4 Surface Water Sampling Results for Pesticides from the Detention Pond at the Manufactured Gas Plant

Analyte	SD-1	SD-2	SD-3	SD-4	SD-5	SD-6	SD-7	SD-8	SD-9	SD-10	SD-11	SD-12	SD-13	SD-14	SD-15
beta-BHC	<0.003	<0.003	<0.003	<0.003	<0.003	<0.003	<0.003	<0.003	<0.003	<0.003	<0.003	<0.003	<0.003	<0.003	<0.003
delta-BHC	<0.006	<0.006	<0.006	<0.006	<0.006	<0.006	<0.006	<0.006	<0.006	<0.006	<0.006	<0.006	<0.006	<0.006	<0.006
gamma-BHC (Lindane)	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005
Chlordane	<0.014	<0.014	<0.014	<0.014	<0.014	<0.014	<0.014	<0.014	<0.014	<0.014	<0.014	<0.014	<0.014	<0.014	<0.014
4,4'-DDD	<0.011	<0.011	<0.011	<0.011	<0.011	<0.011	<0.011	<0.011	<0.011	<0.011	<0.011	<0.011	<0.011	<0.011	<0.011
4,4'-DDE	<0.004	<0.004	<0.004	<0.004	<0.004	<0.004	<0.004	<0.004	<0.004	<0.004	<0.004	<0.004	<0.004	<0.004	<0.004
4,4'-DDT	<0.012	<0.012	<0.012	<0.012	<0.012	<0.012	<0.012	<0.012	<0.012	<0.012	<0.012	<0.012	<0.012	<0.012	<0.012
Dieldrin	<0.002	<0.002	<0.002	<0.002	<0.002	<0.002	<0.002	<0.002	<0.002	<0.002	<0.002	<0.002	<0.002	<0.002	<0.002
Endosulfan I	<0.007	<0.007	<0.007	<0.007	<0.007	<0.007	<0.007	<0.007	<0.007	<0.007	<0.007	<0.007	<0.007	<0.007	<0.007
Endosulfan II	<0.011	<0.011	<0.011	<0.011	<0.011	<0.011	<0.011	<0.011	<0.011	<0.011	<0.011	<0.011	<0.011	<0.011	<0.011
Endosulfan Sulfate	<0.066	<0.066	<0.066	<0.066	<0.066	<0.066	<0.066	<0.066	<0.066	<0.066	<0.066	<0.066	<0.066	<0.066	<0.066
Endrin	<0.015	<0.015	<0.015	<0.015	<0.015	<0.015	<0.015	<0.015	<0.015	<0.015	<0.015	<0.015	<0.015	<0.015	<0.015
Endrin aldehyde	<0.023	<0.023	<0.023	<0.023	<0.023	<0.023	<0.023	<0.023	<0.023	<0.023	<0.023	<0.023	<0.023	<0.023	<0.023
Heptachlor	<0.055	<0.055	<0.055	<0.055	<0.055	<0.055	<0.055	<0.055	<0.055	<0.055	<0.055	<0.055	<0.055	<0.055	<0.055
Heptachlor epoxide	<0.083	<0.083	<0.083	<0.083	<0.083	<0.083	<0.083	<0.083	<0.083	<0.083	<0.083	<0.083	<0.083	<0.083	<0.083
Methoxychlor	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
Toxaphene	<0.240	<0.240	<0.240	<0.240	<0.240	<0.240	<0.240	<0.240	<0.240	<0.240	<0.240	<0.240	<0.240	<0.240	<0.240

Notes: A number preceded by "<" indicates the chemical was not detected and the number is the analytical reporting limit from the laboratory. Units are  $\mu\text{g/L}$ .

Table 7.5 Surface Water Sampling Results for PCBs and PCDD/Fs from the Detention Pond at the Manufactured Gas Plant

Analyte	SW-1	SD-2	SD-3	SD-4	SD-5	SD-6	SD-7	SD-8	SD-9	SD-10	SD-11	SD-12	SD-13	SD-14
<b>Polychlorinated Biphenyls</b>														
Aroclor-1016	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
Aroclor-1221	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
Aroclor-1232	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
Aroclor-1242	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
Aroclor-1248	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
Aroclor-1254	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
Aroclor-1260	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
Aroclor-1268	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
<b>Chlorinated Dioxins and Furans</b>														
2378-TCDD	4000	4.9	<2.4	<4.2	12,740	28.5	<3.7	760	<4.6	137	<7.3	<4	38	2.9
12378-PeCDD	14	<1.4	<1.9	<3.4	35.4	<4.1	<3.4	<5.6	<3.1	<5.9	<4.1	<0.5	<1.4	<2
123478-HxCDD	28.3	<1	<1.4	<2.9	<3.5	<2.8	10	<3.7	<8.9	<6.2	1.6	<0.8	<1.2	<4.4
123678-HxCDD	95.3	<0.9	<1.3	<2.7	6.4	<2.6	21.6	<3.5	<8.4	<5.8	<3.3	<0.7	<1.1	<4.5
123789-HxCDD	93.5	<4.1	<6.3	<5.9	<7.7	2.8	6.1	1.8	<6.3	<4.1	<6.3	<4.3	<5.9	<7.7
1234678-HpCDD	7.9	<5.2	31.7	<10.9	3	<3.4	<6.4	5.9	<6.0	12.4	<7.2	<6.8	24.3	<8.3
OCDD	14,890	59.8	30.5	74.7	27,700	726	<44.5	2990	40.3	240	<19.3	623	<17.1	18.6
TCDF	30.9	<1.3	<2	<3.8	53.1	<3.1	<4.3	<2.5	<0.3	<0.7	<1.2	<4	<2.7	
12378-PeCDF	36.4	<1.3	<1.7	<3.1	14.1	<2.5	<2.8	<4.8	<2.9	<4.1	<2.8	<0.3	<0.9	<1.3
23478-PeCDF	18.3	<1.3	<1.7	<3.1	28.2	<2.5	<2.8	<4.8	<3	<4.3	<2.9	<0.3	<0.9	<1.3

(continued)

Table 7.5 (Continued)

Analyte	SW-1	SD-2	SD-3	SD-4	SD-5	SD-6	SD-7	SD-8	SD-9	SD-10	SD-11	SD-12	SD-13	SD-14
123478-HxCDF	42.7	<0.7	<1.0	<1.8	2.8	<1.8	16.5	<2.8	<6.4	<4.2	<4.3	<3.1	<3.6	<2.6
123678-HxCDF	34.2	<0.6	<0.8	<1.7	2.8	<1.7	15.5	<2.6	<6	<3.9	1.9	<0.5	<0.8	<3.1
123789-HxCDF	<0.8	<1	<2	6.3	<2.6	2.2	<4.3	<3.2	<7.1	<4.6	<0.2	<0.6	<1	<4
234679-HxCDF	43.6	<0.7	<0.9	<1.8	<2.3	<1.8	16.1	<2.8	<6.3	<4.1	5.9	<0.5	<0.8	<3.3
1234678-HpCDF	580	3.7	2.4	<2.5	29.5	4.3	<3.9	21.6	<6.6	24	<0.7	<1.2	<5.0	<5.3
1234789-HpCDF	50	<1.3	<1.6	<3.3	59.6	<4.3	<3.3	15.5	<11.2	<8.5	6.1	<1	<1.8	<7.6
OCDF	1180	5.1	6.5	14.5	1950	56	20.9	300	<6.4	24.7	<16.4	<31.6	<2.0	2.4

Notes: A number preceded by “<” indicates the chemical was not detected and the number is the analytical reporting limit from the laboratory. Units are ng/L.

Table 7.6 Sediment Sampling Results for Metals from the Detention Pond at the Manufactured Gas Plant

	Al	Sb	As	Ba	Be	Cd	Cr	Co	Cu	Fe	Pb	Mn	Hg	Ni	Se	Ag	Tl	Va	Zn
SD-1	3450	<0.62	1.1	154	0.25	<0.07	12.1	<3.5	1.39	1400	1230	78.5	0.05	,0.64	<0.93	<2.9	<0.43	20.9	2060
SD-2	5530	<0.62	<0.92	155	0.26	<0.07	8.5	<3.0	0.78	910	278	241	0.54	<0.4	<1	<1.2	<0.63	7.4	1550
SD-3	10,000	<0.98	<0.65	38.6	0.79	<0.07	51.7	2.7	0.51	770	0.46	260	0.66	3.7	<1.3	<0.52	<0.5	5.8	578
SD-4	14,500	<0.7	9.7	97.8	0.65	<0.07	329	2.3	0.91	3000	0.83	155	0.23	2.5	<1.4	0.5	10.4	12.4	235
SD-5	5850	3.3	11.6	90.8	4.6	<0.07	112	5.8	0.51	290	10.2	184	<0.01	0.36	<1.1	9.8	8.9	72.4	1050
SD-6	13,300	2.7	10.9	94	4	<0.07	204	3.6	0.091	69	8.9	214	0.13	1.9	<1.6	9.9	<0.9	45.6	491
SD-7	13,500	37.1	1.8	77.4	1.7	<0.1	215	13.4	2.4	250	52.5	44.1	1.2	1.3	<1.3	<3.1	<0.81	11.1	42.3
SD-8	15,100	<2.6	<10.4	163	1.7	<0.1	176	19.6	1.5	2100	373	219	0.2	0.15	<1.1	<2.7	0.95	8.4	302
SD-9	15,400	3.6	<8.9	133	0.44	<0.1	157	<3.1	1.8	800	54.9	67.6	<0.01	0.73	<1.3	0.55	0.84	6.8	276
SD-10	2810	<0.72	2	45.1	1	<0.07	4.7	<2.4	2.4	970	511	98.8	<0.01	0.69	<1.3	0.56	1.19	47.3	49.2
SD-11	2150	<10	2	64.1	0.98	<0.07	4.1	<3.8	0.51	350	11.9	161	<0.01	12.8	<1	<2.2	<1.05	129	86.5
SD-12	6440	<9	7.8	156	0.79	<0.07	93.9	7.2	1.8	380	58.7	99	<0.01	92.2	<1.2	<1.8	<0.79	10.6	<36
SD-13	15,100	1.9	6.1	92.5	0.51	<0.039	176	2.3	3.7	530	595	1490	<0.01	0.15	2.1	9.4	0.76	9.5	<43.1
SD-14	14,000	1.8	2.6	163	1.5	0.039	248	<1.4	9.2	60	854	516	<0.01	1.3	1.6	8.2	1.6	10.2	<29.2
SD-15	3450	0.95	13.7	202	1.4	0.037	147	<1.1	2.1	67	1000	174	<0.01	<5.9	0.94	8.6	1.5	9.8	65
SD-16	5530	0.93	6	22.6	0.33	0.029	178	3.8	2.4	710	7.7	346	<0.01	1.4	1.1	<1.8	<0.43	7.9	105
SD-17	10,000	1.3	4.5	19.4	0.47	0.021	15.8	1.7	1.5	330	174	81.8	<0.01	1.5	<0.98	8.4	<0.73	9.7	82
SD-18	14,500	2.5	8.3	29.5	1.2	<0.06	6.4	1.9	1.8	1900	350	257	<0.01	<0.039	<0.65	2.7	1.02	19.1	159
SD-19	5850	<1.1	9.6	30	0.67	<0.06	331	1.5	2.4	1000	719	111	<0.01	<0.039	1.8	10.6	1.04	8.7	191
SD-20	13,300	<0.92	<0.54	22.1	2.9	<0.06	10.3	2.4	2.3	2500	199	149	<0.01	<0.039	<1.2	6.9	0.6	6.3	300
SD-21	13,500	3.3	<0.64	22.3	3.5	<0.1	120	1.4	0.51	4900	411	333	<0.01	<0.039	<0.77	<4.0	0.47	89.3	1930

Notes: A number preceded by “<” indicates the chemical was not detected and the number is the analytical reporting limit from the laboratory. Units are mg/kg dry weight.

**Table 7.7** Sediment Sampling Results for Polycyclic Aromatic Hydrocarbons from the Detention Pond at the Manufactured Gas Plant

Analyte	SD-1	SD-2	SD-3	SD-4	SD-5	SD-6	SD-7	SD-8	SD-9	SD-10	SD-11	SD-12	SD-13	SD-14	SD-15	SD-16	SD-17	SD-18	SD-19	SD-20	SD-21
2-Chloronaphthalene	570	2400	4600	4200	4800	490	480	2100	9600	990	1900	2000	2500	3600	400	400	4200	490	490	4600	4900
1-Methylnaphthalene	2300	710	930	180	130	500	120	92	520	950	1500	580	78	830	4100	9700	960	1300	9800	420	430
2-Methylnaphthalene	1900	3800	2400	4700	440	2400	4700	4900	4800	400	3800	5800	4100	9700	960	420	4800	4500	1200	100	830
Acenaphthene	1900	530	2400	4700	440	2400	4700	4900	4800	480	400	3800	4800	4100	9700	4800	960	420	4800	410	4600
Acenaphthylene	460	430	660	530	410	580	390	940	420	970	570	2400	4600	4200	4800	490	480	2100	9600	62	1900
Anthracene	410	770	490	260	980	1100	79	550	3900	920	2200	1800	360	380	2500	9800	2500	940	380	750	9900
Benzofluanthracene	2600	1300	3700	3100	380	2600	3900	230	1000	1800	360	62	380	1200	530	250	350	1700	570	2500	280
Benzofluoranthene	400	3400	2400	640	440	380	900	1200	4800	83	400	2600	1200	430	1100	1300	960	420	810	410	1000
Benzofluoranthene	430	3600	2400	750	440	520	950	1500	580	78	400	3200	1500	550	1100	3200	960	55	690	410	1000
Benzofluoranthene	4800	5000	990	2100	1700	690	1200	4800	4700	3600	6300	1500	2300	710	930	180	130	500	120	92	100
Benzofluoranthene	440	2400	2500	1500	1500	5500	510	130	480	3300	490	460	340	420	850	59	66	1200	500	1300	3500
Chrysene	1000	1200	2200	4300	3200	2700	1700	4700	19,000	3300	5200	1400	1600	370	260	500	4100	2400	950	440	1100
Dibenzo[a,h]anthracene	1700	130	480	2100	9600	130	1900	2000	2500	3600	400	400	4200	120	340	920	4900	2500	4900	500	78
Fluoranthene	1200	9500	2400	1400	440	900	1600	2500	840	320	46	5800	3100	740	1900	4800	960	110	1200	410	2300
Fluorene	2200	1800	360	380	2500	9800	2500	320	2500	430	730	450	470	940	380	400	9800	420	430	6600	530
Indeno[1,2,3-c,d]pyrene	310	2200	2400	600	440	320	600	950	920	4800	400	1700	830	4100	9700	960	1300	420	660	410	830
Naphthalene	1900	3800	2400	4700	440	2400	4700	4900	4800	410	3800	9600	4800	420	960	800	2100	950	460	2100	860
Phenanthrene	890	7000	2400	580	440	350	820	810	4800	170	400	2900	4100	9700	2200	96,045	510	410	1100	2700	14,000
Pyrene	1000	8100	2400	1200	440	710	1500	2300	620	2100	4100	1600	3500	960	67	1400	410	4000	23,000	1400	630

Notes: A number preceded by “-” indicates the chemical was not detected and the number is the analytical reporting limit from the laboratory. Units are mg/kg dry weight.

Table 7.8 Sediment Sampling Results for PCBs and PCDD/Fs from the Detention Pond at the Manufactured Gas Plant

Analyte	SD-1	SD-2	SD-3	SD-4	SD-5	SD-6	SD-7	SD-8	SD-9	SD-10	SD-11	SD-12	SD-13	SD-14	SD-15	SD-16	SD-17	SD-18	SD-19	SD-20	SD-21
Polychlorinated Biphenyls (µg/kg)																					
Aroclor-1016	<0.14	<2	2.5	2.4	2.3	2.3	2.4	6.3	4.7	<5	4.5	4.7	4.6	2.1	4.1	2.2	2.1	2.42	4.2	8.6	<0.035
Aroclor-1221	<0.29	2.2	2.5	2.4	2.3	2.3	2.4	15.7	11.7	12.6	11.3	11.6	11.5	2.1	10.3	2.2	2.1	2.42	10.6	21.5	<0.07
Aroclor-1232	<0.14	2.2	2.5	2.4	2.3	2.3	2.4	6.3	4.7	5	4.5	4.7	4.6	2.1	4.1	2.2	2.1	2.42	4.2	8.6	<0.035
Aroclor-1242	2.5	2.3	2.3	2.1	2.1	2.2	2.1	2.42	2.1	4.3	<0.035	<0.038	<0.035	<0.035	<0.18	<0.038	<0.36	<0.048	2.3		
Aroclor-1248	2.5	2.4	2.3	2.3	2.4	3.1	2.3	2.5	2.3	2.3	2.3	2.1	2.1	2.2	2.1	2.42	2.1	4.3	<0.035	<0.038	<0.035
Aroclor-1254	0.044	2.2	2.5	2.4	2.3	2.3	2.4	3.1	2.3	2.5	2.3	2.3	2.3	2.1	2.1	2.2	2.1	2.42	2.1	4.3	<0.035
Aroclor-1260	0.032	2.2	2.5	2.4	2.3	2.3	2.4	3.1	2.3	2.5	2.3	2.3	2.3	2.1	2.1	2.2	<0.1	2.42	2.1	4.3	<0.035
Aroclor-1268	2.2	4.8	2.4	2.3	2.4	6.6	2.3	2.5	2.3	3.3	3.3	2.1	2.1	2.2	2.4	2.42	9.1	9.5	<0.035	<0.038	
PCBs (high risk)	5.04	9.1	12.1	11.8	11.4	12.1	11.7	20.3	16.4	11.9	17.9	13.8	13.6	8.5	12.4	9.02	8.4	11.6	10.5	21.5	2.3
PCBs (low risk)	2.37	7.2	7.4	7.1	6.9	7	11.4	11.7	9.5	9.8	10.1	9.3	9	6.3	8.4	6.8	4.62	13.9	15.8	12.9	0.108
Chlorinated Dioxins and Furans (µg/kg)																					
2378-TCDD	0.12	0.087	0.032	0.404	0.018	0.019	0.048	0.195	0.029	0.161	0.264	0.019	0.112	0.029	<0.007	0.469	0.611	7.987	3.534	10.051	7.468
12378-PeCDD	<0.007	<0.002	0.0005	0.0032	<0.002	<0.0007	<0.0008	0.002	<0.0005	<0.0009	<0.0008	<0.0007	<0.0011	<0.0006	<0.0007	0.0013	0.0019	0.0072	0.0135	0.019	0.0129
123478-HxCDD	<0.003	<0.001	<0.0003	0.006	<0.0008	<0.0005	<0.0004	0.0032	<0.0006	0.0015	0.0016	<0.0005	0.0013	<0.0003	<0.0006	0.0017	<0.0014	0.0077	0.0235	0.0356	0.0233
123678-HxCDD	0.0076	0.0032	0.0022	0.016	—	0.0025	—	0.0097	0.0099	0.0031	0.004	—	0.0062	0.0020	—	0.0073	0.0087	0.0422	0.0714	0.089	0.0706
123789-HxCDD	0.0031	0.0011	0.0022	0.016	<0.0008	0.0015	0.0009	0.0107	0.0017	0.0036	0.0043	0.0014	0.0053	0.0017	0.0005	0.0116	0.0091	0.0422	0.0670	0.0761	0.0844
1234678-HpCDD	0.215	0.0044	0.0023	0.34	<0.016	<0.045	<0.011	0.190	<0.020	<0.077	<0.089	<0.01	<0.096	<0.025	<0.009	<0.159	<0.220	0.709	1.424	1.607	1.787
OCDD	1.30	<0.087	<0.043	<1.9	<0.131	<0.255	<0.077	<1.8	<0.119	<0.36	<0.559	<0.069	<0.878	<0.163	<0.025	<0.942	<1.576	4.568	8.641	9.156	111541
TCDF	0.009	<0.42	<0.26	0.020	0.0043	0.005	0.052	0.019	<0.0004	0.0079	0.007	0.0061	<0.0005	<0.0006	<0.0009	0.0057	0.025	0.0453	0.047	0.0426	
12378-PeCDF	<0.004	0.0041	0.0039	0.0019	—	—	0.0017	0.0019	0.0006	—	0.0003	0.0008	0.0022	0.0002	—	0.0013	0.0016	0.0075	0.0094	0.0079	0.0092

(Continued)

Table 7.8 (Continued)

Analyte	SD-1	SD-2	SD-3	SD-4	SD-5	SD-6	SD-7	SD-8	SD-9	SD-10	SD-11	SD-12	SD-13	SD-14	SD-15	SD-16	SD-17	SD-18	SD-19	SD-20	SD-21
23478—PcCDF	<0.003	—	0.0008	0.0024	<0.001	<0.0008	0.0015	0.0026	0.0009	<0.0023	0.0014	0.0007	0.0024	0.0006	<0.0004	0.0021	0.0028	0.0126	0.0115	0.0195	0.0181
123478—HxCDF	—	<0.001	0.0012	0.0051	0.0013	0.0047	0.0022	0.0051	—	—	0.0058	0.0014	0.0075	—	—	0.0032	0.0122	0.0336	0.0447	0.0424	—
123678—HxCDF	0.0053	—	0.0028	0.0033	—	0.0002	0.0019	0.0041	0.0013	—	0.0036	0.0006	0.0027	0.0014	—	0.0013	0.0045	0.0236	0.0343	0.036	0.0325
123789—HxCDF	—	—	0.0015	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
234679—HxCDF	0.0051	—	—	0.0024	—	0.001	0.0025	0.0011	—	0.0033	—	0.0024	0.001	—	—	0.0029	0.0112	0.0213	0.018	0.0221	—
1234678—HpCDF	0.0786	<0.003	0.0012	0.028	<0.001	0.018	<0.0013	0.051	<0.0004	0.015	0.142	0.0046	0.039	0.009	<0.0006	0.022	<0.0031	0.354	0.644	—	<0.0081
1234789—HpCDF	<0.006	<0.003	0.022	<0.0015	<0.001	0.002	<0.0024	<0.0008	<0.0005	0.0023	0.001	<0.0009	0.0018	<0.0005	<0.0008	<0.0012	<0.0034	<0.0053	0.021	0.031	0.0296
OCDF	<0.13	—	0.0013	<0.053	<0.015	<0.023	—	<0.071	<0.009	<0.029	<0.058	<0.008	<0.054	<0.011	—	<0.033	<0.088	<0.311	<0.582	—	1.158

Notes: A number preceded by '' indicates the chemical was not detected and the number is the analytical reporting limit from the laboratory. Units are  $\mu\text{g}/\text{kg}$  dry weight.

Table 7.9 Sediment Sampling Results for Pesticides from the Detention Pond at the Manufactured Gas Plant

Analyte	SD-1	SD-2	SD-3	SD-4	SD-5	SD-6	SD-7	SD-8	SD-9	SD-10	SD-11	SD-12	SD-13	SD-14	SD-15	SD-16	SD-17	SD-18	SD-19	SD-20	SD-21
beta-BHC	<2.4	<2.1	<2.2	<2.5	<2.5	32	<2.4	<2.2	<2.4	2.6	<2.5	<2.0	<1.9	<2.5	<2.6	<2.4	<2.1	<2.2	<2.5	<1.8	<2.0
delta-BHC	<1.9	<2.0	<2.6	<2.4	<2.5	<2.1	<2.4	<2.5	<2.2	<2.5	<2.0	<2.5	<2.0	<1.9	<2.5	<2.6	<2.4	<2.1	<1.9	<2.3	<2.2
gamma-BHC (Lindane)	2.5	2.5	2.4	2.4	2.4	2.1	2.1	2.1	2.2	2.2	2.2	2.5	2.5	2.5	2.4	2.4	2.4	2.3	2.3	2.3	2.4
Chlordane	<1.9	<2.0	<2.6	<2.5	<2.3	<2.4	18	8.7	7	<.25	<2.0	14	2.7	5.3	2.8	4.1	<2.5	15	<2.1	>2.2	10
4,4'-DDD	5.8	5	4.9	4.8	4.9	4.9	5	5	5	4.8	5	4	7.3	3.5	4	4.6	3.8	3.7	4.9	5	4.9
4,4'-DDE	<3.7	3.8	5	5.2	4.4	4.7	4.8	4.3	4.8	4.9	3.9	3.8	4.8	31	4.7	4.7	4.8	4.2	4.8	4.6	4
4,4'-DDT	5.1	3.8	5	4.8	4.4	4.7	4.8	6.2	4.8	4.9	3.9	3.8	4.8	4	4.7	4.7	4.8	4.2	4.8	4.6	4
Dieldrin	13	<3.8	<5.0	22	<4.4	13	47	100	23	<4.9	<3.9	<3.8	<4.8	<4.0	<4.7	<4.8	<4.2	41	<4.0	16	7.2
Endosulfan I	<2.4	<2.1	<3.0	<2.1	<4.8	<5.3	<1.9	<2.2	<2.3	<5.5	<2.1	<2.2	<3.5	<2.0	<2.1	<3.9	<4.8	<2.5	<5.0	>2.4	<2.2
Endosulfan II	<3.7	<3.8	<5.0	<4.8	<4.4	<4.7	10	18	<4.8	<4.9	<3.9	<3.8	8.2	88	22	13	<4.8	<4.2	<4.8	<4.0	<4.2
Endosulfan Sulfate	<4.	<4.8	<4.2	<4.8	<4.8	<4.6	<4.0	<4.2	<4.8	<4.6	5.4	5.7	<4.3	<4.6	<5.8	<4.7	11	<4.0	<5.0	<4.6	<3.7
Endrin	<3.7	<3.8	<5.0	9.1	<4.4	<4.7	28	<4.9	13	<4.9	<3.9	<3.8	<4.8	<4.0	<4.7	<4.8	<4.6	<4.0	<4.2	21	9.9
Endrin aldehyde	<4.6	<4.4	<4.6	19	<4.6	38	<4.7	3.6	5.4	<4.0	<5.0	<4.6	<4.3	<3.7	<3.6	<4.9	<5.0	<5.8	<4.9	<3.8	<4.0
Heptachlor	2.5	2.5	2.4	2.4	2.1	2.1	2.2	2.2	2.2	2.5	2.5	2.5	2.5	2.4	2.4	2.4	2.3	2.3	2.3	2.4	
Heptachlor epoxide	<4.9	<3.9	<3.8	<4.8	<4.0	<4.7	<4.8	<4.6	<4.0	<4.9	<1.9	<2.0	<2.6	<2.4	<2.5	<1.9	<2.0	<2.6	<2.4	<4.0	<5.0
Metoxychlor	<20	<24	<22	<19	<25	39	<26	<25	<26	<26	<23	<18	<20	<25	39	<26	<25	<26	<24	<22	<19
Toxaphene	<190	<200	<260-	<230	<250	<240	<250	<200	<190	<210	<240	<250	<220	<240	<230	<240	<250	<200	<190	<210	<240

Notes: A number preceded by “<” indicates the chemical was not detected and the number is the analytical reporting limit from the laboratory. Units are  $\mu\text{g}/\text{kg}$  dry weight.

Table 7.10 Sediment Sampling Results for Metals from the River Near the Confluence of the Tributary

	Al	Sb	As	Ba	Be	Cd	Cr	Co	Cu	Fe	Pb	Mn	Hg	Ni	Se	Ag	Tl	Va	Zn
R-SD-1	2967	<0.62	2	9.1	0.19	0.021	13.5	<1.4	1.39	980	3.5	42	0.23	0.5	<1.3	0.5	0.84	9.01	451
R-SD-2	1039	1.8	6	56.1	0.11	<0.06	37.7	2.3	1.39	297	5.6	50	0.66	27.8	<1.2	2.7	1.19	2.16	15
R-SD-3	2465	<0.70	<0.92	15.5	0.05	<0.06	39.7	1.5	1.8	207	0.8	22	<0.01	18.5	<1.2	<1.8	<0.9	4.18	22
R-SD-4	841	0.93	<0.54	1.9	0.17	<0.1	15.6	7.2	1.5	175	23.3	30	<0.01	0.5	<0.65	<1.8	0.6	0.47	71
R-SD-5	5366	3.6	1.1	6.3	0.04	<0.07	16.6	19.6	9.2	287	0.2	567	0.23	0.3	<0.65	9.9	<0.63	2.32	22
R-SD-6	1187	<0.53	<0.54	8.4	0.66	<0.039	71.0	1.5	0.91	117	312.1	23	0.66	30.6	<1.3	<2.2	1.19	2.81	102
R-SD-7	624	1.8	<0.64	11.1	0.06	<0.07	8.8	<3.0	2.3	148	0.1	67	0.66	0.3	<1.2	8.6	<0.81	2.95	13
R-SD-8	482	3.3	13.7	14.1	0.12	<0.06	43.7	1.7	0.091	46	111.6	574	<0.01	0.0	<1.1	<1.2	<0.43	3.79	100
R-SD-9	3471	0.93	2	8.9	0.15	<0.07	4.8	2.3	2.4	79	18.8	52	1.2	30.4	<1	8.6	<0.63	1.65	29
R-SD-10	1203	1.9	<0.65	2.6	0.02	<0.07	30.3	5.8	0.91	31	18.4	32	0.2	0.2	<1.1	<1.2	8.9	3.77	131

Notes: A number preceded by “<” indicates the chemical was not detected and the number is the analytical reporting limit from the laboratory. Units are mg/kg dry weight.

Table 7.11 Sediment Sampling Results for PCBs and PCDD/Fs from the River Near the Confluence of the Tributary

Analyte	R-SD-1	R-SD-2	R-SD-3	R-SD-4	R-SD-5	R-SD-6	R-SD-7	R-SD-8	R-SD-9	R-SD-10
<b>Polychlorinated Biphenyls (µg/kg)</b>										
<b>Chlorinated Dioxins and Furans (µg/kg)</b>										
Aroclor-1016	2.1	<.2	2.2	2.1	<.2	4.2	2.4	8.6	2.1	4.5
Aroclor-1221	2.5	11.7	<0.29	2.4	21.5	2.5	11.7	2.1	11.7	<0.29
Aroclor-1232	2.2	2.2	2.42	4.2	4.6	2.3	4.1	2.2	2.5	2.42
Aroclor-1242	2.3	<0.36	<0.035	2.1	2.2	2.3	2.2	<0.038	<0.038	4.3
Aroclor-1248	2.1	4.3	2.3	2.3	2.1	2.1	2.3	2.3	2.3	<0.035
Aroclor-1254	2.2	2.2	<0.035	4.3	0.044	2.3	2.3	2.3	2.3	2.1
Aroclor-1260	3.1	0.032	2.1	<0.035	2.2	2.3	2.1	2.5	<0.035	2.5
Aroclor-1268	9.5	<0.038	<0.035	6.6	2.1	2.1	2.3	3.3	3.3	9.5
2378-TCDD	0.0079	0.195	<0.0007	0.029	0.087	0.161	<0.0007	0.123	0.029	0.018
12378-PeCDD	0.0013	0.0072	<0.0007	<0.0008	<0.0008	<0.0007	0.0005	<0.0007	0.002	0.0013
123478-HxCDD	<0.0004	0.0032	0.0356	0.0032	<0.0006	<0.0003	<0.003	0.0077	<0.0006	0.0013
123678-HxCDD	0.0714	0.0062	0.0025	—	0.0022	0.089	0.016	0.002	—	0.016
123789-HxCDD	0.016	0.0036	<0.0008	0.0014	0.0053	0.0422	0.0017	0.0031	0.0017	0.0014
1234678-HpCDD	1.607	0.0023	<0.01	0.0044	<0.089	<0.025	0.215	<0.0009	<0.01	1.424
OCDD	<0.087	<0.878	<0.025	<0.043	<0.025	<0.025	<0.163	<0.163	<0.255	<0.087
TCDF	0.019	0.052	0.0426	<0.0009	0.0061	0.025	<0.0005	0.0057	0.0453	0.052
12378-PeCDF	0.0013	0.0006	<0.004	0.0079	0.0008	0.0006	0.0008	0.0002	0.0022	0.0079
23478-PeCDF	<0.0004	0.0015	0.0126	0.0008	0.0008	0.0115	0.0014	<0.0023	0.0181	0.0006

(Continued)

Table 7.11 (Continued)

Analyte	R-SD-1	R-SD-2	R-SD-3	R-SD-4	R-SD-5	R-SD-6	R-SD-7	R-SD-8	R-SD-9	R-SD-10
123478-HxCDF	0.0075	0.0447	0.0424	0.0447	0.0058	0.0336	—	<0.001	0.0032	—
123678-HxCDF	0.0019	0.0236	0.0014	0.0014	0.0013	—	0.0343	0.0045	0.0041	0.002
123789-HxCDF	—	—	—	0.0015	—	—	—	—	—	—
234679-HxCDF	0.012	0.0025	—	0.0025	0.018	—	—	0.0029	0.0025	—
1234678-HpCDF	0.015	0.022	0.039	0.644	0.009	<0.0006	0.022	0.0046	0.644	0.018
1234789-HpCDF	<0.0015	0.0023	0.0296	<0.0012	<0.0053	<0.006	<0.0005	<0.0008	0.0296	<0.0005
OCDF	<0.011	1.158	0.0013	<0.033	0.0013	<0.088	—	—	<0.009	<0.054

Notes: A number preceded by "<" indicates the chemical was not detected and the number is the analytical reporting limit from the laboratory. Units are mg/kg dry weight.

Table 7.12 Sediment Sampling Results for Polycyclic Aromatic Hydrocarbons from the River Near the Confluence of the Tributary

Analyte	SD-1	SD-2	SD-3	SD-4	SD-5	SD-6	SD-7	SD-8	SD-9	SD-10
2-Chloronaphthalene	166	627	57	163	70	229	318	91	58	743
1-Methylnaphthalene	31	122	245	10	18	26	18	28	41	39
2-Methylnaphthalene	83	629	63	351	18	137	71	876	192	104
Acenaphthene	895	46	643	338	673	375	106	630	22	84
Acenaphthylene	113	66	19	28	19	19	1323	8	1184	142
Anthracene	60	26	27	14	105	352	62	217	15	46
Benzo[a]anthracene	14	181	34	20	108	109	176	67	157	308
Benzo[a]pyrene	21	870	91	86	57	24	6	13	444	63
Benzo[b]fluoranthene	77	14	369	166	60	86	51	137	399	6
Benzo[g,h,i]perylene	24	21	34	177	5	12	360	344	550	492
Benzo[k]fluoranthene	16	88	10	708	425	511	61	292	25	148
Chrysene	24	111	52	606	131	111	181	313	187	213
Dibenz[a,h]anthracene	21	434	88	644	29	70	74	328	5	1691
Fluoranthene	262	131	910	10	310	25	3	55	105	55
Fluorene	608	15	157	1681	20	44	106	410	1455	215
Indeno[1,2,3-c,d]pyrene	296	81	80	384	160	200	27	33	133	13
Naphthalene	73	286	394	42	165	18	27	645	485	378
Phenanthrene	43	150	116	141	210	257	23	52	146	1217
Pyrene	175	88	76	79	126	139	4435	961	81	103

Notes: A number preceded by “<” indicates the chemical was not detected and the number is the analytical reporting limit from the laboratory. Units are  $\mu\text{g}/\text{kg}$  dry weight.

Table 7.13 Sediment Sampling Results for Pesticides from the River Near the Confluence of the Tributary

Analyte	SD-1	SD-2	SD-3	SD-4	SD-5	SD-6	SD-7	SD-8	SD-9	SD-10
Beta-BHC	<2.4	<2.1	<2.2	2.6	<2.4	<2.4	<2.6	<2.2	<2.5	<2.1
Delta-BHC	<2.3	<1.9	<2.4	<2.5	<1.9	<2.5	<2.2	<2.0	<2.4	<2.2
Gamma-BHC (Lindane)	2.1	2.4	2.2	2.4	2.5	2.4	2.4	2.3	2.2	2.4
Chlordane	10	<2.5	8.7	<1.9	4.1	8.7	<2.0	<2.5	2.8	<2.6
4,4'-DDD	3.7	3.5	4.9	4.9	4.6	4.9	5	3.8	4.8	4.9
4,4'-DDE	4	3.8	3.8	5.2	4.8	5	4.6	3.8	4.6	4.7
4,4'-DDT	4.2	5	5	5.1	3.9	5	4.2	4.7	4.8	5.1
Dieldrin	<4.4	<3.8	41	<4.7	16	13	<4.2	<4.9	<4.4	13
Endosulfan I	<2.0	<2.1	<5.0	<2.3	<4.8	<2.3	<2.1	<2.2	<5.5	<2.2
Endosulfan II	<4.0	<4.2	22	<5.0	<4.8	<3.9	<4.8	<4.4	18	<4.8
Endosulfan Sulfate	11	<4.0	<4.8	<4.8	<5.8	<4.8	<4.2	<4.8	<4.6	<5.0
Endrin	21	<4.4	<4.6	<4.2	<5.0	<3.8	<4.0	<4.4	<4.7	<3.8
Endrin aldehyde	<4.0	<5.0	<4.0	<4.6	<5.0	<4.0	3.6	<4.7	<4.7	<4.9
Heptachlor	2.5	2.4	2.4	2.2	2.4	2.4	2.4	2.1	2.2	2.5
Heptachlor epoxide	<2.6	<4.8	<4.8	<3.9	<4.9	<4.0	<4.0	<2.6	<2.6	<3.9
Methoxychlor	<26	<26	<26	<26	<20	<26	<25	<26	<19	<26
Toxaphene	<200	<250	<240	<190	<240	<250	<240	<190	<240	<210

Notes: A number preceded by “<” indicates the chemical was not detected and the number is the analytical reporting limit from the laboratory. Units are  $\mu\text{g/kg}$  dry weight.

Table 7.14 COPEC Screening for Metals in Surface Water in the Detention Pond

Chemical	Units	N	#	Freq.	Min.	Max.	Min.	Max.	Arithmetic	NAWQC	OSWER	EPA R3	Potential	COPEC	95%
				Det.	ND	ND	ND	ND	Mean (ND2)	Acute/ Chronic	Ambient Water	Freshwater Screening Benchmark	for Bioaccum.	(Y/N)	UCL
Aluminum	µg/L	16	13	81%	<0.02	22	840	152.4	750/87		87		Y	389 <sup>1</sup>	
Antimony	µg/L	16	0	0%	<5	<5	—	—	—		30		N		
Arsenic	µg/L	16	0	0%	<5	<5	—	—	—	340/150	190	5	Y	N	
Barium	µg/L	16	16	100%	—	—	34	87	45		3.9	4	Y	50.28 <sup>2</sup>	
Beryllium	µg/L	16	0	0%	<1	<1	—	—	—		5.1	0.66	N		
Cadmium	µg/L	16	13	81%	<0.05	<0.05	0.14	2.9	0.72		0.25	Y	N		
Chromium	µg/L	16	13	81%	<0.05	<0.05	0.27	7.4	1.265	570/74	180	85		N	
Cobalt	µg/L	16	0	0%	<0.01	<0.01	—	—	—		3	23		N	
Copper	µg/L	16	15	94%	<0.05	<0.05	1.6	5	2.802	13/9	11	9	Y	N	
Iron	µg/L	16	16	100%	—	—	220	700	401		1000	300	Y	458.1 <sup>3</sup>	
Lead	µg/L	16	2	13%	<0.05	<0.05	0.95	27	1.769	65/2.5	2.50	2.50	Y	24.78 <sup>4</sup>	
Manganese	µg/L	16	16	100%	—	—	42	104	73		80	120	Y	85.59 <sup>5</sup>	
Mercury	µg/L	16	0	0%	<0.01	<0.01	—	—	—	1.4/0.77	1.3	0.026	Y	N	
Nickel	µg/L	16	15	94%	<1	<1	200	21,48	470/52	160	52	52	Y	97.09 <sup>5</sup>	

<sup>1</sup> 95% KM (Chebychev).<sup>2</sup> 95% Approx. Gamma.<sup>3</sup> 95% Student's t.<sup>4</sup> 99% KM (Chebychev).<sup>5</sup> 97.5% KM (Chebychev).

(Continued)

Table 7.14 (Continued)

Chemical	Units	N	#	Freq.	Min.	Max.	Min.	Max.	Arithmatic	NAWQC	OSWER	EPA R3	Potential	COPC	95%
				Det.	ND	ND	ND	Mean	Acute/Chronic	Ambient	Freshwater	for	(Y/N)	UCL	
								(ND/2)	Screening	Water	Screening	Bioaccum.			
									Benchmark	Quality	Benchmark	Benchmark			
									Criteria	Criteria	Criteria	Criteria			
Selenium	µg/L	16	2	13%	<0.2	<0.2	1.1	5.2	0.481	5	5	1	Y	Y	
Silver	µg/L	16	7	44%	<0.05	<0.05	0.400	0.57	0.227	3.2	3.2	3.2	Y	N	
Thallium	µg/L	16	0	0%	<1	<1	—	—	—	—	—	0.8	—	N	
Vanadium	µg/L	16	0	0%	<10	<10	—	—	—	—	—	19	20	N	
Zinc	µg/L	16	2	13%	<10	<10	4.5	2800	179.7	120	100	120	Y	Y	
															2560 <sup>a</sup>

Notes: Units for all values are µg/L.

Table 7.15 COPEC Screening for PAHs in Surface Water in the Detention Pond

Chemical	Units	N	#	Freq.	Min. ND	Max. ND	Min. Detect	Max. Detect	Arithmetic Mean (ND/2)	EPA R3/R5/ R6 Freshwater Screening Benchmark	Potential for Bioaccum.	COPEC (Y/N)	95% UCL
2-Chloronaphthalene	µg/L	2	0	0%	<5	<5	—	—	—	54	Y	N	
1-Methylnaphthalene	µg/L	15	0	0%	<1	<1	—	—	—	2.1	Y	N	
2-Methylnaphthalene	µg/L	14	2	14%	<0.5	<0.5	11	210	16	4.7	Y	Y	109.6 <sup>1</sup>
Acenaphthene	µg/L	21	8	38%	<0.2	<0.2	0.25	160	12.74	5.8	Y	Y	103.7 <sup>2</sup>
Acenaphthylene	µg/L	21	3	14%	<0.1	<0.1	1.2	10	0.96	4840	Y	N	
Anthracene	µg/L	21	2	10%	<0.8	<0.8	10	16	1.6	0.012	Y	Y	10.97 <sup>3</sup>
Benzo[a]anthracene	µg/L	21	2	10%	<0.05	<0.05	0.09	5	0.265	34.6	Y	N	3.533 <sup>2</sup>
Benzo[a]pyrene	µg/L	21	2	10%	<0.1	<0.1	0.1	5	0.288	0.015	Y	Y	3.537 <sup>2</sup>
Benzo[b]fluoranthene	µg/L	21	1	5%	<0.1	<0.1	4.5	4.5	4.5	9.07	Y	N	
Benzo[g,h,i]perylene	µg/L	21	0	0%	—	—	—	—	—	7.64	Y	N	
Benzo[k]fluoranthene	µg/L	21	2	10%	<0.1	<0.1	1.3	5	0.345	NA	Y	N	
Chrysene	µg/L	21	2	10%	<0.1	<0.1	0.2	4.8	0.283	7	Y	N	
Dibenz[a,h]anthracene	µg/L	21	0	0%	<1	<1	—	—	—	5	Y	N	
Fluoranthene	µg/L	21	5	24%	<0.07	<0.07	0.9	6	0.655	1.9	Y	Y	2.314 <sup>4</sup>

<sup>1</sup> 95% KM (Chebychev).<sup>2</sup> 99% KM (Chebychev).<sup>3</sup> 95% KM (bootstrap).<sup>4</sup> 95% KM percentile bootstrap.

(Continued)

Table 7.15 (Continued)

Chemical	Units	N	# Det.	Freq.	Min. ND	Max. ND	Min. Detect	Max. Detect	Arithmetic Mean (ND/2)	EPA R3/R5/ R6 Freshwater Screening Benchmark	Potential for Bioaccum.	COPEC (Y/N)	95% UCL	
Fluorene	µg/L	21	2	10%	<0.5	4.4	62	3.388	11	Y	Y	30.78 <sup>5</sup>		
Indeno[1,2,3-c,d]pyrene	µg/L	21	1	5%	<1	5	5	5.00	4.31	Y	Y	NA <sup>6</sup>		
Naphthalene	µg/L	21	3	14%	<0.2	<0.2	8	520	26.51	13	Y	Y	83.49 <sup>7</sup>	
Phenanthrene	µg/L	21	3	14%	<0.2	<0.2	5.5	84	5.205	0.4	Y	Y	1758	
Pyrene	µg/L	21	5	24%	<0.08	<0.08	1.7	10	0.93	0.025	Y	Y	2.937	

Notes: Units for all values are µg/L.

<sup>5</sup> 97.5% KM (Chebyshev).

<sup>6</sup> not processed by ProUCL.

<sup>7</sup> 95% KM (t).

Table 7.16 COPEC Screening for PCDD/Fs in Surface Water in the Detention Pond

Chemical	Units	N	#	Freq.	Min. ND	Max. ND	Min. Detect	Max. Detect	EPA R4	EPA R5	EPA R3	Potential for Bioaccum.	COPC (Y/N)	95% UCL
									Chronic Screening Benchmark	ESL Screening Benchmark	Screening Benchmark			
2378-TCDD	pg/L	14	8	57%	<2.4	<7.3	2.9	12,740	2214					
12,378-PeCDD	pg/L	14	2	14%	<0.5	<5.9	14	35	24.7					
123,478-HxCDD	pg/L	14	3	21%	<0.8	<8.9	1.6	28.3	13.3					
123,678-HxCDD	pg/L	14	3	21%	<0.7	<8.4	6.4	95.30	41.1					
123,789-HxCDD	pg/L	14	4	29%	<4.1	<7.7	1.8	94	26.05					
1,234,678-HpCDD	pg/L	14	5	36%	<3.4	<24.3	3	31.70	12.18					
OCDD	pg/L	14	11	79%	<17.1	<44.5	18.6	27,700	4308					
TCDF	pg/L	14	2	14%	<0.3	<4.3	30.9	53.10	42					
12,378-PeCDF	pg/L	14	1	7%	<0.3	<14.1	36.4	36.40	36.4					
23,478-PeCDF	pg/L	14	1	7%	<0.3	<28.2	18.3	18.3	18.3					
123,478-HxCDF	pg/L	14	2	14%	<0.7	<16.5	2.8	42.7	22.75					
123,678-HxCDF	pg/L	14	3	21%	<0.5	<15.5	1.9	34.2	12.97					
123,789-HxCDF	pg/L	14	2	14%	<0.2	<7.1	2.2	6.3	4.25					
234,679-HxCDF	pg/L	14	3	21%	<0.5	<6.3	5.9	43.6	21.87					

(Continued)

Table 7.16 (Continued)

Chemical	Units	N	# Det.	Freq.	Min. ND	Max. ND	Min. Detect	Max. Detect	Arith. Mean of Detections	EPA R4 Chronic Screening Benchmark	EPA R5 ESL Screening Benchmark	EPA R3 Screening Benchmark	Potential for Bioaccum.	COPC (Y/N)	95% UCL
1,234,678-HpCDF	pg/L	14	7	50%	<0.7	<6.6	2.4	580	95.07						
1,234,789-HpCDF	pg/L	14	4	29%	<1	<11.2	6.1	59.6	32.8						
OCDF	pg/L	14	10	71%	<2	<31.6	2.4	1950	356						
Mammalian TEQ	µg/L	14	14	100%			3.12E-06	1.28E-02	1.28E-03	1.00E-05	3.00E-09	3.10E-09	Y	Y	2.836
Avian TEQ	µg/L	14	14	100%			3.57E-06	1.29E-02	1.29E-03	1.00E-05	3.00E-09	3.10E-09	Y	Y	3.06
Fish TEQ	µg/L	14	14	100%			2.90E-06	1.28E-02	1.28E-03	1.00E-05	3.00E-09	3.10E-09	Y	Y	3.049

Notes: All UCL values were calculated using the 95% percentile bootstrap.

Table 7.17 COPEC Screening for Metals in Sediment in the Detention Pond

Chemical	Units	N	# Det.	Freq.	Min. ND	Max. Detect	Max. Detect	Arithmetic Mean(ND/2)	EPA R3 Screening Benchmark	EPA R4 Screening Benchmark	EPA R5 Screening Benchmark	EPA R6 Screening Benchmark	COPC (Y/N)	95% UCL	
Aluminum	mg/kg	21	21	100%	<0.62	<10	2150	15,400	9679	2	12		Y	14280 <sup>1</sup>	
Antimony	mg/kg	21	11	52%	<0.54	<10.4	1.1	13.7	6.513	9.8	7.24	9.79	2	Y	14.23 <sup>2</sup>
Arsenic	mg/kg	21	15	71%	<0.54	<10.4							5.9	Y	6.841 <sup>3</sup>
Barium	mg/kg	21	21	100%			19.4	202	89.15				Y	119.4 <sup>4</sup>	
Beryllium	mg/kg	21	21	100%			0.25	4.6	1.411				Y	1.977 <sup>4</sup>	
Cadmium	mg/kg	21	4	19%	<0.039	<0.1	0.02	0.04	0.032	1		0.99	0.6	N	
Chromium	mg/kg	21	21	100%			4.1	331	119	43.4	52.3	43.4	37.3	Y	196.2 <sup>4</sup>
Cobalt	mg/kg	21	21	100%			1	19.6	4.19	50		50		N	
Copper	mg/kg	21	21	100%			0.091	9.2	2	316	18.7	316	35.7	Y	2.719 <sup>4</sup>
Iron	mg/kg	21	21	100%			60	4900	1109	20,000			20,000	N	
Lead	mg/kg	21	21	100%			0.46	1230	353.700	35.8	30.2	35.8	35	Y	696.3 <sup>5</sup>
Manganese	mg/kg	21	21	100%			44.1	1490	251	460			460	Y	351.4 <sup>4</sup>
Mercury	mg/kg	21	7	33%	<0.01	<0.01	0.05	1.20	0.430	0.18	0.13	0.17	0.15	Y	0.352 <sup>6</sup>
Nickel	mg/kg	21	15	71%	<0.039	<0.64	0.15	92.2	8.439	22.7	15.9	18	20.9	Y	49.82 <sup>7</sup>
Selenium	mg/kg	21	5	24%	<0.65	<1.6	0.94	2.1	1.51	2				Y	1.217 <sup>3</sup>
Silver	mg/kg	21	12	57%	<0.52	<4	0.500	10.6	6.34	1	2	0.5	1	Y	9.711 <sup>2</sup>
Thallium	mg/kg	21	12	57%	<0.43	<1.05	0.47	10.4	2.439					Y	2.653 <sup>3</sup>
Vanadium	mg/kg	21	21	100%			5.8	129	26.10					Y	57.52 <sup>1</sup>
Zinc	mg/kg	21	18	86%	<29.2	<43.1	42.3	2060	530.700	121	124	121	150	Y	1065 <sup>8</sup>

Notes: Units for all values are mg/kg dry weight.

<sup>1</sup> 95% Chebychev (Mean, SD) UCL.<sup>2</sup> 97.5% KM (Chebychev).<sup>3</sup> 95% KM (t).<sup>4</sup> 95% Approx. Gamma.<sup>5</sup> 95% Adjusted Gamma.<sup>6</sup> 95% KM (percentile bootstrap).<sup>7</sup> 99% KM (Chebychev).<sup>8</sup> 95% KM (Chebychev).

Table 7.18 COPEC Screening for PAHs in Sediment in the Detention Pond

Chemical	Units	N	# Det.	Freq.	Min. ND	Max. ND	Min. Detect	Max. Detect	Arithmetic Mean (ND/2)	Effect Concentrations	Potential for Bioaccum.	COPEC (Y/N)	95% UCL
2-Chloronaphthalene	mg/kg	21	21	100%	—	—	400	9600	2653	Assessed as total PAHs			
1-Methylnaphthalene	mg/kg	21	21	100%	—	—	78	9800	1720				
2-Methylnaphthalene	mg/kg	21	21	100%	—	—	100	9700	3174				
Acenaphthene	mg/kg	21	21	100%	—	—	400	9700	3145				
Acenaphthylene	mg/kg	21	21	100%	—	—	62	9600	1762				
Anthracene	mg/kg	21	21	100%	—	—	79	9900	1951				
Benzol[al]anthracene	mg/kg	21	21	100%	—	—	62	3900	1371				
Benzol[al]pyrene	mg/kg	21	21	100%	—	—	83	4800	1203				
Benzol[b]fluoranthene	mg/kg	21	21	100%	—	—	55	3600	1158				
Benzol[g,h,i]perylene	mg/kg	21	21	100%	—	—	92	6300	2021				
Benzol[k]fluoranthene	mg/kg	21	21	100%	—	—	59	5500	1307				
Chrysene	mg/kg	21	21	100%	—	—	260	19,000	2934				
Dibenz[a,h]anthracene	mg/kg	21	21	100%	—	—	78	9600	2067				
Fluoranthene	mg/kg	21	21	100%	—	—	46	9500	2022				
Fluorene	mg/kg	21	21	100%	—	—	320	9800	2092				
Indeno[1,2,3-c,d]pyrene	mg/kg	21	21	100%	—	—	310	9700	1660				
Naphthalene	mg/kg	21	21	100%	—	—	410	9600	2729				
Phenanthrene	mg/kg	21	21	100%	—	—	170	96,045	7254				
Pyrene	mg/kg	21	21	100%	—	—	67	23,000	2926				
Total PAHs	mg/kg	21	21	100%			24,835	136,424	45,147	TEC	PEC	Y	53435 <sup>1</sup>

Notes: Units for all values are mg/kg dry weight.

<sup>1</sup> 95% Approx. Gamma UCL.

Table 7.19 COPEC Screening for PCBs in Sediment in the Detention Pond

Chemical	Units	N	# Det.	Freq.	Min. ND	Max. ND	Min. Detect	Max. Detect	Arithmetic Mean (ND/2)	Effect Concentrations	Potential for Bioaccum.	COPEC (Y/N)	95% UCL
Aroclor-1016	µg/kg	21	13	62%	<0.035	<5	2.1	8.6	3.1	70/7	Assessed as total PCBs		
Aroclor-1221	µg/kg	21	15	71%	<0.07	<0.29	2.1	21.5	6.662				
Aroclor-1232	µg/kg	21	14	67%	<0.035	<0.14	2.1	8.6	3.319				
Aroclor-1242	µg/kg	21	6	29%	<0.035	<0.36	2.1	4.3	1.401				
Aroclor-1248	µg/kg	21	8	38%	<0.035	<0.038	2.1	4.3	2.099	30			
Aroclor-1254	µg/kg	21	9	43%	<0.035	<0.035	0.044	4.3	2.204	63/60			
Aroclor-1260	µg/kg	21	9	43%	<0.035	<0.1	0.032	4.3	2.106	0.005			
Aroclor-1268	µg/kg	21	11	52%	<0.035	<0.038	2.1	9.5	3.001				
Total PCBs	µg/kg	21	21	100%	2.442	2.442	47.36	24.01	59.8	676	Y	N	

Notes: Units for all values are µg/kg dry weight.

Table 7.20 COPEC Screening for PCDD/Fs in Sediment in the Detention Pond

Chemical	Units	N	# Det.	Freq.	Min. ND	Max. ND	Min. Detect	Max. Detect	Arith. Mean of Detections	Screening Benchmark	Potential for Bioaccum.	COPC (Y/N)	95% UCL
2378-TCDD	ng/kg	21	20		<0.7	<0.7	18	10,050	1583				
12,378-PeCDD	ng/kg	21	10		<0.5	<7	0.5	19	6.23				
123,478-HxCDD	ng/kg	21	10		<0.3	<3	1.3	35.6	10.5				
123,678-HxCDD	ng/kg	17	17		<0	<0	0.9	89	20.4				
123,789-HxCDD	ng/kg	21	20		<0.8	<0.8	0.5	84.4	17.4				
1,234,678-HpCDD	ng/kg	21	9		<0.9	<220	2.3	1787	698				
OCDD	ng/kg	21	6		<25	<1900	1300	111,500	22,830				
TCDF	ng/kg	21	15		<0.4	<420	0.7	52	19.6				
12,378-PeCDF	ng/kg	17	16		<4	<4	0.2	9.4	3.41				
23,478-PeCDF	ng/kg	20	15		<0.4	<3	0.6	19.5	5.33				
123,478-HxCDF	ng/kg	15	14		<1	<1	1.2	44.7	12.2				
123,678-HxCDF	ng/kg	17	17		<0	<0	0.6	36	9.48				
123,789-HxCDF	ng/kg	1	1		<0	<0	1.5	1.5	1.5				
234,679-HxCDF	ng/kg	14	11		<0	<0	1	22.1	6.86				
1,234,678-HpCDF	ng/kg	20	14		<0.4	<8.1	1.2	644	101				
1,234,789-HpCDF	ng/kg	21	8		<0.5	<6	1	31	13.8				
OCDF	ng/kg	17	2		<8	<582	1.3	1158	580				
Mammalian TEQ	ng/kg	21	21				0.923	10,130	1527	2.5–25	Y	Y	5719 <sup>1</sup>
Avian TEQ	ng/kg	21	21				1.27	10,160	1551	21–210	Y	Y	5743 <sup>1</sup>
Fish TEQ	ng/kg	21	21				0.978	10,120	1522	60–100	Y	Y	5705 <sup>1</sup>

Notes: Units for all values are ng/kg dry weight.

<sup>1</sup> 97.5% Chebychev (mean, SD) UCL.

Table 7.21 COPEC Screening for Pesticides in Sediment in the Detention Pond

Chemical	Units	N	# Det.	Freq.	Min. ND	Max. Detect	Max. Detect	Arithmetic Mean(ND/2)	EPA R3 Screening Benchmark	EPA R4 Screening Benchmark	EPA R5 Screening Benchmark	EPA R6 Screening Benchmark	COPC (Y/N)	95% UCL
beta-BHC	µg/kg	21	1	5%	<1.8	<2.6	32	32	5	5	5	5	N	
delta-BHC	µg/kg	21	0	0%	<1.9	<2.6							N	
gamma-BHC (Lindane)	µg/kg	21	0	0%	<2.1	<2.5							N	
Chlordane	µg/kg	21	10	48%	<0.25	<2.6	2.7	18	4.713	3.24	1.7	3.24	4.5	7.655 <sup>1</sup>
4,4'-DDD	µg/kg	21	21	100%			3.5	7.3	4.8	1.22	3.3	4.88	1.22	5.101 <sup>2</sup>
4,4'-DDDE	µg/kg	21	20	95%	<3.7	<3.7	3.8	43	7.512	2.07	3.3	1.42	2.07	17.09 <sup>3</sup>
4,4'-DDT	µg/kg	21	1	5%	<3.8	<5.1	6.2	6.2	6.2	1.19	3.3	1.19	1.19	N
Dieldrin	µg/kg	21	9	43%	<3.8	<5	7.2	100	14.68	1.9	3.3	295	2.85	26.13 <sup>1</sup>
Endosulfan I	µg/kg	21	0	0%	<1.9	<5.5				2.9			3.26	N
Endosulfan II	µg/kg	21	6	29%	<3.7	<5	8.2	88	9.148	14		1.94	Y	20.47 <sup>1</sup>
Endosulfan	µg/kg	21	3	14%	<3.7	<5.8	5.4	11	2.993	5.4		3.46	Y	6.231 <sup>1</sup>
Sulfate														
Endrin	µg/kg	21	5	24%	<3.7	<5	9.1	28	5.529	2.22	3.3	2.22	2.67	Y 12.75 <sup>1</sup>
Endrin aldehyde	µg/kg	21	4	19%	<3.6	<5.8	3.6	38	4.964			480		Y 9.477 <sup>1</sup>
Heptachlor	µg/kg	21	0	0%	<2.1	<2.5				68		0.6		N
Heptachlor epoxide	µg/kg	21	0	0%	<1.9	<4.9					2.47	0.6		N
Methoxychlor	µg/kg	21	2	10%	<18	<26	39	39	39	18.7		13.6	Y	39 <sup>4</sup>
Toxaphene	µg/kg	21	0	0%	<190	<260				0.1		0.077		N

Notes: Units for all values are µg/kg dry weight.

<sup>1</sup> 95% KM (t) UCL.<sup>2</sup> 95% Student's t UCL.<sup>3</sup> 95% KM (Chebychev) UCL.<sup>4</sup> Maximum value.

Table 7.22 COPEC Screening for Metals in Sediment in the River

Chemical	Units	N	# Det.	Freq.	Min. ND	Max. ND	Min. Detect	Max. Detect	Arithmetic Mean(ND/2)	EPA R3 Screening Benchmark	EPA R4 Screening Benchmark	EPA R5 Screening Benchmark	EPA R6 Screening Benchmark	COPC (Y/N)	95% UCL	
Aluminum	mg/kg	10	10	100%	<0.53	<0.7	0.93	3.6	1.519	2	12	7.24	9.79	2	N	
Antimony	mg/kg	10	7	70%	<0.54	<0.92	1.1	13.7	2.645	9.8	7.24	9.79	5.9	Y	2.30 <sup>1</sup>	
Arsenic	mg/kg	10	5	50%	<0.54	<0.92	1.1	13.7	2.645	13.41	13.41	13.41	13.41	Y	5.51 <sup>1</sup>	
Barium	mg/kg	10	10	100%			1.87	56.1							N	
Beryllium	mg/kg	10	10	100%			0.0166	0.66	0.157						N	
Cadmium	mg/kg	10	1	10%	<0.039	<0.07	0.21	0.21	0.21	1	1	0.99	0.99	0.6	N	
Chromium	mg/kg	10	10	100%			4.76	71.0	28.17	43.4	52.3	43.4	43.4	37.3	Y	39.97 <sup>2</sup>
Cobalt	mg/kg	10	1	10%	<1.4	<3	1.5	19.6	4.41	50	50	50	50		N	
Copper	mg/kg	10	10	100%			0.091	9.2	2.189	31.6	18.7	31.6	31.6	35.7	N	
Iron	mg/kg	10	10	100%			31.4	980	236.7	20,000				20,000	N	
Lead	mg/kg	10	10	100%			0.123	312.1	49.44	35.8	30.2	35.8	35.8	35	Y	235.4 <sup>3</sup>
Manganese	mg/kg	10	10	100%			22.0	573.6	145.9	460				460	Y	455 <sup>4</sup>
Mercury	mg/kg	10	7	70%	<0.01	<0.01	0.2	1.2	0.386	0.18	0.13	0.17	0.17	0.15	Y	0.64 <sup>1</sup>
Nickel	mg/kg	10	10	100%			0.022	30.6	10.9	22.7	15.9	18	18	20.9	N	
Selenium	mg/kg	10	0	0%	<0.65	<1.3			2						N	
Silver	mg/kg	10	5	50%	<1.2	<2.2	0.5	9.9	3.44	1	2	0.5	0.5	1	Y	5.77 <sup>1</sup>
Thallium	mg/kg	10	5	50%	<0.43	<0.9	0.6	8.9	1.442						N	
Vanadium	mg/kg	10	10	100%			0.466	9.02	3.312						N	
Zinc	mg/kg	10	10	100%			12.67	450.7	95.5	121	124	121	121	150	N	

Notes: Units for all values are mg/kg dry weight.

<sup>1</sup> 95% KM (t) UCL.<sup>2</sup> 95% Student's t UCL.<sup>3</sup> 95% Adj. Gamma UCL.<sup>4</sup> 95% Chebychev (mean, SD) UCL.

Table 723 COPEC Screening for PAHs in Sediment in the River

Chemical	Units	N	# Det.	Freq.	Min. ND	Max. ND	Max. Detect	Arithmetic Mean (ND/2)	Effect Concentrations	Potential for Bioaccum.	COPEC (Y/N)	95% UCL
2-Chloronaphthalene	mg/kg	10	10	100%	—	—	0.057	0.473	0.252	Assessed as total PAHs		
1-Methylnaphthalene	mg/kg	10	10	100%	—	—	0.01	0.245	0.058			
2-Methylnaphthalene	mg/kg	10	10	100%	—	—	0.018	0.876	0.252			
Acenaphthene	mg/kg	10	10	100%	—	—	0.022	0.895	0.381			
Acenaphthylene	mg/kg	10	10	100%	—	—	0.008	1.323	0.292			
Anthracene	mg/kg	10	10	100%	—	—	0.014	0.352	0.092			
Benz[a]anthracene	mg/kg	10	10	100%	—	—	0.014	0.308	0.117			
Benz[a]pyrene	mg/kg	10	10	100%	—	—	0.006	0.870	0.168			
Benz[b]fluoranthene	mg/kg	10	10	100%	—	—	0.006	0.399	0.137			
Benz[g,h]perylene	mg/kg	10	10	100%	—	—	0.005	0.550	0.202			
Benz[k]fluoranthene	mg/kg	10	10	100%	—	—	0.01	0.708	0.228			
Chrysene	mg/kg	10	10	100%	—	—	0.024	0.606	0.193			
Dibenz[a,h]anthracene	mg/kg	10	10	100%	—	—	0.005	1.691	0.338			
Fluoranthene	mg/kg	10	10	100%	—	—	0.003	0.910	0.187			
Fluorene	mg/kg	10	10	100%	—	—	0.015	1.681	0.471			
Indeno[1,2,3-c,d]pyrene	mg/kg	10	10	100%	—	—	0.013	0.384	0.141			
Naphthalene	mg/kg	10	10	100%	—	—	0.018	0.645	0.251			
Phenanthrene	mg/kg	10	10	100%	—	—	0.023	1.217	0.236			
Pyrene	mg/kg	10	10	100%	—	—	0.076	4.435	0.626			
Total PAHs	mg/kg	10	10	100%			2.71	7.43	4.62	1.610	22.8	5.58 <sup>3</sup>

Notes: Units for all values are mg/kg dry weight.

Table 7.24 COPEC Screening for PCBs in Sediment in the River

Chemical	Units	N	# Det.	Freq.	Min. ND	Max. ND	Min. Detect	Max. Detect	Arithmetic Mean (ND/2)	Effect Concentrations	Potential for Bioaccum.	COPEC (Y/N)	95% UCL
Aroclor-1016	µg/kg	10	9	90%	<0.2	<0.2	0.2	8.6	2.85				Assessed as total PCBs
Aroclor-1221	µg/kg	10	8	80%	<0.29	<0.29	2.1	21.5	6.639				
Aroclor-1232	µg/kg	10	10	100%			2.2	4.6	2.914				
Aroclor-1242	µg/kg	10	6	60%	<0.035	<0.36	2.1	4.3	1.564				
Aroclor-1248	µg/kg	10	9	90%	<0.035	<0.035	2.1	4.3	2.232				
Aroclor-1254	µg/kg	10	9	90%	<0.035	<0.035	0.044	4.3	2.237				
Aroclor-1260	µg/kg	10	8	80%	<0.035	<0.035	0.032	3.1	1.687				
Aroclor-1268	µg/kg	10	8	80%	<0.035	<0.038	2.1	9.5	3.874				
Total PCBs	µg/kg	10	10				9.22	35.04	23.77	TEC	PEC		27.63 <sup>1</sup>

Notes: Units for all values are µg/kg dry weight.

<sup>1</sup> 95% Student's t UCL.

Table 725 COPEC Screening for PCDD/Fs in Sediment in the River

Chemical	Units	N	# Det.	Freq.	Min. ND	Max. ND	Min. Detect	Max. Detect	Arith. Mean of Detections	Screening Benchmark Range	Potential for Bioaccum.	COPC (Y/N)	95% UCL
2378-TCDD	ng/kg	10	8	80%	<0.7	7.9	195	86					
12,378-PeCDD	ng/kg	10	5	50%	<0.7	<0.8	0.5	7.2	2.46				
123,478-HxCDD	ng/kg	10	5	50%	<0.3	<3	1.3	35.6	10.2				
123,678-HxCDD	ng/kg	8	8	100%	<0	<0	2	89	25.7				
123,789-HxCDD	ng/kg	10	9	90%	<0.8	<0.8	1.4	42.2	8.49				
1,234,678-HpCDD	ng/kg	10	6	60%	<0.9	<89	2.3	1607	544				
OCDD	ng/kg	10	0	0%	<10	<10							
TCDF	ng/kg	10	8	80%	<0.5	<0.9	5.7	52	31				
12,378-PeCDF	ng/kg	10	9	90%	<4	<4	0.2	7.9	2.48				
23,478-PeCDF	ng/kg	10	8	80%	<0.4	<2.3	0.6	18.1	5.91				
123,478-HxCDF	ng/kg	8	7	88%	<1	<1	3.2	44.7	26				
123,678-HxCDF	ng/kg	9	9	100%	<0	<0	1.3	34.3	8.28				
123,789-HxCDF	ng/kg	1	1	100%	<0	<0	1.5	1.5	1.5				
234,679-HxCDF	ng/kg	6	6	100%	<0	<0	2.5	18	6.73				
1,234,678-HpCDF	ng/kg	10	9	90%	<0.6	<0.6	4.6	644	158				
1,234,789-HpCDF	ng/kg	10	3	30%	<0.5	<6	2.3	29.6	20.5				
OCDF	ng/kg	8	3	38%	<9	<88	1.3	1158	387				
Mammalian TEQ	ng/kg	10	10				9.34	217	82.6	0.052–1.4	Y	Y	124 <sup>1</sup>
Avian TEQ	ng/kg	10	10				6.86	264	102	0.07–3.5	Y	Y	149 <sup>1</sup>
Fish TEQ	ng/kg	10	10				6.35	215	78	0.56	Y	Y	120 <sup>1</sup>

Notes: Units for all values are µg/kg dry weight.

<sup>1</sup> 95% Student's t UCL.

**Table 7.26 COPEC Screening for Pesticides in Sediment in the River**

Chemical	Units	N	# Det.	Freq.	Min. ND	Max. ND	Max. Detect	Max. Detect	Arithmetic Mean(ND/2)	EPA R3 Screening Benchmark	EPA R4 Screening Benchmark	EPA R5 Screening Benchmark	EPA R6 Screening Benchmark	COPC (Y/N)	95% UCL	
beta-BHC	µg/kg	10	0		<2.1	<2.6			5		5	5	5	N		
delta-BHC	µg/kg	10	0		<1.9	<2.5			6400		71,500			N		
gamma-BHC (Lindane)	µg/kg	10	10	50%	<1.9	<2.6	2.8	10	4.005	3.24	3.3	3.24	4.5	N		
Chlordane	µg/kg	10	5	50%	<1.9	<2.6	2.1	2.5	2.33	1.7	1.7	1.22	4.88	4.84 <sup>1</sup>		
4,4'-DDD	µg/kg	10	10				3.5	5	4.5	3.3	3.3	3.3	1.22	2.07	4.739 <sup>1</sup>	
4,4'-DDE	µg/kg	10	10				3.8	5.2	4.43	2.07	3.3	3.3	1.42	2.07	4.978 <sup>2</sup>	
4,4'-DDT	µg/kg	10	10				3.9	5.1	4.7	1.19	3.3	3.3	1.19	1.19	Y	
Dieldrin	µg/kg	10	4	40%	<3.8	<4.9	13	41	9.62	1.9	3.3	295	2.85	Y		
Endosulfan I	µg/kg	10	0		<2	<5.5				2.9			3.26	N		
Endosulfan II	µg/kg	10	2	20%	<3.9	<5	18	22	5.795	14			1.94	Y	19.38 <sup>3</sup>	
Endosulfan Sulfate	µg/kg	10	1	10%	<4	<5	11	11		5.4			3.46	N		
Endrin	µg/kg	10	1	10%	<3.8	<5	21	21		2.22	3.3		2.22	2.67	N	
Endrin aldehyde	µg/kg	10	0		<3.6	<5					480			N		
Heptachlor	µg/kg	10	10				2.1	2.5	2.35	68			0.6	N		
Heptachlor epoxide	µg/kg	10	0		<2.6	<4.9				2.47			2.47	0.6	N	
Methoxychlor	µg/kg	10	0		<19	<26				18.7			13.6	N		
Toxaphene	µg/kg	10	0		<190	<250				0.1			0.077	N		

Notes: Units for all values are µg/kg dry weight.

<sup>1</sup> 95% Student's t UCL.<sup>2</sup> 95% Approx. Gamma UCL.<sup>3</sup> 95% KM (t) UCL.

Table 7.27 Preliminary Range of Hazard Quotients for COPECs in Sediment in the River

Chemical	Units	Average Conc.	95% UCL	Max. Detect	Threshold Effect Level <sup>1</sup>	Probable Effect Level <sup>2</sup>	Range of Hazard Quotients
Inorganic Substances							
Antimony	mg/kg	1.52	2.305	3.6	2	25	0.06 — 2
Arsenic	mg/kg	2.65	5.52	13.7	9.79	33	0.08 — 1
Chromium	mg/kg	28.2	39.97	71	43.4	111	0.25 — 2
Lead	mg/kg	49.4	235.4	312	35.8	128	0.4 — 9
Manganese	mg/kg	146	574	455	460	0.1	— 0.7
Mercury	mg/kg	0.386	0.646	1.2	0.18	1.06	0.4 — 7
Silver	mg/kg	3.44	5.77	3.44	1.000	4	0.9 — 6
Polycyclic Aromatic Hydrocarbons							
Total PAHs	mg/kg	4.62	5.58	7.43	1.61	23	0.2 — 5
Polychlorinated Biphenyls							
Total PCBs	µg/kg	23.77	27.63	35.04	59.8	676	0.04 — 0.6
PCDD/Fs							
PCDD/Fs (TEQ-mammalian)	ng/kg	82.6	124	217	0.52	1	60 — 400
PCDD/Fs (TEQ-avian)	ng/kg	102	149	264	0.7	4	30 — 400
PCDD/Fs (TEQ-fish)	ng/kg	78	120	215	0.56	NA	140 — 500

<sup>1</sup> For metals, PAHs and PCBs, the TEL was the consensus TEC; for dioxin-like chemicals (PCDDs/Fs), the threshold effect level was the lower end of the range from Oregon DEQ (2007).

<sup>2</sup> For metals, PAHs and PCBs, the PEL was the consensus PEC; for dioxin-like chemicals (PCDDs/Fs), the threshold effect level was the upper end of the range from Oregon DEQ (2007) reported in Klamath.

Table 7.28 Sampling Results from Trout Obtained from the River

Congener	Fish Sample									
	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10
TCDD	1.74	8.41	6.74	4.03	6.69	3.67	3.87	11.10	10.53	10.59
12378PeCDD	2.24	0.60	2.31	4.37	1.97	2.88	2.33	1.13	1.72	0.81
123478HxCDD	1.69	0.37	1.89	4.00	0.44	1.23	1.72	1.10	1.07	0.21
123678HxCDD	0.69	1.91	1.27	3.83	5.01	2.33	3.28	1.68	0.84	10.26
123789HxCDD	1.05	0.51	0.04	0.64	1.67	1.01	0.64	0.25	1.35	0.72
1234678HpCDD	1.27	0.98	14.59	24.51	3.67	11.99	0.76	1.20	9.62	5.12
OCDD	16.18	23.61	59.01	179.06	19.86	42.00	31.46	10.87	25.33	6.95
TCDF	0.94	0.34	0.35	0.40	0.14	1.23	0.71	0.41	1.19	0.25
12378PeCDF	1.20	1.08	1.65	1.64	0.68	1.27	1.15	2.08	2.96	2.99
23478PeCDF	9.47	15.86	7.81	8.26	15.14	35.21	9.97	18.63	13.43	28.04
123478HxCDF	0.33	0.72	1.02	1.48	2.01	0.74	0.25	0.42	0.34	3.49
123678HxCDF	0.19	0.52	0.26	0.57	0.17	0.11	0.11	0.43	0.26	0.26
123789HxCDF	2.79	1.23	1.15	3.15	0.56	1.65	1.83	0.84	1.17	0.43
234678-HxCDF	2.64	1.22	1.38	1.24	0.24	0.43	2.88	1.16	1.38	0.46
1234678HpCDF	2.20	1.21	0.89	0.90	0.20	0.42	1.47	0.71	0.74	0.24
1234789HpCDF	4.12	2.18	1.76	1.27	0.33	0.47	2.04	1.01	0.94	0.43
OCDF	17.60	40.05	56.19	123.93	21.07	36.21	28.42	8.52	27.58	11.77

Notes: Units in ng/kg wet weight.

Table 7.29 Summary Statistics and UCL Calculation for PCDD/F Congeners in Trout

Chemical	Units	N	# Det.	Freq.	Min. ND	Max. ND	Min. Detect	Max. Detect	Arith. Mean of Detections	95% UCL	Method
2378-TCDD	ng/kg	10	10	100%	—	—	1.74	11.1	6.737	8.679	95% Student's t
12378-PeCDD	ng/kg	10	10	100%	—	—	0.6	4.37	2.036	2.673	95% Student's t
123478-HxCDD	ng/kg	10	10	100%	—	—	0.21	4.0	1.372	2.007	95% Student's t
123678-HxCDD	ng/kg	10	10	100%	—	—	0.69	10.26	3.11	5.29	95% Approx. Gamma
123789-HxCDD	ng/kg	10	10	100%	—	—	0.04	1.67	0.788	1.074	95% Student's t
1234678-HpCDD	ng/kg	10	10	100%	—	—	0.76	24.51	7.371	15.55	95% Approx. Gamma
OCDD	ng/kg	10	10	100%	—	—	6.95	179.1	41.43	76.92	95% Approx. Gamma
TCDF	ng/kg	10	10	100%	—	—	0.14	1.23	0.596	0.826	95% Student's t
12378-PeCDF	ng/kg	10	10	100%	—	—	0.68	2.99	1.67	2.125	95% Student's t
23478-PeCDF	ng/kg	10	10	100%	—	—	7.81	35.21	16.18	21.42	95% Student's t
123478-HxCDF	ng/kg	10	10	100%	—	—	0.25	3.49	1.08	1.885	95% Approx. Gamma
123678-HxCDF	ng/kg	10	10	100%	—	—	0.11	0.57	0.288	0.383	95% Student's t
123789-HxCDF	ng/kg	10	10	100%	—	—	0.43	3.15	1.48	2.001	95% Student's t
234679-HxCDF	ng/kg	10	10	100%	—	—	0.24	2.88	1.303	1.811	95% Student's t
1234678-HpCDF	ng/kg	10	10	100%	—	—	0.2	2.2	0.898	1.251	95% Student's t
1234789-HpCDF	ng/kg	10	10	100%	—	—	0.33	4.12	1.455	2.12	95% Student's t
OCDF	ng/kg	10	10	100%	—	—	8.52	123.9	37.13	61.31	95% Approx. Gamma
Mammalian TEQ	ng/kg	10	10	100%	—	—	9.886	27.24	18.05	21.32	95% Student's t
Fish TEQ	ng/kg	10	10	100%	—	—	10.35	26.27	18.16	21.23	95% Student's t

Notes: Concentrations are ng/kg wet weight. Avian TEQs are not calculated here because these will be applied to the modeled concentrations in the eggs of Great Blue Heron.

“I’ll collect ‘em myself. I got a fishin’ buddy in the analytical lab we use. I’ll take him fishing, and maybe we can get a deal.”

Once back at his desk, it took the risk assessor only about 10 minutes to locate a publication on the energy requirements of trout that would enable him to calculate feeding rates.<sup>48</sup> He obtained statistics on the size of the trout from the state Department of Natural Resources and learned that the average size of year-old fish was 1 pound. He obtained data on food consumption rates and body weights for the heron and otter from EPA’s *Wildlife Exposure Factors Handbook*.<sup>49</sup> For the food chain model, he knew he would also need biota-sediment accumulation factors, and was able to put these together from a number of sources.

Then the risk assessor called his friend to plan the fishing trip. He figured between them they could get ten trout to analyze. He then called the state Department of Natural Resources and got a permit for fish collection.

The risk assessor had a successful fishing trip, and the analytical results are shown in Table 7.28. Summary statistics and ProUCL outputs are also provided in Table 7.29.

### 7.3.6 Assessment and Measurement Endpoints

From his conversation with the project manager, the risk assessor identified assessment endpoints as toxicity to growth and reproduction to fish and high-trophic level avian and mammalian piscivores. These classifications are often known as “guilds,” and are characterized by feeding strategy, food source, and trophic level. The Great Blue Heron (*Ardea herodias*) and mink (*Mustela vison*) were chosen to represent these two guilds. The most sensitive processes for the toxicity of PCDD/Fs in these guilds are reproduction and embryonic development.

Hence, the assessment endpoints would be:

- assessment of toxicity to fish;
- assessment of development risk to avian piscivore embryos;
- assessment of development risk to mammalian piscivore embryos.

The corresponding measurement endpoints would be:

- measured fish tissue concentrations;
- modeled concentrations in the eggs of avian piscivores;
- modeled PCDD/F intakes in mammalian piscivores

Generally, ecological risk assessments compare risks or concentrations in a reference area with the area under consideration. The risk assessor knew he needed a reference area that would be relatively similar to the river, but would have background levels of PCDD/Fs. It proved to be impossible to find a suitable reference area; he provided a description of his efforts in a memo to the project manager.

### 7.3.7 Toxicity Reference Values

Prior to the fishing trip, the risk assessor had planned to use bioaccumulation factors to estimate fish tissue concentrations based on those in river sediment. However, the planned fish collection would make that part of the food chain modeling unnecessary. Then his real work began—collection of appropriate toxicity reference values, and development of the exposure factors used in food chain modeling.

For TRVs in fish, the Army Corps of Engineers had published a straightforward method for deriving fish tissue benchmarks from published data.<sup>50</sup> He used the methods in that paper and the data on trout. Combining the data from this paper for Brook Trout, Lake Trout and Rainbow Trout, the geometric mean value for the no-effect level in tissue was 0.06 µg/kg and the lowest effect level in tissue was 0.104 µg/kg (Table 7.30).

Toxicity reference values derived from both laboratory- and field-based studies were used to assess the modeled concentrations in Great Blue Heron eggs. EPA had previously developed an egg-based TRV by taking the geometric mean of the effect concentrations in three Double-Crested Cormorant (*Phalacrocorax auritus*) egg-injection studies.<sup>51</sup> In these studies, PCDD/Fs were injected into cormorant eggs that were artificially incubated until hatching. Based on embryo mortality, the resulting NOAECs and LOAECs in eggs were 3670 and 11,090 ng total avian TEQ/kg wet weight respectively. In addition, field studies of Great Blue Heron that included egg collection provided field-based NOAEC and LOAEC values. In one

**Table 7.30 Derivation of No-Effect and Low-Effect Tissue Levels for Dioxin Toxic Equivalents in Trout**

Species	No-effect tissue conc.	Lowest-effect tissue conc.
Brook Trout	0.084	0.156
Brook Trout	0.135	0.185
Lake Trout	0.035	
Lake Trout	0.023	0.05
Lake Trout	0.034	0.04
Lake Trout	0.044	0.055
Lake Trout	0.034	0.055
Lake Trout	0.033	0.044
Rainbow Trout		0.279
Rainbow Trout	0.194	0.291
Rainbow Trout	0.176	0.244
Geometric Mean	0.06	0.104

*Note:* Units are ng/g or µg/kg wet weight.

study, a mean concentration of 220 ng TEQ/kg wet weight in eggs was not associated with reduction in the number of successful nests and number of fledglings per nest.<sup>52</sup> However, in a second study, Great Blue Heron eggs with a mean concentration of 360 ng TEQ/kg wet weight revealed health effects in hatchlings produced by incubation.<sup>53</sup>

The predominant environmental exposure pathway in mink is through ingestion.<sup>49</sup> A study on the mink collected from near the Saginaw River in Michigan was considered most appropriate—the study employed multiple doses and used environmental sources of PCDD/Fs that had undergone many years of weathering and were thus likely similar to the PCDD/Fs found in the river considered in this risk assessment.<sup>54</sup> Concentrations of PCBs, PCDDs, and PCDFs were measured in the diet. This study tested doses of 2.1 (control group), 22.4, 36.5, and 56.6 ng TEQ/kg (wet weight in food) over a period of approximately 120 days. Eight of the kits per dose group were also maintained on treatment dosing until they were 27 weeks old. No adverse effects on reproductive or developmental endpoints were observed at any of the doses tested. There were no statistically significant adverse effects on ecologically relevant reproductive or developmental endpoints such as breeding success, whelping success, gestation length, litter size, or survival of kits. Hence, the largest dietary dose in this study—56.6 ng TEQ/kg, wet wt. diet—is the NOAEL.

### 7.3.8 Risk Assessment Results

Risks to all receptors were assessed using a hazard quotient approach. This involved calculation of the ratio between the measurement endpoint and the TRV expressed in the same units. This process is very similar to the hazard quotient approach in human health, where the measure of risk is the ratio between an estimated intake dose and a reference dose.

#### 7.3.8.1 Development of Exposure Concentrations

Exposure concentrations for trout, Great Blue Heron and mink were calculated using a TEF approach, and measured concentrations in fish, modeled concentrations in heron eggs, and modeled ingestion doses to mink. The calculations and exposure concentrations are shown in Table 7.31.

#### 7.3.8.2 Risk to Trout

The wet weight concentrations in whole fish of 23.95 ng TEQ/kg wet weight (Table 7.31) were compared to the NOAEL and LOAEL toxicity reference values in trout (Table 7.30). Please note that the units are different, and the TRVs will need to be multiplied by 1000 to express them in similar units. Dividing the TRV values by the tissue concentrations gives a NOAEL-based hazard index (HI) of 0.4 and a LOAEL-based HI of 0.2. Hence, the risk of PCDD/Fs to trout in the river would be considered very low.

**Table 7.31 Exposure Concentrations of Toxic Equivalents of PCDD/Fs in Fish and Modeled Toxic Equivalents in Great Blue Heron Eggs, Based on Fish Tissue/Bird Egg Biomagnification Factors (BMFs)**

Congener/Group	95% UCL Concentration in Fish (ng/kg wet wt.)	Fish TEF	TEQ in Fish	Selected BMF (Fish tissue/bird egg)	Bird TEF	Modeled TEQ in GBH Eggs (ng/kg wet wt.)	Mammalian TEF	Fish Intake TEQ for Mink (ng/kg wet wt.)
TCDD	8.679	1	8.68	21	1	182.26	1	8.68
12378PeCDD	2.673	1	2.67	9.7	1	25.93	1	2.67
123478HxCDD	2.007	0.5	1.00	125	0.05	125.44	0.1	0.20
123678HxCDD	5.29	0.01	0.05	154	0.01	8.15	0.1	0.53
123789HxCDD	1.074	0.01	0.01	125	0.1	1.34	0.1	0.11
1234678HpCDD	15.55	0.001	0.02	154	0.001	2.39	0.01	0.16
OCDD	76.92	0.0001	0.01	174	0.0001	1.34	0.0001	0.01
TCDF	0.826	0.05	0.04	0.42	1	0.02	0.1	0.08
12378PeCDF	2.125	0.05	0.11	32	0.1	3.40	0.05	0.11
23478PeCDF	21.42	0.5	10.71	32	1	342.72	0.5	10.71
123478HxCDF	1.885	0.1	0.19	15	0.1	2.83	0.1	0.19
123678HxCDF	0.383	0.1	0.04	15	0.1	0.57	0.1	0.04
123789HxCDF	2.001	0.1	0.20	15	0.1	3.00	0.1	0.20
234678HxCDF	1.811	0.1	0.18	15	0.1	2.72	0.1	0.18
1234678HpCDF	1.251	0.01	0.01	15	0.01	0.19	0.01	0.01
1234789HpCDF	2.12	0.01	0.02	15	0.01	0.32	0.01	0.02
OCDF	61.31	0.0001	0.01	5.7	0.0001	0.03	0.0001	0.01
Exposure concentrations in fish tissue, bird eggs and intakes for mink (TEQ ng/kg wet weight)					23.95	948.3		23.90

### 7.3.8.3 Risk to Great Blue Heron

The risk to Great Blue Heron was assessed as the ratio of the modeled wet weight concentrations in eggs to the NOAEL and LOAEL values of 220 and 360 ng TEQ/kg wet weight, discussed above. The modeled TEQ in Great Blue Heron eggs was 948.3 ng TEQ/kg wet weight (Table 7.31). The NOAEL-based HI would be 4, and the LOAEL-based HI would be 3. Hence, the predicted risk to Great Blue Heron using the field-based TRVs would warrant further investigation—possibly, the collection of bird eggs for PCDD/F analysis. However, using the laboratory-based TRVs (NOAEL = 3670 ng/kg; LOAEL = 11,090 ng/kg), the NOAEL-based HI would be 0.3, and the LOAEL-based HI would be 0.09.

### 7.3.8.4 Risk to Mink

The exposure factors for the mink are shown in Table 7.32. Again, care with unit conversions is warranted. A mink weighing 550 g would consume 121 g of food per day. For this assessment, trout were assumed to compose 100% of the diet. Hence, using the intake concentration for mink from Table 6.31, the daily intake of TEQ would be 2.89 ng/day and the daily dose would be 5.26 ng/kg BW/day. This value is over ten-fold lower than the NOAEL of 56.6 ng/kg/d, and the HI would be 0.1.

The risk assessor also prepared a summary table so that all the information would be in one place. This table is not shown; instead, one of the exercises at the end of the chapter is to prepare such a summary table.

### 7.3.9 Scientific Management Decision Point #2

“So the only hazard indexes above 1 are the heron, and that’s only for the field-based TRVs, right?” asked the project manager, perusing the tables the risk assessor had prepared. “Highest risk is 4—that’s not much.”

“I agree,” said the risk assessor. “You mentioned a paper mill. Do you know any more about that? If any sediment from the lake got flushed into the river, that could account for these dioxin levels. I really don’t think this came from the pond—otherwise, I think we’d see some PCBs, and the PAHs would likely be higher as well.”

**Table 7.32 Exposure Factors for the Mink**

Functional Group	Default Primary Indicator Species	Body Weight (BW) (kg)	Food Ingestion Rate (g wet wt./g-d)	Dietary Composition	Water Ingestion Rate (g/g-d)	Home Range (HR) (ha)
Freshwater mammalian piscivore	Mink ( <i>Mustela vison</i> )	0.55	0.22	Trout 78% Forage fish 9% Arthropods 13% Assumed all trout	0.11	20.4

“There’s no way to clean up,” she said. “I can’t make a case for dredging an internationally famous trout fishery and then hoping the fishing will recover.”

“Agreed. Here’s what I’ll do—write up the results and show the range of HQs for each receptor. I think you can make a case that there’s no real risk to the birds—and if there’s still some concern, I can set up to collect eggs and have them analyzed.”

“I hate to do things like that,” she said. “Collecting new data, well, you don’t know where it’ll lead. Besides, I like birds. I’d rather those eggs turn into birds than data.”

“Yeah, but we might really need those egg results to put this to bed,” said the risk assessor. “I can do it myself, but I need a team of two other guys. One has to be a tree climber, spikes and all. I know where to hire them. The eggs are in the nests about the end of May, and hatch from July 1 on. So we’ve got a little time.”

“I’ll get back to you on that,” she said. “Anyway, now you have fish concentrations, there’s one other thing I need—human health. If there’s no risk to people, it’ll be easier to communicate no risk to critters.”

“Sorry,” said the risk assessor. “Can’t help you there. My esteemed colleague Joe, who sits in the next office from me, does human health. I’ll tell him to come and see you.”

“You can’t do it?”

“Nope. I don’t do human health. But then Joe doesn’t fish, nor does he know how to collect bird eggs.”

“Geez! And I thought we were siloed!”

## 7.4 EXERCISES FOR THOUGHT AND DISCUSSION

### 7.4.1 Summary Table

Prepare a summary table of risks from the ecological risk assessment shown here. Realize that the details such as TEQ, the many calculations, may not be of great interest to the project manager. What is the most relevant information? What is the most uncertain information? How can the risks and uncertainties be best communicated in a single table?

### 7.4.2 Toxicity Equivalence Factors for Wildlife

Please use the internet to obtain a copy of Van den Berg et al. (1998) “Toxic equivalency factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife,” *Environ Health Perspect* 106:7455–792. Also, download EPA’s *Framework for Application of the Toxicity Equivalence Methodology for Polychlorinated Dioxins, Furans and Biphenyls in Ecological Risk Assessment* from [www.epa.gov/risk/framework-application-toxicity-equivalence-methodology-polychlorinated-dioxins-furans-and](http://www.epa.gov/risk/framework-application-toxicity-equivalence-methodology-polychlorinated-dioxins-furans-and). After reading both documents, can you think of any ways to improve the risk assessment presented in this chapter?

### 7.4.3 Ecological Risk Assessment of the Former Gold Mine

Using the data provided in Chapter 6 on the former gold mine, prepare a screening level ecological risk assessment. Assume the gold mine is in Alaska, and try to find state-specific guidance that will direct your efforts. This guidance is available on the internet.

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## CHAPTER 8

# Bias, Conflict of Interest, Ignorance, and Uncertainty

## *Where Are We Heading?*

The real purpose of the scientific method is to make sure nature hasn't misled you into thinking you know something you actually don't know.

**Robert M. Pirsig**

*Zen and the Art of Motorcycle Maintenance: An Inquiry into Values*

The present geologic epoch has come to be called the “Anthropocene” in the popular press. The name signifies the increasing effect of humans on the global environment. In 2012, the National Research Council (NRC) pointed out that the problems faced by humans in the Anthropocene epoch are “wicked problems.” Wicked problems have multiple causes, are resistant to solutions, difficult to define, and socially and politically complex, with multiple stakeholders holding differing views on both the desired outcome and how it should be achieved. Furthermore, wicked problems span the understanding of several scientific disciplines, each with a set of “deep” uncertainties surrounding the problem.<sup>1</sup>

Attempts to solve wicked problems, however well meant, are doomed to fail. These problems occur on very large scales, both temporal and social. The situation engendering a wicked problem likely possesses multiple unknown interactions and feedback loops that will likely respond in unpredictable ways to any intervention or attempted solution. It is exactly the intractability of wicked problems that reveals the hubris in the attitude of “just do something” that underlies the precautionary principle.<sup>2</sup>

### 8.1 RISK AND RESILIENCE

A growing recognition among scientists and decision-makers is that the “unknown unknowns” will get you—whatever you do. The idea of the “unknown unknowns” was made popular in a 2002 speech by US Secretary of Defense Donald Rumsfeld.<sup>3</sup>

Shortly before Rumsfeld's speech, Nassim Nicholas Taleb, author of *The Black Swan: The Impact of the Highly Improbable*, gave a speech at the Department of Defense and likely spurred Rumsfeld's thinking.<sup>4</sup> Taleb and a growing number of thinkers in the disciplines of social science, economics, cognitive science, and philosophy share the view that the current sense of disruption and vulnerability stemming from the volatility of today's world will require an adaptive shift toward resilience—the ability to bounce back from unforeseen shocks and surprises. The need for resilience is all too evident in the often-devastating severe weather incidents such as tornados and flooding that appear to be increasing as a part of climate change.<sup>5,6</sup> Taleb has characterized this ability as anti-fragility—the idea embodied in the famous quote by Friedrich Nietzsche from *The Twilight of the Idols*, “What does not kill me, makes me stronger.”<sup>7,8</sup>

This idea of resilience and strength through adversity has been popularized in two popular songs, both named “Stronger,” by Kanye West and Kelly Clarkson. One can guess about the extent of unknown unknowns in any problem situation, and increasingly, the expectation that scientific predictions can provide a sufficient basis for decision-making seems like so much fake news. The body of scientific knowledge, whether weak or compelling, is irrelevant in the face of the unknown unknowns. Indeed, risk analysis itself seems out of place in an unpredictable world. So why bother?

### 8.1.1 Fear and Possibilistic Thinking

Fear of the unknown unknowns spawned the precautionary principle and the advent of possibilistic (as opposed to probabilistic) risk assessment. The claim that risk assessment is accurate because it is based on science cannot be supported—science is based on evidence, and the accumulation of evidence is never complete. The sense of disruption and vulnerability experienced by many in society today has engendered an expectation of the worst possible outcomes and a fatalistic view of the future.<sup>9–11</sup>

Those who hold this view find it easy to see the current problem as too difficult or complex to understand, and so ask, “Why bother?” This view of the world diminishes the potential for scientific understanding or advancement and exacerbates the sense of impotence. Those who espouse the precautionary principle and possibilistic risk assessment thrive on a sense of panic.<sup>12</sup> These “fear entrepreneurs” actively promote the idea that the dangers faced by humankind in the 21st century are so catastrophic and the need to address these dangers so immediate and overwhelming that decision-makers simply cannot wait for the information that would inform their decisions.<sup>10,13</sup>

Possibilistic thinking attempts to transmit the cultural pessimism of the fear entrepreneurs to the public in the “sheep’s clothing” of science. However, the precautionary principle and possibilistic thinking are, in fact, anti-science, with a cavalier attitude towards evidence. Several years ago, a bumper sticker was given away at the annual meeting of the Society for Environmental Toxicology and Chemistry which read: “We don’t need no stinkin’ statistics.”\* Embodied in this attitude is the precautionary motto: “Absence of evidence is not evidence of absence.” In *An Essay Concerning Human Understanding*, written in 1689, John Locke legitimized this

\* This is a paraphrase of the statement “We don’t need no stinkin’ badges” from the 1948 Humphrey Bogart film *The Treasure of the Sierra Madre*.

belief, calling it an “argument from ignorance.”<sup>14</sup> In general, Locke was logically correct; his thinking was based on the notion that all evidence was of high quality and incontrovertible. But scientific evidence is of varying quality, both high and low—study design, statistical power, risk of bias, and other aspects of evidentiary quality must be taken into account when basing decisions on scientific information.

What this argument from ignorance proposes for decision-making in the face of uncertainty is that acting on the basis of an absence of evidence is equally valid as acting on the basis of evidence. The sentiment behind the argument from ignorance is that it is precisely the absence of evidence that constitutes the proof that precautionary action needs to be taken.

Logically, the absence of any evidence of harm from these chemicals does not mean the chemicals observed ubiquitously in our bodies are not producing harm. This is the position of the National Research Council in its 2006 report on human biomonitoring. The NRC opines:

absence of evidence of effects is not identical with evidence of absence of effects—a distinction that must be clear to constituents. Otherwise there is a large practical communication and ethical risk attached to simply saying that the presence of chemicals in human tissue does not imply health effects.<sup>15</sup>

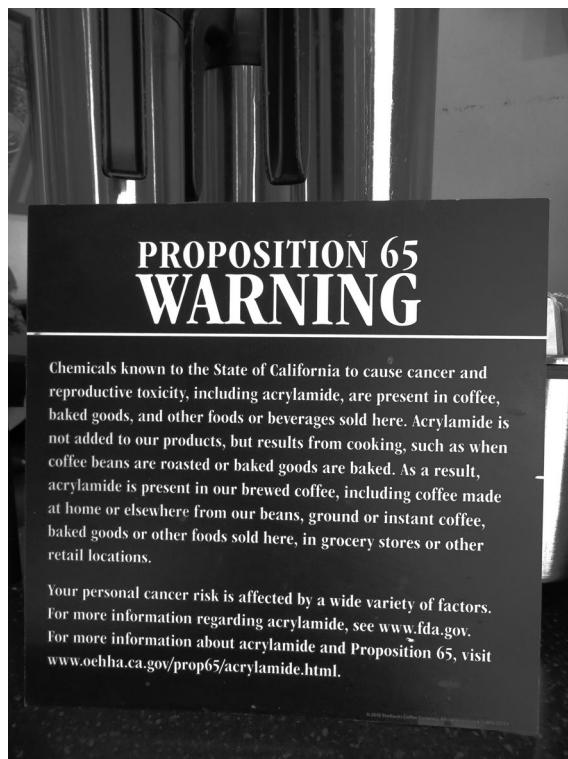
The presence of measurable, albeit vanishingly tiny, concentrations of environmental chemicals within our bodies pales in comparison to the increase in the human lifespan in the developed world that occurred simultaneously with the increase of the number of chemicals in commerce during the 20th century.

Many individuals in the United States and other developed nations have become so risk-averse and potentially litigious that every human experience comes with a health warning. Proposition 65 in California requires warning labels for carcinogens. Until very recently, every Starbucks in California was required by the state to post a warning that the carcinogen acrylamide is present in the coffee and pastries one could otherwise be enjoying (Figure 8.1).

In 2010, the Council for Education and Research on Toxics (CERT), a non-profit group founded in 2002 by Martyn Smith, a professor at UC Berkeley, sued Starbucks and other coffee companies under Proposition 65 for failing to warn consumers about acrylamide in coffee.<sup>16</sup> After eight years of litigation by the coffee producers against CERT, Judge Elihu Berle of the Los Angeles County Superior Court ruled in favor of CERT in March of 2018. In June of 2018, the California Office of Environmental Health Hazard Assessment (OEHHA) announced it was siding with science and issued a notice of rulemaking as follows:

Exposures to Proposition 65-listed chemicals in coffee that are produced as part of and inherent in the processes of roasting coffee beans and brewing coffee pose no significant risk of cancer.<sup>17</sup>

Fear entrepreneurs are largely responsible for these campaigns that use chemical exposure and other public health issues to devalue knowledge and institutionalize ignorance. These unscrupulous purveyors of fear seem to feel no compunction in exploiting the general lack of scientific literacy.



**Figure 8.1** Proposition 65 warning about acrylamide in coffee and pastries seen in a Starbucks coffee shop in California.

One reason for this lack is that scientific education in primary and secondary school concentrates on learning science as information—with little attention given to critical thought, logic, and the scientific method. The ability to reason and think critically about science is a necessary life skill: without this ability, how can one discuss treatment options with one's physician or give informed consent for a medical procedure? The lack of general scientific literacy in the world today represents a significant educational failure and will have consequences for years to come. The body of scientific knowledge will always be a work in progress, and every science-based decision will bear a level of uncertainty.

The fear mongering that appears in popular culture is based on the discomfort many people feel about engaging with and comprehending uncertainty. The attacks on science by Peter Waldman of the *Wall Street Journal* and Mark Obmascik of the *Denver Post* were discussed earlier in this book, and are examples of such fear mongering. The overall result is a mood of confusion, pessimism, vulnerability, powerlessness, and the institutionalization of insecurity that has pushed environmental regulatory agencies to embrace probabilistic risk assessment and chase phantom cancer risks based on Herman Muller's lie in his Nobel Prize speech.

### 8.1.2 Key Characteristics of Carcinogens and IARC Monographs

In 2015, Martyn Smith and co-workers from the International Agency for Research on Cancer (IARC), EPA and various universities published a paper in the journal *Environmental Health Perspectives* describing ten key characteristics of carcinogens (KCCs), holding that a KCC:

- is electrophilic or can be metabolically activated;
- is genotoxic;
- alters DNA repair or causes genomic instability;
- induces epigenetic alterations;
- induces oxidative stress;
- induces chronic inflammation;
- is immunosuppressive;
- modulates receptor-mediated effects;
- causes immortalization;
- alters cell proliferation, cell death or nutrient supply.

The KCCs represent an attempt to repurpose the hallmarks of cancer to describe specific chemical characteristics, rather than the acquired characteristics of cancer cells that provide the Darwinian selective advantage discussed in Chapter 5.<sup>18,19</sup> The KCCs are an outgrowth of the position of IARC on mode of action (MOA) that questions whether an MOA approach, as suggested in both EPA and World Health Organization guidance, would be useful in informing cancer hazard identification. IARC divides substances into five groups, based on the group's evaluation of cancer hazard:

- Group 1: carcinogenic to humans;
- Group 2A: probably carcinogenic to humans;
- Group 2B: possibly carcinogenic to humans;
- Group 3: not classifiable as to its carcinogenicity to humans;
- Group 4: probably not carcinogenic to humans.

The KCCs resulted from a loose relationship between the prior identification of a substance as “carcinogenic” by IARC, i.e., Groups 1, 2A, or 2B, and whether the substance could be implicated in one or more key mechanisms involved in human carcinogenesis.<sup>20</sup> These key mechanisms were not identified in the paper. The later work of Smith and co-workers identified those mechanisms by a judgment-based approach, and paved the way for ToxCast™/Tox21 data to be used in IARC hazard evaluations.<sup>21</sup>

Expert panels convened by IARC assigned various high-throughput *in vitro* assays to seven of the ten KCCs and used these to elevate causal determinations from probable (IARC Group 2A) to known (Group 1) human carcinogen, from possible (Group 2B) to probable (Group 2A), and from not classifiable (Group 3) to either possible (Group 2B) or probable (Group 2A).<sup>22</sup>

In 2016, following the publication of the KCCs, Dr. Richard A. Becker, director of the Long Range Initiative Program at the American Chemistry Council, recruited

a team of scientists to critically examine the use of the KCCs for identifying cancer hazard and the assignment by IARC of high-throughput screening (HTS) assays to the KCCs. This effort relied on a set of data-rich chemicals evaluated as either carcinogenic or non-carcinogenic chemicals identified by EPA's Office of Pesticide Programs' Cancer Assessment Review Committee for carcinogenic hazard; the designation was based on good laboratory practice (GLP)-conducted rodent cancer bioassays using EPA or Organisation for Economic Co-operation and Development test guidelines. A variety of statistical prediction methods to examine whether or not the set of HTS assays linked by IARC to seven out of ten KCCs could indeed predict. ToxCast™ data were available for 54 chemicals identified by EPA as carcinogenic and 194 identified as non-carcinogenic.

The paper was initially submitted to *Environmental Health Perspectives* as a brief 5000-word commentary, but editor Martin van den Berg of Utrecht University in the Netherlands declined to send it out for review because it was "too statistical." Shortly after submission, scientists in EPA's ToxCast™ program published an evaluation of non-specific responses in the HTS assays. These non-specific responses were identified as concentration-dependent burst activity indicative, and were observed both in cell-free biochemical assays and as cytotoxicity in cell-based assays.<sup>23</sup> IARC did not account for this burst activity when evaluating the assays to predict carcinogenic hazard.

Following this early publishing setback, Becker's team of scientists conducted their evaluations again, this time using the HTS data corrected for cytotoxicity. Whether the ToxCast™/Tox21 data were analyzed with and without adjusting for the cytotoxicity burst effect, the ability to predict cancer hazard for KCCs alone or in combination was no better than chance.<sup>22</sup> In 2018, the Risk Assessment Specialty Section (RASS) awarded this effort "best paper of the year." That recognition was no doubt gratifying to Becker and his team, but did not stop the organizers of the RASS webinar series inviting Martyn Smith to present a webinar early in 2019.

The hallmarks of cancer provide a conceptual basis for the functional characteristics of tumor cells that have undergone malignant transformation. The purpose of identifying the hallmarks was to make sense of the complexity of tumorigenesis and the wide variety of tumor types. The goal was to advance the treatment of cancer:

With holistic clarity of mechanism, cancer prognosis and treatment will become a rational science, ... One day, we imagine that cancer biology and treatment—at present, a patchwork quilt of cell biology, genetics, histopathology, biochemistry, immunology, and pharmacology—will become a science with a conceptual structure and logical coherence that rivals that of chemistry or physics.<sup>18</sup>

These hallmarks occur through basic cellular processes; three such processes associated with development of cancer hallmarks are: (1) epigenetic changes, including alterations of DNA methylation in critical portions of the genome, (2) epistasis or gene–gene interactions, and (3) dysregulation of cellular energetics.

The phenotypic fate of developing cells depends on activation of coordinated programs of gene expression during the appropriate time window. The state of

chromatin is a significant factor in enabling these programs to occur. DNA methylation, histone alteration, and movement of chromosomes within the nucleus to bring appropriate genes into the transcription compartment all play a role.<sup>24–28</sup> Epistasis occurs when the expression of a gene at a specific locus is dependent on the ongoing genetic background: in other words, the interaction between different genes that affects gene expression. Epistasis occurs during both normal development and tumorigenesis.<sup>29,30</sup> The use of big data on gene expression and machine learning is revealing epistatic interactions underlying a variety of diseases.<sup>31</sup> Cancer cells rely more heavily on glycolysis than on oxidative phosphorylation for their energy needs, and in terms of energetics, resemble single-celled organisms during the early history of the earth when oxygen was absent. As life on earth evolved, the transition to aerobic metabolism also occurred, with the concomitant development of anti-oxidant systems to prevent the toxicity of reactive oxygen species generated by aerobic metabolism. Unlimited growth capacity was a feature of these early organisms, and is shared with cancer cells.<sup>32</sup>

The “bad luck” theory of cancer discussed in Chapter 3 seems to be only part of the story of tumorigenesis. The epigenetic, transcriptional, and metabolic changes discussed above enable cell proliferation that increases the likelihood of a “bad luck” mutation and progress to cancer.<sup>33</sup>

### 8.1.3 Risk Assessment Is about Probabilities, Not Possibilities

The fear entrepreneurs have rejected evidence-based decision-making and the idea of risks as probabilities. Given that their message is to view innovation and “thinking outside the box” with dread and loathing, these merchants of fear reject as irresponsible and dangerous any sort of risk evaluation that honestly considers probabilities.

The pioneers of risk estimation were gamblers—Pascal, Galileo, Bernoulli—they possessed a gambler’s hope, and they longed for a challenge.<sup>34</sup> The fear entrepreneurs would likely not have been able to influence them. The best practice of risk assessment determines the most accurate probabilities of various outcomes to inform decisions. The numbers that were calculated in Chapter 6 of the likelihood of cancer were probabilities. In fact, probabilistic risk assessment has been fully endorsed in the risk assessment community.<sup>35–37</sup> Probabilistic thinking offers a concrete approach to problem solving, and a positive outlook. The argument made by the advocates of possibilism is that because the threats faced by humanity are unknown, there is insufficient information upon which to base any realistic estimate of probabilities.

The next chapter begins with a quote from William Faulkner’s Nobel Prize acceptance speech—a message of hope that speaks of the infinite capabilities of humankind to better its fortunes. This chapter begins with a trenchant statement about the scientific method. The preface to the book noted the personal value of entering a field that needs new blood and quick young minds capable of engaging in the details of a field of exponentially growing complexity. An environmental risk practitioner who can see the practical side of an issue, but who has scientific ability as well as the ethics and confidence to challenge the norms, will be in constant demand.

If you believe in the power of science to enable humankind to know and understand the world, then you also believe a good faith, science-based risk assessment provides a valuable and necessary decision tool. This viewpoint is exactly where those on the leading edge of environmental risk assessment in the 21st century have landed.

## 8.2 21ST-CENTURY RISK ASSESSMENT: NEW DATA SOURCES AND NEW METHODS

The 21st century is indeed an exciting time to be entering the field. There are so many new methods and types of data to be considered and potentially used for informing risk assessment. Several of these will be discussed here. It seems doubtful they will completely supplant traditional risk assessment methodology that was presented in the previous chapters of this book. However, scientists are just beginning to learn how to use the new methods and data, and in such a situation, a good idea is an opportunity—just like the old advice about a better mousetrap.

However, there are philosophical and conceptual roadblocks to the implementation of these new methods, and after presentation of the new data and tools, these obstacles will be considered.

### 8.2.1 Toxicity Testing in the 21st Century

Risk assessment and regulation of chemicals are in the midst of transformation in terms of data sources and the manner in which the data are translated into evidence to support risk management. Some of the reasons are: (1) the growing number of substances in commerce for which there exist little or no toxicity information, (2) animal welfare concerns, and (3) the realization that the results of high-dose *in vivo* animal testing do not represent responses in a heterogeneous human population exposed to much lower doses.

Recent advances in toxicogenomics, bioinformatics, systems biology, and computational toxicology are both remarkable and humbling. The goal of 21st-century toxicology is to change the nature of toxicity evaluations and transform hazard evaluation and risk assessment from a system that uses high-dose *in vivo* animal bioassays to one based primarily on computational profiling and *in vitro* methods. If this transformation is to be successful, a clear focus is needed for identifying relevant human health risks with a defined degree of confidence from the *in vitro* results. Initially, these results would be used for prioritization and screening of chemicals; with time and experience, hazard prediction may be possible.<sup>38–47</sup>

To implement this *in vitro* testing, EPA has initiated a number of activities in an effort to incorporate the use of high-throughput/high content (HT/HC) *in vitro* assays into risk assessment. The most visible of these is EPA's ToxCast™ program, consisting of a battery of both commercial and publicly developed HT/HC assays. Initially, the ToxCast™ approach has been designed to utilize the vast array of commercially available HT/HC assays to screen substances of interest to EPA. ToxCast™ is

part of EPA's contribution to a collaboration that includes the Food and Drug Administration and the National Institutes of Health.

This approach has both advantages and disadvantages, and the two primary areas of discussion are validation of the assays and the use of prediction models.<sup>47–51</sup> Many of these commercial methods used in ToxCast<sup>TM</sup> are proprietary, so details about assay development, replicability, sensitivity, and specificity are not necessarily available for independent evaluation and scientific peer review—in many ways, these proprietary assays are “black boxes.” However, one distinct and obvious advantage is that these assays can be robotically automated to generate data very quickly.

The majority of high-throughput (HT) and high-content (HC) advanced screening techniques that are currently being applied in ToxCast<sup>TM</sup> were first developed for pharmaceutical purposes, and were adapted for screening of commodity and environmental chemicals. In the pharmaceutical industry, the assays are used to search for likely drug candidates with potent biological activities already predicted by computational methods such as quantitative structure–activity relationships (QSAR). In contrast, commodity chemicals are selected based their physicochemical properties, with the goal of improving the specific performance of a product—commodity chemicals typically possess much lower biological activity than do drug candidate molecules.

This difference between commodity chemicals and drug candidates begs the question of whether these *in vitro* assays are even capable of producing meaningful results in a risk assessment context. First, exposure must be considered, and testing commodity chemicals at artificially high concentrations in HT/HC assay systems simply to elicit measurable responses will obviously have little or no real-world significance. Second, each assay or collection of assays must be anchored in biological knowledge—without this anchor, neither evaluation of the biological context within one or more modes of action nor an understanding of the meaning of the assay doses in terms of real-world exposures is possible.<sup>52–55</sup>

### **8.2.1.1 Details of ToxCast<sup>TM</sup>**

Phase 1 of ToxCast<sup>TM</sup>, was completed in 2009 and profiled over 300 well-studied chemicals, primarily pesticide active ingredients.<sup>56</sup> The entire Phase 1 ToxCast<sup>TM</sup> dataset is available at <http://epa.gov/ncct/toxcast/data.html>. ACToR stands for the Aggregated Computational Toxicology Resource.<sup>57</sup> ACToR is an online database that is EPA's online warehouse of publicly available chemical toxicity data, including ToxCast<sup>TM</sup>. Table 8.1 shows assay results for 17 $\beta$ -estradiol and the pesticide methoxychlor in two ToxCast<sup>TM</sup> assays from Attagene that measure gene transactivation by the estrogen receptor; Figure 8.2 shows plots and Hill model fits to these data. The Hill model is one of the continuous models in EPA's Benchmark Dose Software discussed in Chapter 3. For completeness, the Hill model equation is shown in Figure 8.2. As an exercise, look up the EC<sub>50</sub> values for methoxychlor in estrogenic assays in EPA's CompTox Dashboard at <https://comptox.epa.gov/dashboard>. Type “methoxychlor” in the search bar, and when the screen changes, click on “Bioactivity” in the list on the left of the screen. Choose “EDSP21” from the list to view the assay results (EDSP21 stands for Endocrine Disruptor Screening Program 21st Century). From

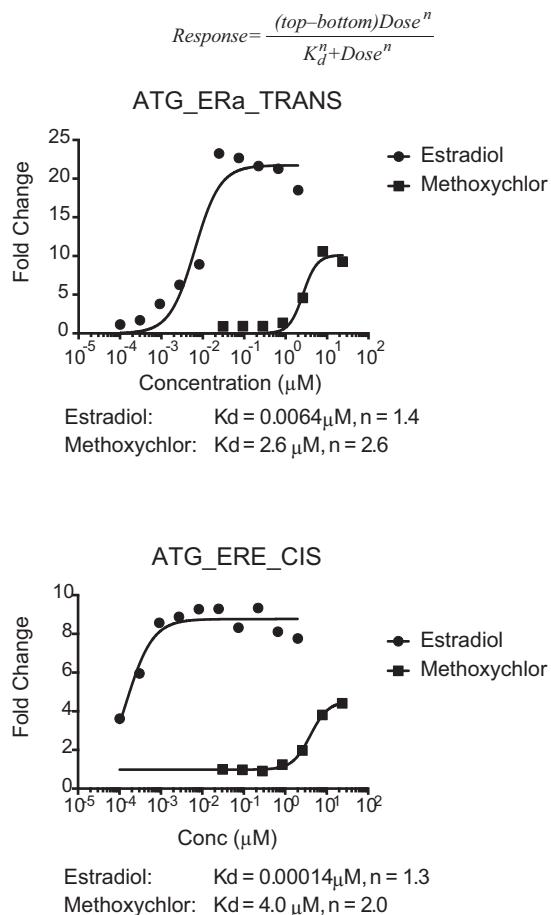
Table 8.1 ToxCast™ Data for Estradiol and Methoxychlor from the Attagene (ATG) Assays Related to Estrogenic Effects

Sourcename SID	CASRN	Chemical Name	Assay Component	Concentration (µm)	Value	Value Type
PC01		Estradiol	ATG_ERa_TRANS	0.000101611	1.158695025	fold_change
PC01		Estradiol	ATG_ERa_TRANS	0.000304832	1.692233664	fold_change
PC01		Estradiol	ATG_ERa_TRANS	0.000914495	3.793282648	fold_change
PC01		Estradiol	ATG_ERa_TRANS	0.002743484	6.27312097	fold_change
PC01		Estradiol	ATG_ERa_TRANS	0.0008230453	8.936194784	fold_change
PC01		Estradiol	ATG_ERa_TRANS	0.024691358	23.26166875	fold_change
PC01		Estradiol	ATG_ERa_TRANS	0.074074074	22.6788567	fold_change
PC01		Estradiol	ATG_ERa_TRANS	0.222222222	21.63025695	fold_change
PC01		Estradiol	ATG_ERa_TRANS	0.6666666667	21.28919257	fold_change
PC01		Estradiol	ATG_ERa_TRANS	2	18.52064286	fold_change
PC01		Estradiol	ATG_ERe_CIS	0.000101611	3.617676324	fold_change
PC01		Estradiol	ATG_ERe_CIS	0.000304832	5.957038338	fold_change
PC01		Estradiol	ATG_ERe_CIS	0.000914495	8.570793093	fold_change
PC01		Estradiol	ATG_ERe_CIS	0.002743484	8.881709102	fold_change
PC01		Estradiol	ATG_ERe_CIS	0.0008230453	9.27690957	fold_change
PC01		Estradiol	ATG_ERe_CIS	0.024691358	9.297512438	fold_change
PC01		Estradiol	ATG_ERe_CIS	0.074074074	8.320749195	fold_change
PC01		Estradiol	ATG_ERe_CIS	0.222222222	9.338718174	fold_change
PC01		Estradiol	ATG_ERe_CIS	0.6666666667	8.110974539	fold_change
PC01		Estradiol	ATG_ERe_CIS	2	7.766344747	fold_change
DSSTOX_40522	72-43-5	Methoxychlor	ATG_ERa_TRANS	0.030786013	0.906776181	fold_change

(Continued)

Table 8.1 (Continued)

Sourcename SID	CASRN	Chemical Name	Assay Component	Concentration ( $\mu\text{m}$ )	Value	Value Type
DSSTOX_40522	72-43-5	Methoxychlor	ATG_ERa_TRANS	0.09329095	0.922053388	fold_change
DSSTOX_40522	72-43-5	Methoxychlor	ATG_ERa_TRANS	0.282699848	0.93338809	fold_change
DSSTOX_40522	72-43-5	Methoxychlor	ATG_ERa_TRANS	0.856666206	1.365555216	fold_change
DSSTOX_40522	72-43-5	Methoxychlor	ATG_ERa_TRANS	2.5959582	4.597453799	fold_change
DSSTOX_40522	72-43-5	Methoxychlor	ATG_ERa_TRANS	7.86654	10.58464066	fold_change
DSSTOX_40522	72-43-5	Methoxychlor	ATG_ERa_TRANS	23.838	9.274828257	fold_change
DSSTOX_40522	72-43-5	Methoxychlor	ATG_ERE_CIS	0.030786013	0.9977885196	fold_change
DSSTOX_40522	72-43-5	Methoxychlor	ATG_ERE_CIS	0.09329095	0.977945619	fold_change
DSSTOX_40522	72-43-5	Methoxychlor	ATG_ERE_CIS	0.282699848	0.912688822	fold_change
DSSTOX_40522	72-43-5	Methoxychlor	ATG_ERE_CIS	0.856666206	1.249848943	fold_change
DSSTOX_40522	72-43-5	Methoxychlor	ATG_ERE_CIS	2.5959582	1.975830816	fold_change
DSSTOX_40522	72-43-5	Methoxychlor	ATG_ERE_CIS	7.86654	3.812084592	fold_change
DSSTOX_40522	72-43-5	Methoxychlor	ATG_ERE_CIS	23.838	4.409195062	fold_change



**Figure 8.2** Hill model fits of  $17\beta$ -estradiol and methoxychlor from two of Attagene transcription assays in the ToxCast™. The equation for the Hill model is shown above the two plots.

the plots, what else can you say about the potency and intrinsic activity of methoxychlor relative to estradiol?

In conjunction with ToxCast™ Phase 1, EPA assembled a large database of mammalian *in vivo* toxicity data for these substances from pesticide registration studies submitted to EPA. This database is known as ToxRefDB. This resource was developed to help facilitate investigations of the correlations between ToxCast™ results and *in vivo* effects.

ToxCast™ is based on the premise that toxicity is driven by interactions between chemicals and biomolecular targets. Since these targets, and indeed the modes of action for most chemicals, have yet to be fully understood, the focus of ToxCast™ is a multiple-target matrix with multiple data domains ordered in terms of increasing biological relevance and increasing cost.<sup>58</sup>

Phase 1 of ToxCast™ was meant to be a proof-of-concept phase using approximately 300 substances for which extensive animal testing results were available. These chemicals were chosen to afford the opportunity to determine the correspondence between the resulting ToxCast™ data and *in vivo* results.<sup>59</sup>

Activity profiles of the Phase 1 ToxCast™ chemicals have to date revealed both expected and unexpected results for chemicals in signaling and metabolic pathways.<sup>56</sup> Phase 2 of ToxCast™, which commenced in 2010, is currently screening almost 1000 chemicals from industrial and consumer products, food additives, and failed pharmaceuticals using the assays as in Phase 1 and some additional assays.<sup>60</sup>

ToxCast™ activities are ongoing, and information on progress is continually emerging. Not all the data and information are currently available, and this creates an unfortunate impression of lack of transparency. Sharing and publicizing details about the assays and the prediction models fosters scientific debate and leads to a demonstration of the true level of rigor of the methods.

### **8.2.1.2 Knowledge of Mode of Action Is Necessary to Understand and Use ToxCast™ Results**

Mode of action is the main focus of EPA's *Guidelines for Carcinogen Risk Assessment*.<sup>61</sup> MOA should be the main focus of the way in which to use the results of *in vitro* assays and HT/HC advanced screening approaches. One of the uses of MOA is to address the question of human relevance of responses observed in animals, and MOA should also be used to determine the human relevance of responses from *in vitro* assays and HT/HC approaches.<sup>40,62,63</sup>

Knowledge of MOA should also be used to inform the prediction models used for translating assay results to real-world exposures. Therefore, these predictive models must be built upon a firm understanding of the interaction of a substance with all relevant biological processes. Knowledge of toxicokinetics, toxicodynamics, and dose-response relationships of key events is needed for a full exploration of the MOA underlying an adverse outcome. Ideally, individual assays or assay suites will be associated with biomarkers or measured biological responses. If the quantitative relationships (1) between the assay results and the biomarkers associated with the assays and (2) between the biomarkers and the occurrence of adverse effects both become known, then the assays can be used for hazard prediction and the vision of expressed by NRC in *Toxicity Testing in the 21st Century* will be realized.<sup>64,65</sup>

A weight of evidence approach will be needed to examine the evidentiary support (or lack of it) between assay results, biomarkers, and disease.<sup>66–68</sup> Toxicity pathways are, in fact, biological response pathways, and in general, they are either linked or identical to normal cellular response pathways that maintain homeostasis and normal function in the face of both internal and external stressors. Toxicity can be thought of as failure of homeostasis and resulting maladaptive and biologically inappropriate activity in these response pathways.

The measurable events further down the pathway that are experimentally or toxicologically associated with the adverse outcome may be observable by biomarkers.

If necessary to the occurrence of the adverse outcome, an event is truly a key event in the MOA.<sup>69–71</sup>

### **8.2.1.3 Early Prediction Models**

Early in the history of ToxCast<sup>TM</sup>, hazard prediction was both the primary goal and primary challenge.<sup>58</sup> However, the use of biochemical or genomic assays to build predictive models of toxicity was limited because of incomplete knowledge of the underlying biology. Some studies used regression/correlation approaches to examine the relationship between *in vivo* lower exposure limit values and *in vitro* half-maximal activity concentration (AC50) values from ToxRefDB and ToxCast DB respectively.<sup>60</sup> In addition, the occurrence of cytotoxicity as a “false positive” in many HTS assays needed to be identified.<sup>23</sup>

One particular thorny aspect of the prediction models is dosimetry or pharmacokinetics. An early attempt at incorporating dosimetry used a simple one-compartment toxicokinetic model that incorporated metabolism and renal excretion to predict oral human equivalent doses in mg/kg/d from AC50 or LEC values from ToxCast<sup>TM</sup>. These were compared to oral human exposure values estimated from the National Health and Nutrition Examination Survey (NHANES) or high-throughput exposure models.<sup>50,53,55,72</sup>

In 2012, ToxCast<sup>TM</sup> Phase 1 data were evaluated comprehensively by attempting to predict 60 *in vivo* endpoints using 84 different statistical classification models with the data from more than 600 *in vitro* assays.<sup>73</sup> In addition, the predictive power of these statistical models was compared with that of QSAR and chemical descriptors. The predictive power of the assays was not any better than that of the chemical descriptors, and the conclusion was that, at best, the assays could be used to identify “risk factors” for particular chemicals that could conceivably be useful in screening. The first author of this paper was Dr. Russell S. (Rusty) Thomas. In 2013, EPA had the wisdom to hire him from the Hamner Institute to lead the EPA’s National Center for Computational Toxicology.

In summary, both the diversity and complexity of the prediction models used with ToxCast<sup>TM</sup> data are increasing. This is hardly surprising given the relative “newness” of the data and prediction models. The happy consequence of this diversity of approaches is that the field of *in vitro*-to-*in vivo* prediction models is rapidly maturing.

If the new approaches are to be successful, they must be strongly focused on identifying human health risks with a defined degree of confidence relative to that of existing animal testing methods. Also, discriminating those assay responses that are relevant to human health risk from those that are irrelevant will require anchoring the assay to one or more key events within an MOA and confidence in the translation of assay results to environmentally relevant exposure levels.<sup>74,75</sup>

### **8.2.1.4 How Many Toxicity Pathways: Are They All Covered by ToxCast<sup>TM</sup>?**

ToxCast<sup>TM</sup> assays were selected on the basis of convenience, and this has led to another area of uncertainty: does the suite of ToxCast<sup>TM</sup> assays cover the entire range of toxicity pathways in humans. The large number of assays within ToxCast<sup>TM</sup>

(currently over 1000) suggests that the range of toxicity pathways and modes of action may be largely covered.<sup>76</sup> For understanding these results within the context of MOA, the distinction between an adverse effect and an adaptive effect needs to be made clear—as noted in Chapter 5, changes in enzyme levels are considered adverse in some Integrated Risk Information System (IRIS) assessments.<sup>77</sup>

In thinking about just how many pathways might exist, one might conclude that “evolution cannot have left too many Achilles heels given the number of chemicals surrounding us and the astonishingly large number of healthy years we enjoy on average.”<sup>78</sup> Although there are evolutionary and energetic constraints on the complexity of human biology,<sup>79</sup> the question of coverage by ToxCast™ of the entire domain of toxicity pathways remains unknown, and the question of whether a sufficient number of pathways are represented remains unanswered.

The set of pathways that are important for toxicity are not yet known, and for the ones that are identified with toxicity, the magnitude of perturbations of the pathway that result in toxicity also remains to be discovered. ToxCast™ assays were chosen for convenience and availability. What is likely is that ToxCast™ will end up being a hypothesis generator and may help identify new pathways or parts of pathways that are important for toxicity.<sup>80–82</sup>

## **8.2.2 Science and Decisions: Advancing Risk Assessment—the “Silver Book”**

In 2009, in response to a request from EPA, the National Research Council published this report that, like other such documents, was nicknamed for the color chosen for the cover. Immediately, the “Silver Book” became controversial because of the recommended approach to dose response. Because of the burgeoning amount of scientific data, risk analyses of increasing difficult issues were being sought; these issues included multiple chemical exposures, variation in susceptibility, cumulative risk assessment, life-cycle impacts, cost–benefit considerations, and risk–risk tradeoffs. In order to meet these demands, the report focused on recommendations to improve both the quality of the technical analysis in risk assessments and the utility of risk assessments for decision-making.

### **8.2.2.1 *Improvements in Problem Formulation***

One area of concern to the authors of the report was problem formulation. This aspect of risk assessment was discussed at length in Chapter 2. *Science and Decisions* urged a greater focus on the upfront stages of risk assessment—planning, scoping and problem formulation.<sup>83</sup>

The report also recommended consideration of uncertainty and variability in all phases of risk assessment. In 2001, EPA’s Superfund Program released *Risk Assessment Guidance for Superfund, Volume III, Part A: Process for Conducting Probabilistic Risk Assessment*. This document actively discouraged the application of probabilistic methods to dose–response assessment.<sup>37</sup> Of course, including variation in exposure only in a probabilistic risk assessment gives only part of the picture.<sup>84</sup>

Hence, *Science and Decisions* encouraged inclusion of quantitative estimates of uncertainty and variability at all key computational steps in a risk assessment.<sup>83,85</sup>

### **8.2.2.2 Replacing Defaults with Data**

Back in 1983, the “Red Book” recommended the use of uniform inference guidelines, as discussed in Chapter 1. This recommendation resulted in a number of advances such as the Cancer Guidelines; the recommendation also resulted in the proliferation of default values for many widely used quantitative factors in risk assessment. Over time, these default values became “set in stone,” and the original thinking and scientific basis of these numbers was more often than not forgotten. In many risk assessments, the ascendancy of the defaults often trumped measured values that were directly applicable to the problem at hand.<sup>83,85</sup>

For example, considering the example in Chapter 6 of the former gold mine, using the EPA default value of 60% for arsenic bioavailability or even the earlier regulatory practice of not accepting any value other than 100% for bioavailability would have significantly changed the outcome of the risk assessment.

The NRC committee recommended using alternative assumptions or values in lieu of the default if the alternative can be demonstrated to be superior. The committee also indicated that many defaults without any seeming basis had become ingrained in risk assessment practice. Often, regulators are hesitant to abandon defaults, even when data indicate that the default is overly conservative/protective.<sup>86</sup>

### **8.2.2.3 “Silver Book” Recommendations for Dose Response**

For a number of years, EPA has been attempting (or so it says) to “harmonize” non-cancer and cancer risk assessment. In 1997, a colloquium organized by EPA’s Risk Assessment Forum concluded that EPA needed to “push the envelope” in terms of consideration of mode of action, and such consideration was likely the means of harmonization.<sup>87</sup>

The NRC committee also wanted to address the scientific limitations of current approaches to dose–response assessment, as presented in Chapter 5. The committee reasoned that because of background exposures and ongoing disease processes, variations in susceptibility would exist within the human population.

EPA’s current dose–response paradigm includes an immediate and artificial separation between cancer and non-cancer outcomes. When one uses the slope factor methodology for cancer risk assessment that assumes low dose linearity, quantitative estimates of risk are available on both an individual and population basis. Hence, these estimates, correct or not, can be used in cost–benefit analyses and consideration of risk–risk tradeoffs.

In contrast, a hazard index from a non-cancer assessment provides no such information. How can one quantify risk either above or below the reference dose in a way that enables quantitative risk comparisons? The regulatory cancer risk range of 1E-06 to 1E-06 can represent a regulatory target at the population level, but for non-cancer hazards, no similar quantity can provide insight into the magnitude of

population risk that might be considered acceptable—the “bright line” of a hazard index value of unity provides no insight at all as to the likelihood of adversity.

The uncertainty factors used for low-dose extrapolation and interspecies extrapolation represent a mixture of uncertainty and variability, thus their use is contrary to EPA’s 1997 *Policy for the Use of Probabilistic Analysis in Risk Assessment*.<sup>36</sup> At present, the utility of non-cancer assessment is limited and hinders the ability to conduct quantitative analyses of risk–risk tradeoffs, to weigh costs and benefits, or to provide transparency in decisions.

The “Silver Book” recommended a unified approach to dose response, using MOA to determine the shape of the dose–response curve in the low-dose region. The exploration of a possible default value for interindividual variation in cancer susceptibility was also recommended. The examples provided in the “Silver Book” did not explicitly demonstrate that linear low-dose extrapolation would be used for both cancer and non-cancer dose-response. However, the NRC report suffered from being less than clear about the specifics of low-dose extrapolation, and this lack of clarity engendered a great deal of comment within the risk assessment community.

The “Silver Book” described three conceptual models for dose response whether or not the low-dose response was linear on an individual or population level. As an exercise at the end of this chapter, these three models will be explored.<sup>83</sup> This exercise should help you decide for yourself whether or not the “Silver Book” did indeed recommend the assumption of a linear dose response in the low-dose region for all adverse effects. Notwithstanding this controversy, there remains great benefit in providing a dose–response assessment resulting in quantitative estimates of toxicity appropriate for use in a decision-analytic approach that can determine the societal value of a range of risk management options.

#### **8.2.2.4 Separating Incidence and Severity**

In 2002, Dr. Dale Hattis of Clark University in Worcester, Massachusetts proposed a “straw man” for the reference dose.<sup>88</sup> His paper advocated separation of the magnitude or severity of a particular health effect from the population incidence. For increasing exposure, both incidence at a given effect magnitude or degree of severity in the population would increase.

This “straw man” was fleshed out in the 2014 World Health Organization *Guidance Document on Evaluating and Expressing Uncertainty in Hazard Characterization*. The document was written by Drs. Wehsueh Chiu and Wout Slob of EPA and the National Institute of Public Health and the Environment of the Netherlands. They codified the separation of effect magnitude and severity into the human dose producing a given effect magnitude and at a given population incidence, or  $HD_M^I$ .<sup>89,90</sup> In 2018, Dr. Chiu worked with Dr. Kan Shao of Indiana University to develop an automated workflow to calculate  $HD_M^I$  values. Developing an  $HD_M^I$  distribution requires application of extrapolation factors specified in Chapter 4 of the World Health Organization guidance. These factors are based on historical evidence. The factors for human variability are assembled mostly from data on pharmaceuticals. Whether these data are applicable to environmental chemicals remains an open question.<sup>91</sup>

### 8.2.3 Cumulative Risk Assessment

In 2003, EPA's Risk Assessment Forum released the *Framework for Cumulative Risk Assessment*.<sup>92</sup> Before and after that, the idea of cumulative risk assessment had been the subject of many publications.<sup>93–95</sup> The idea was likely popularized at EPA by Dr. Gershon Bergeisen, a physician who served as the special assistant to the director of Superfund in the 1990s and now operates a family medical practice in Hawaii. Dr. Bergeisen's influence may have been the start of the wish at EPA to move away from single-chemical single-pathway assessments and toward more holistic considerations of multiple exposures in real-world community contexts. This more holistic approach provides both challenges and opportunities—challenges when the stressor more likely related to the health outcome of concern is beyond EPA's regulatory mandate, e.g., smoking, and opportunities to utilize the newer *in vitro* approaches and knowledge of MOA for assessment of multiple chemicals with multiple dimensions of exposure.<sup>87</sup> In Chapter 5, the frankly daunting challenges of mixture risk assessment were presented.

Toxicology by itself cannot provide much information of psychosocial and lifestyle factors that may influence the occurrence of adverse outcomes; nonetheless, epidemiology may be able to address these factors, but is limited in its ability to demonstrate causal connections with multifactorial health outcomes. Indeed, the interface between toxicology and epidemiology is an area of growing interest among risk assessors.<sup>96</sup> Creativity in applying methods and results from a variety of disciplines to develop insights into cumulative risk methods and techniques will be a growing field. Diet and nutrition certainly affect susceptibility to chemical exposures.<sup>97–99</sup> The interaction of smoking, radon exposure, and other factors that influence lung cancer is being explored, and ideally will provide insight into how to account for the effects of multiple stressors on a common endpoint.<sup>100–102</sup> A number of computational techniques for cumulative risk assessment are emerging.<sup>103–108</sup> The use of biomarkers and community-based assessments will also provide another point of view.<sup>109–112</sup>

Lifestyle and social factors such as smoking, poor nutrition, lack of exercise, poverty, and other factors may produce significant exacerbation of the risk of health outcomes related to environmental chemical exposure. In consequence, regulators will face the difficult task of determining whether the attributable risk from environmental exposures warrants active risk management, i.e. pollution control measures. The other choice would be to lobby other public health agencies such as the Centers for Disease Control to increase their efforts toward lifestyle alterations and health education. In addition, the presentation of comparative risks that includes consideration of lifestyle factors may alienate many of the stakeholders.

Psychosocial stress and socioeconomic status (SES) are often mentioned as contributors to risk. Much of this psychosocial stress stems from poverty.<sup>113–117</sup> Poverty is obviously not a problem that can be addressed within the current rubric of environmental regulation, and there is a larger issue: does poverty stem from accident of birth, or is it the result of an individual's life decisions? This question is well beyond the scope of this book. However, if SES is indeed considered as a factor in a risk assessment, what would be done with this information? How could regulatory

activities address any risk attributable to SES? What, if any, actions could be taken in a capitalist democratic society that would constitute an appropriate response to SES as a risk factor?

Stressors other than chemical exposure may contribute a large portion of the disease burden in a community. In such a case, the most appropriate question is whether reduction of chemical exposures would have benefits that exceeded the cost of doing so. Experienced risk communicators are well aware that such risk comparisons often serve only to drive a wedge between risk assessors and the community they are trying to protect.<sup>118</sup> For consideration of the risk of non-chemical stressors, such as SES, boundaries and limits need to be established upfront that both define the purpose of including non-chemical stressors in the risk assessment and also make clear the extent of any regulatory capacity to address these stressors.

The “Silver Book” points out that in any process in which government, communities, and other stakeholders come together for a decision, there will be inevitable differences in the ability of different stakeholders to influence the process. These differences stem from imbalance in political and economic power. Risk assessors should be aware of these issues, and addressing them should be discussed during the problem formulation stage of any cumulative risk assessment.

#### **8.2.4 The Alliance for Risk Assessment**

Because of the general negative response to the dose–response assessment presented in the “Silver Book”, Dr. Michael Dourson of Toxicology Excellence in Risk Assessment assembled the Alliance for Risk Assessment (ARA), a broad-based non-profit government and non-government organization coalition. ARA recruited well-known scientists with expertise in risk assessment to serve on its Science Panel. Others presented case studies that explored various aspects of the “Silver Book” methodology to the Science Panel. The Science Panel and interested workshop participants developed an interactive framework for organizing case study methods, and the Science Panel used the framework to identify additional case studies that address important gaps in methodology. ARA has been holding workshops for about seven years, and transitioning to an “evergreen” approach that includes a standing panel that reviews methods and issues on a semi-annual basis, leading to updating of the framework. Readers are encouraged to explore the ARA website at [www.alliance-forrisk.org/](http://www.alliance-forrisk.org/).

#### **8.2.5 Exposure: Should We Even Care about Toxicity?**

One consequence of the transformation in toxicity testing is that exposure characterization of humans using biomarkers in blood and urine, as currently conducted by the National Health and Nutrition Examination Survey of the Centers for Disease Control, can be combined with relatively simple pharmacokinetics and used for screening.

ToxCast™ data were used in one such evaluation. ToxCast™ data are reported as the AC50, which is concentration producing 50% of the maximum activity in the

assay, or LEC, which is the lowest effective concentration observed in the assay. The values are reported in units of  $\mu\text{M}$ . Reliance on the reported assay results could potentially misrepresent *in vivo* effects of chemicals—what is lacking is any information on toxicokinetics that would determine actual internal exposure. Hepatic metabolism and plasma protein binding were experimentally measured for 239 ToxCast™ Phase 1 chemicals, and these data were used in a population-level toxicokinetic model that performed the necessary *in vitro*-to-*in vivo* extrapolation. For each chemical, the model produced an estimate of the distribution of the daily human oral dose that would result in steady-state *in vivo* blood concentrations equivalent to *in vitro* AC50 or LEC. The estimated steady-state oral equivalent doses associated with the *in vitro* assays were compared with chronic aggregate human oral exposure estimates to assess whether *in vitro* bioactivity would be expected at the dose-equivalent level of human exposure. For 90% of the 239 chemicals, the 95th percentile values of exposure estimates from human urinary concentrations were lower than the range of oral equivalent doses, often by several orders of magnitude. The remaining 10% of exposure estimates overlapped the lower end of the range of oral equivalent doses.<sup>119</sup>

This relatively early study demonstrates the ability to use exposure data along with *in vitro* results to determine whether a chemical might pose a risk at current human exposure levels. In essence, this is an exposure-based risk assessment that uses biological activity as a measure and asks whether current human exposures could result in biological activity. This clever approach does away with the need for both hazard identification and dose-response assessment.<sup>53,120,121</sup> Instead of estimating exposure with the uncertain models presented in Chapter 4, these methods use either NHANES biomarkers or high-throughput exposure estimates.

These biomarkers also represent the exposome. The exposome has been defined as all environmental exposures from conception onwards, including those related to diet and lifestyle.<sup>122</sup> The exposome also includes endogenous exposures to chemicals, as discussed in Chapter 5. Because the exposome represents these combined exposures in their entirety, it provides an unbiased agnostic assessment for evaluating the causes of disease, environmental or otherwise.<sup>123</sup> Assessed by sampling and analysis of body fluids, the exposome represents a top-down approach to exposure, whereas measurements of chemicals in soil, air, water, and food would represent a bottom-up approach to exposure.

The exposome is an intriguing concept, but the necessary details can never be completely measured. One would need to measure an increasing number of factors in the body at ever smaller time intervals even to hope of getting a handle on the variation of a single individual's exposome over time. Currently, a snapshot in time of an individual's exposome would likely consist of the list of environmental toxicants currently in the NHANES suite, blood lipid and enzyme profiles, screening tests for a variety of diseases, DNA and hemoglobin adducts, alterations in lipids, genomic, epigenomic, and proteomic changes, alterations in the microbiome, and likely others. As currently envisioned, the exposome is a dream come true for proponents of big data.

The question remains: how can the exposome help inform regulatory activities or the promotion of human health?

In 2012, the National Research Council released a report titled *Exposure Science in the 21st Century: A Vision and a Strategy*.<sup>124</sup> The report recommended that information on biomarkers be combined with data derived from remote sensing, Global Positioning System, satellite imaging, and other sources using an informatics approach. The development of the informatics necessary to combine these diverse data in a meaningful way was emphasized in the document. EPA's ExpoCast program was recently developed as a complement to ToxCast™, with the goal of developing high-throughput exposure measures that integrate many data sources.

What some envision is the advent of environment-wide association studies (EWAS), comparable to the genome-wide association studies (GWAS) in genetic epidemiology. Recently, an EWAS revealed a relationship between the metabolic products of the gut flora and cardiovascular disease.<sup>125</sup> However, experience with GWASs indicates that careful examination of the results is warranted before using the results for any sort of prognostication.<sup>126</sup>

The exposome concept is continuing to evolve.<sup>127</sup> What will likely come about is an integrated approach that uses both internal and external exposure assessment and combines these into a top-to-bottom approach. In sum, the picture of exposure science in the 21st century is still emerging.

The importance of exposure assessment as a screening tool cannot be underestimated. Currently, the estimate of the number of untested chemicals in commerce ranges up to 100,000. Animal testing for these chemicals is clearly not possible in a timely fashion and would be extremely costly. Addressing these chemicals is one of the goals of EPA's ToxCast™ program. However, if some measure of exposure to a particular chemical could be determined—through an estimate developed from the use scenario or even from a biomarker—then this exposure estimate could be compared with an estimate of toxicity, possibly from an *in vitro* assay. If the exposure estimate were a hundredfold less than the toxicity estimate, this might indicate a lack of concern was justified, and the resulting margin of exposure estimate would likely be sufficient for risk management purposes. Similarly, if the estimate of toxicity could be compared with that of substances found ubiquitously in healthy food, the exposure–activity ratios could be used as a screen.<sup>128</sup>

### 8.2.6 Mode of Action

EPA's Cancer Guidelines was not the first document to highlight mode of action. A very recent paper by the Alliance for Risk Assessment Science Panel written in response to the recommendations in *Science and Decisions*, advanced the concept of a fit-for-purpose dose–response assessment.<sup>129</sup> The idea of fit-for-purpose is that the level of complexity and effort of the dose–response assessment be no greater than that needed to select between risk management alternatives—consistent with the increased focus on problem formulation.<sup>83</sup>

ARA expressed dismay that MOA was used only rarely in the dose–response assessment. In fact, the leadership of EPA's IRIS program seems intent on ignoring MOA. ARA indicated that integration of MOA information into the dose–response

assessment should occur as early as possible. Ignoring MOA until later in the dose-response assessment limits the ability to use this information for low-dose and inter-species extrapolation, identification of susceptible populations, and population-level estimates of the range of variability in response. The consideration of MOA should fit the purpose of the risk assessment and conform in complexity and scope to the risk management decision.

Early in the history of risk assessment, the notion was advanced that background disease processes and exposures could linearize the dose response.<sup>130</sup> The statement was originally made well before the idea of MOA even existed, and this same idea made its way into the “Silver Book”: “effects of exposures that add to background processes and background endogenous and exogenous exposures can lack a threshold if a baseline level of dysfunction occurs without the toxicant and the toxicant adds to or augments the background process.”<sup>83</sup> As more is learned about fundamental biological processes and systems biology, the faulty concept of a linear dose response will hopefully die quietly.<sup>131–143</sup>

The adoption of the linear no-threshold hypothesis by the Safe Drinking Water Committee of the National Academy of Sciences (see Chapter 5) was partly based on the idea that DNA is pristine. In fact, DNA is far from pristine. Every cell has a steady-state background of at least 50,000 endogenous DNA lesions. Under conditions of oxidative stress, this number is expected to increase. If DNA replication occurs before these lesions are repaired, the result can be mutations. But mutations are not the sole causal factor in cancer pathogenesis.

One aspect of consideration of mode of action is that it seems daunting for some—especially those not schooled in biology. In this regard, individuals come to the field of risk assessment from a variety of disciplines. Many are from engineering or fields such as operations research, and while highly knowledgeable in areas such as statistics or mathematical modeling, they are frankly uncomfortable dealing with biology. This discomfort is a possible reason that MOA has been given short shrift within the IRIS program. What would help greatly is a catalog of potential modes of action. Thomas Hartung, director of the Center for Alternatives to Animal Testing (CAAT) at Johns Hopkins, suggests there cannot be all that many toxicity pathways or modes of action for adverse effects.<sup>78</sup> One of the projects in CAAT is to map the human toxome. To provide guidance on selecting modes of action consistent with current biological knowledge, the International QSAR Foundation, the American Society of Cellular and Computational Toxicology, and others are developing collections of known MOAs that can be assembled into a Wiki.<sup>144–148</sup> Read-across and other methods that develop a limited number of modes of action from chemical structure will also likely be informative.<sup>42,149–152</sup>

### **8.2.7 The Advent of Evidence-Based Toxicology**

An evidence-based approach to toxicology is an area of intense interest. The model for this approach is that of evidence-based medicine (EBM).<sup>153</sup> The term “evidence-based toxicology” was first used in 2005.<sup>67</sup> Dr. Thomas Hartung is a pioneer in the application of evidence-based approaches in toxicology.<sup>154</sup>

Evidence-based medicine is based on assessing the totality of evidence regarding a particular medical intervention. Evidence-based toxicology attempts to apply similar approaches to the assessment of the totality of evidence regarding the toxicity of substances. This evidence includes studies in animals, humans, cells, or tissues *in vitro*, computational toxicology, and predictive methods such as QSAR. The practices of systematic reviews of evidence, transparency in decisions, open data disclosure, synthesis of different types of evidence, and assessment of bias/credibility are just beginning to be applied in toxicology.<sup>68,96,155–161</sup>

## 8.3 OBSTACLES TO THE ADVANCEMENT OF RISK ASSESSMENT

The fear entrepreneurs would generally like to remove the science from societal decision-making. When science is brought in, the quality of the science itself, the relevance of the information to the decision at hand, and the acceptability of that decision based on non-scientific factors must all be determined. Societal decisions may be taken for a variety of reasons—science-based or otherwise. What is absolutely necessary is that an honest statement of the basis for the decision and the evidence for and against need to be provided. Because of the general lack of scientific knowledge by many in the population, some decision-makers may wish to “tweak” or “adjust” the scientific evidence to lend support to the preferred decision alternative. Honest scientists who strive to be objective and as free from bias as possible provide the best support to decision-makers, even if the evidence might not support the wishes of these decision-makers.

### 8.3.1 Conflict of Interest (COI) and Bias: They’re Everywhere!

Scientists at any academic, industry, government, or non-government institution may have conflicts of interest, both financial and non-financial. One can define COI as follows: an individual is in conflict if he/she owes a duty of loyalty or responsibility to two distinct parties, both of which are likely to be affected in different ways by the activity in which the individual is engaged. COI policies generally address financial but not non-financial conflicts of interest. Policies for handling financial COI issues generally rely on disclosure as a mechanism to manage COI.<sup>162</sup>

Conflict of interests or competing interests may arise because of financial interests, organizational affiliations, or personal biases. Scientists working to support the chemical industry are assumed by environmental activists to have competing interests because of financial sponsorship—other sources of bias are ignored by the activists.<sup>163</sup> The unfortunate misdeeds of some in the tobacco industry have produced much skepticism about the scientific credibility of all industries.<sup>164–167</sup> The Society of Toxicology provides useful definitions of conflict of interest, bias, and advocacy.<sup>168</sup>

Academic scientists are not immune from COI. Unfortunately, the publication bias against negative results may influence some academics. The publish-or-perish climate of academia and the cutthroat competition for a decreasing pool of government grant money have negative influences on science.<sup>169</sup> Journals and journal

editors have a bias toward publishing positive results.<sup>170–172</sup> Thus, many academics have become prisoners of publication bias.

Notwithstanding the almost universal practice of disclosure of financial support, more often than not individuals in conflict have trouble recognizing their own conflicts—even individuals of high character and morals. An aspect of the human condition may be a perceptual blind spot that hinders honest and critical self-examination. If so, disclosure as a policy for addressing COI is worthless.<sup>162</sup>

Bias is inherent in all scientific endeavors. Hypothesis generation and testing involves expectation and creates a bias in the author of the hypothesis.<sup>173</sup> All scientists have opinions about their work and that of others in their field—they cannot help having bias. Money aside, scientists are often unconsciously biased toward results that confirm their preconceptions.<sup>174–176</sup>

There exists a growing literature purporting to find that research funded by private industry produces results that favor the industry funding the research more often than research on the same topic relying on other funding sources. Bias in pharmaceutical and medical device studies has been considered in a Cochrane review, and the evidence of bias in drug studies was “convincing and consistent.”<sup>177,178</sup>

There appear to be a number of sources of bias in toxicological studies.<sup>179</sup> Good laboratory practice is one means of reducing bias. Studies carried out under GLP are subject to external inspection that includes an audit of raw data, data completeness, and data accuracy. With GLP, the results of experiments that do not meet the experimenter’s preconceptions cannot be trashed, because accounting of supplies and animals is part of GLP.<sup>180</sup> Hence, one can have confidence in both positive and negative results in studies conducted with GLP.

During the 1970s, environmental activists were instrumental in raising the public consciousness of the need for environmental protection. However, lately, the groups of activists that are most vocal are unanimous in decrying any results funded by the chemical industry—without regard for the results. Sadly, these activists have joined the ranks of the fear entrepreneurs.

In November 2012, EPA held a public stakeholder meeting on the IRIS program at its offices in Crystal City, Virginia. One of the invited speakers was Dr. Richard Denison of the Environmental Defense Fund. Dr. Denison indicated in his comments that industry-funded toxicology studies should never be used in IRIS assessments—the clear implication was that such studies were too biased to use.

Industry-funded studies are conducted with GLP, thus there is a great deal of accountability. Often, industry-funded toxicological investigations use an external peer review committee that reviews study design, results, and pre-publication drafts, e.g., the recent mode of action study of hexavalent chromium occurring in 2011 and 2012.<sup>181</sup>

When it comes to bias, funding sources may actually be a result of a scientist’s bias, not a cause of it. Scientific interpretations will always reflect the biases of the authors. Even scientists who appear apolitical and disinterested may possess a worldview by virtue of their education or disciplinary orientation that others might view as bias.

### 8.3.1.1 *Shielding Oneself from Bias*

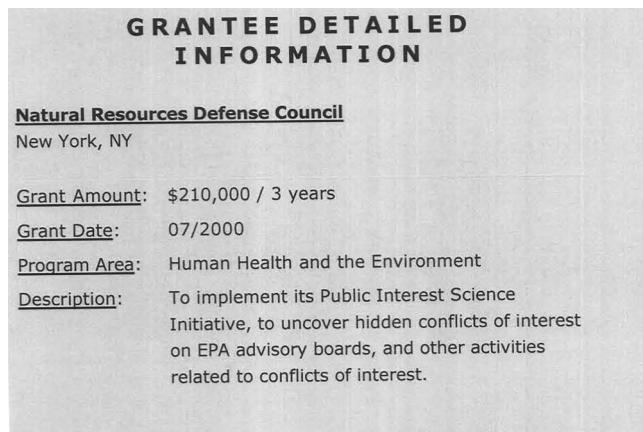
All of us are biased. Our preconceptions result from our entire past life experience. Good scientists strive for objectivity in spite of bias. Karl Popper, the 20th-century philosopher and exponent of the scientific method, opined that all good theories were falsifiable, and that it was vital to be able to test a theory by virtue of experiment or observation. The evidence provided by these experiments or observations would either support or falsify the theory.<sup>182</sup>

By considering science as evidence and the scientific methods as the testing of theories and hypotheses, deductively using the specifics of the evidence has formed the basis of current thinking about mode of action.<sup>183</sup> Deductive reasoning and strict adherence to the scientific method can remove some bias.

The stridency with which some environmental activists suggest that use of industry-funded science in developing toxicity criteria is inappropriate provides an example of such bias—with reason: risk assessment is replete with examples of how science can be corrupted by the exigencies of decision-making.<sup>184</sup> Today, most journals require that the funding source of the work be acknowledged explicitly, making it all too easy to dismiss any inconvenient evidence based solely on funding source. Some scientists have likened this criticism to an assault on science driven by post-modern thinking; this type of thinking questions the very existence of a real world. Post-modern thinking claims that scientific knowledge is merely an alternate reality. Scientists have just as much right to believe in the big bang theory or human evolution as non-scientists have a right to believe the moon is made of green cheese or that flying spaghetti monsters once ruled the skies.<sup>185</sup>

Some scientists have suggested that information about funding sources should not be included in scientific publications. This would force the readers to judge the quality of the science itself.<sup>173,186,187</sup> What rankled many scientists funded by the chemical industry was that environmental activists who often published papers decrying industry-funded work did not reveal the sources of their funding.<sup>188,189</sup> As noted, the work of many activist groups has been important in raising the consciousness of environmental issues—those who work for such groups are motivated by an honest desire to make the world a better place. Sadly, this desire makes many activists susceptible to manipulation by the purveyors of fear.

The Beldon Fund ([www.beldon.org/](http://www.beldon.org/)) provides funding to states and environmental activist groups for a variety of activities. From 2003 through 2005, the fund gave \$100,000 to the Center for Science in the Public Interest to “to expose and prevent the destructive influence of corporate interests on scientific research, publications, and science-based policy.” In 2006, this amount was increased to \$150,000. In 2003, the fund provided \$200,000 to the National Resources Defense Council “to ensure that the science used by government in developing regulations of toxic chemicals is free from manipulation by industry groups.” In 2006, the NRDC was given \$250,000 to combat “industry influence on the science and on the defense of precautionary toxic chemical policy through coalitions with state government officials.” All of this information is available at the Beldon Fund’s website in its annual reports at [www.beldon.org/programs-impact.html](http://www.beldon.org/programs-impact.html).



**Figure 8.3** Screenshot of the Beldon Foundation announcement of the award to the National Resources Defense Council.

The Annual Report for 2000 cannot be downloaded from the website. That year, the fund provided \$210,000 to the National Resources Defense Council “to uncover hidden conflicts of interest on EPA advisory boards, and other activities related to conflicts of interest.” The web listing was taken down, but can be seen in Figure 8.3.

To get past this “he said, she said” back-and-forth, various considerations/criteria have been advanced as a basis for judging the quality of science with a view to better supporting regulatory determinations.<sup>109,110,154,160,161,190</sup> The most recent includes ten specific criteria, including funding source, independent of the investigator from undue influence by the funders, reproducibility by other investigators, and others.<sup>160</sup> These criteria have been criticized, likely because they were developed with input from the chemical industry.<sup>191-194</sup>

### 8.3.2 Misinformation and the Lack of Scientific Literacy

In this section, two obstacles to progress in risk assessment will be discussed: conflict of interest and bias, and resistance to change

The legitimization of alternative worldviews and diminishing of science as a means of understanding has its roots in education (or lack thereof), the role of the media, and the hesitation of scientists to engage in science communication.<sup>195-198</sup> The ascendance of the precautionary principle may be due to these factors and the failure to recognize and communicate that the risks of various management options, including maintaining the status quo, must be balanced against each other.<sup>199-202</sup>

#### 8.3.2.1 *Lightning Revisited*

For a moment, we will return to the example in Chapter 2 of the risk of being struck by lightning while swimming in an indoor pool. Mr. Matt Laverne, manager of Douglas County’s Office of Risk and Security, was generous with his time and

knowledge in answering my questions. Mr. Laverne agreed with my risk estimates, but pointed out that the lightning wasn't really the issue, but rather that what the lifeguards at the pool have to deal with is the potential fear of lightning in the minds of the patrons of Boundary Waters Aquatic Center. He also noted that thunder could indicate tornados, and the pool has many large windows that could instantly become sharp objects flying willy-nilly through the air; clearing the pool was one less step in the process of moving people away from the windows to a place of relative safety should a tornado arrive. Mr. Laverne pointed out to me that dealing with a crowd of frightened people, many of whom are children, was a recipe for a disaster. His job is not so much to assess risk as to manage risk—and, to his credit, he's chosen to protect children to the greatest extent possible. I agreed with him without hesitation that having emergency medical technicians take a child out on a stretcher was a situation that called for a precautionary approach.

Mr. Laverne pointed out that the article from the National Recreation and Parks Association (NRPA) also provides a statement from Carl Swanson and Steven Clark, both of the Lightning Data Center. Swanson and Clark begin their statement by pointing out the inconsistency of responses to lightning and thunder at indoor pools. They conclude as follows:

We have not found a single lightning researcher who endorses staying in a pool, indoor or outdoor, in an electrical storm. Remember, absolute protection from lightning is impossible. We believe the risk of electrical shock from lightning is greater than the inconvenience of evacuating the pool.<sup>203</sup>

As a scientist, what do you think of the use of a data-free consensus statement as the basis for a policy decision? Most scientists view such an appeal to authority as unconvincing.<sup>67</sup> At least the statement by Tom Griffiths quoted in Chapter 2 that no documented reports of fatal lightning strikes in indoor pools provides a datum. The NRPA likely provided both statements to support swimming pool managers in any pool closure decision they chose.

The lifeguards receive their training from the American Red Cross, whose lifeguarding manual instructs lifeguards to clear everyone from the water at the first sound of thunder or first sight of lightning. The manual is not specific whether this instruction applies to outdoor pools only or both indoor and outdoor pools.<sup>204</sup>

The lifeguards are all fine young men and women; for many of them, lifeguarding is their first job. Reflecting on what Mr. Laverne said, my expectation that any of the lifeguards would provide a satisfactory message about the reasons for clearing the pool at the first rumblings of thunder was naïve.

The communication of the risk was imperfect, but the intentions underlying the risk management action of clearing the pool were above reproach. To be clear, communicating risks to fearful people is almost impossible due to their lack of receptivity.<sup>205</sup>

Two examples follow of scientific ignorance and the political influences on science. In these two situations, the intentions behind the decisions were likely not so honorable as those behind clearing the pool for thunder. Judge for yourself.

### **8.3.2.2 So What Do Attorneys Know about Formaldehyde?**

A glaring example of “not knowing what you don’t know” is provided by Ms. Rena Steinzor during a meeting of the Subcommittee on Oversight of the House Science, Space and Technology Committee. Ms. Steinzor is the president of the Center for Progressive Reform, based in Edgewater, Maryland. This subcommittee hearing was titled “EPA’s IRIS Program: Evaluating the Science and Process behind Chemical Risk Assessment.” At about 2 hours and 14 minutes into the hearing, Ms. Steinzor said:

My son, who's twenty, is sitting behind me. One of the most distressing things I've heard today is that he has formaldehyde in his body and he exhales it at levels much higher than the reference dose set by EPA's database. That didn't happen because he's walking through a natural paradise on the Chesapeake Bay. It's because the air is polluted. We live in a non-attainment area that is awash in toxics ....

When I wrote the first edition of this book, the archived recording of the subcommittee hearing could be found online, but now in 2019, I could not find it. You can find a written copy of Ms. Steinzor's testimony at <https://science.house.gov/imo/media/doc/2011%2007%2012%20Steinzor%20Testimony.pdf>.

What Ms. Steinzor apparently didn't know was that formaldehyde occurs naturally in human breath. Ms. Steinzor is an attorney, and heads the Center for Progressive Reform that in 2007 received \$100,000 from the Beldon Foundation “to ensure that state and federal regulatory agencies can rely upon unbiased and reliable scientific information and advice in implementing health, safety, and environmental laws.” This cautionary tale suggests that all of us, risk assessors and others, should likely refrain from substantive statements about disciplines other than those studied in depth.

### **8.3.2.3 Genetically Modified Organisms and European Agriculture**

Europe, and especially France, is justifiably proud of the long heritage of celebrating food and the culture of food. For many years, a significant portion of both farmers and the public have taken a stand against genetically modified organisms (GMOs). Farmers felt that globalization and technology would disempower them. Environmental activists initially raised concerns about environmental damage, citing risks that were hypothetical and not specific to GMOs.

Most GMOs have been engineered to be resistant to specific herbicides. Glyphosate is an organophosphorus compound that inhibits the enzyme 5-enolpyruvylshikimate-3-phosphate synthase, necessary for plant growth. Genetically modified maize has been engineered to be resistant to glyphosate.

The critique of GMOs was oft aired in public, and in 2007, then-President Sarkozy of France made a devil's bargain with activists to ban GMOs in exchange for these activists giving up their crusade against nuclear power.<sup>206</sup> This agreement violated European Union law requiring scientific evidence to uphold the ban. In the spring

of 2012, just before the general elections in France, the French government filed an emergency measure with the European Commission claiming that genetically modified maize produced environmental harm. The European Food Safety Authority observed that the emergency measure contained no new scientific evidence.<sup>207</sup> The ban on GMOs was cancelled, but when Sarkozy lost the election, the new Hollande government attempted to prolong the ban when it took power in late 2012.

Against the political backdrop, the Comité de Recherche et d'Information Indépendantes sur le génie Génétique, an environmental activist group, funded a study led by Gilles-Eric Séralini of the University of Caen. In this chronic study, female Sprague-Dawley rats were fed either a control diet or one containing 11%, 22%, and 33% of Roundup-ready corn, both treated with glyphosate and not treated. Each dose group was comprised of ten animals, not enough to conduct a meaningful statistical analysis. Please recall that chronic bioassays generally require 50 animals per group. In addition, this rat strain is highly prone to cancer, with historical control incidences of mammary tumors in females of about 70%.<sup>208,209</sup> The animals were kept alive as long as possible.

When Séralini published this work in *Food and Chemical Toxicology*, the paper's appearance spurred 24 letters to the editor complaining about unethical treatment of animals and inappropriate use of statistics as well as potential editorial misconduct. You can find a copy of the retracted paper and the letters to the editor at [www.sciencedirect.com/science/article/pii/S0278691512005637?via%3Dihub](http://www.sciencedirect.com/science/article/pii/S0278691512005637?via%3Dihub).

A. Wallace (Wally) Hayes served as editor-in-chief at the time, and announced in November of 2013 that the paper would be retracted because the results "are inconclusive, and therefore do not reach the threshold of publication for *Food and Chemical Toxicology*."<sup>210</sup> Both the European Food Safety Agency and Germany's Federal Institute for Risk Assessment criticized the paper for failing to provide data in support of the conclusions presented.<sup>211</sup>

This is not the end of the story, however. In 2015, the International Agency for Research on Cancer published a monograph linking glyphosate to non-Hodgkin lymphoma. The rationale was the occurrence of oxidative stress and genotoxicity observed in *in vitro* studies. The monograph indicates there is limited evidence for the carcinogenicity of glyphosate in humans. Based on these findings, IARC declared that glyphosate was classified in Group 2a—probably carcinogenic to humans.<sup>212</sup>

Following the publication of the IARC monograph, the epidemiologic evidence on glyphosate was re-examined by a number of experts who could not find conclusive evidence of an association with non-Hodgkin lymphoma.<sup>213-216</sup> The use of oxidative stress and the misapplication of the key characteristics of carcinogens in arriving at this classification for glyphosate were also noted.<sup>217</sup>

The role of IARC as one of the key players in the global fear industry is the likely reason for their questionable decisions regarding glyphosate. The location in Lyon, France and the long anti-GMO stance in Europe may have contributed as well. The 2a classification was used by OEHHA in California to declare glyphosate a carcinogen.

The designation by IARC spurred over 13,000 law suits in the US against Bayer and Monsanto. The recent award of almost \$300 million to a single plaintiff exposed to Roundup has emboldened a horde of litigants and their ambulance-chasing lawyers

to go after the deep pockets of Bayer/Monsanto—all based on the flawed scientific interpretation of IARC in the service of promoting fear.<sup>218</sup>

### **8.3.3 All the Uncertainty You Could Want**

Wicked problems, as discussed at the start of this chapter, are those with deep uncertainties. Experts disagree about the outcomes of various policy alternatives. Without sufficient objective evidence to support rational decision-making and conflict resolution, the decision outcomes are often dictated by passions and unwarranted convictions.<sup>219</sup> Such wicked problems include the effects of climate change, cyber-terrorism, and the threat of weapons of mass destruction.<sup>9</sup>

In any risk assessment activity, one strives to reduce uncertainty. Reducing uncertainty has become almost a slogan, and in some cases means increased complexity, and almost certainly less transparency. The degree of uncertainty in a risk assessment is always relative. For example, an extrapolation factor for development of a reference dose for a chemical is proposed, and the basis is a quantitative comparison of key events in humans and animals; the question that must be addressed is whether the use of this extrapolation factor will reduce the overall uncertainty in the risk assessment relative to the use of the default uncertainty factor, generally having a value of ten.

Usually, one compares the uncertainty of proposed changes in risk methodology relative to commonly used defaults, but this is not always the case. The use of biomarkers to estimate exposure is a way to reduce uncertainty relative to the use of human behavior within specific scenarios, as presented in Chapter 4.

The important question to ask oneself when considering a change in a risk assessment is whether the change will reduce uncertainty in comparison to that associated with current practice. With wicked problems, one may have no clue. In addition, there will be political and social pressure to do something. When will sufficient information be available to support a credible decision? Value-of-information methods, discussed earlier, may be a means of getting an answer. However, this question will be increasingly difficult to answer—especially for wicked problems—but those who choose the field of risk assessment as a career will need provide answers many times over.

## **8.4 CONCLUSIONS**

Of course, it's difficult to predict the future—especially if the world is as unpredictable as some think. Maybe society should abandon risk assessment and put these resources toward building a culture of individual and societal resilience and anti-fragility. Is such a transition even possible? For now, risk assessment provides the “best of the worst” means of determining societal responses to complex threats and problems. Environmental risk assessment has many strengths and weaknesses. Changes will not come from experienced risk assessors, but from the set of new minds that take up this challenge in the 21st century. While the problems and challenges may not have changed that much, the amount of scientific information that can be brought to bear has increased hugely. It will take fresh young minds and new

ways of seeing problems for progress to occur. This situation should not be viewed as a burden—rather, it is a challenge to be met and a great opportunity for those with the imagination and drive to make a change.

## 8.5 EXERCISES FOR THOUGHT AND DISCUSSION

These exercises below have no correct answers. If you have difficulty with them, please realize that so does the rest of the present risk assessment community.

### 8.5.1 Exploring the Three Conceptual Models for Dose Response from the “Silver Book”

Chapter 5 of NRC (2009) *Science and Decisions* describes three conceptual models for dose–response assessment of chemicals.<sup>83</sup> The choice of the model is dependent on background processes and exposures, the biological effects of the chemical being considered, the nature of human variability, and other possible factors. The three models are:

1. nonlinear individual response, low-dose linear population response with background dependence;
2. low-dose nonlinear individual and population response, low-dose response independent of background (i.e., a threshold response for which a reference dose is most appropriate);
3. low-dose linear individual and population dose response (i.e., a non-threshold response for which a slope factor is most appropriate).

Discuss what sorts of data could be collected to inform one about the variability in the population response based on background exposure and ongoing disease processes.

### 8.5.2 Conflict of Interest: Your Own Investigation

Obtain from your university library a copy of a 2007 paper by Hardell et al., “Secret ties to industry and conflicting interests in cancer research,” *Am J Ind Med* 50:227–233). This paper engendered a number of letters to the editor that are printed in the same issue. Read the paper and these letters, and discuss them with a view to characterizing Hardell’s view of COI.

### 8.5.3 Cumulative Risk Assessment

Find the following papers in your university library:

- Love et al. (2010), “Exploring weathering: effects of lifelong economic environment and maternal age on low birth weight, small for gestational age, and preterm birth in African-American and white women,” *Am J Epidemiol* 172:127–134;

- Geronimus et al. (2006), “‘Weathering’ and age patterns of allostatic load scores among blacks and whites in the United States,” *Am J Public Health* 95:826–833;
- Chakraborty et al. (2011), “Disproportionate Proximity to environmental health hazards: methods, models, and measurement,” *Am J Public Health* 101, Suppl 1 S27–S36.

Discuss these papers and determine the feasibility of conducting a cumulative risk assessment that involves psychosocial stress.

#### 8.5.4 Your Own Investigation of Bias

For many years, Dr. Christopher Portier was employed at the National Institute of Environmental Health Sciences. Conduct a Google search for the following terms: “Chris Portier,” “IARC,” and “Glyphosate.” A number of articles from news outlets of various political persuasions will pop up. Read as many as you wish, and form your own opinion of Dr. Portier as a scientist. A discussion with your fellow students would also provide a valuable learning experience.

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## CHAPTER 9

# Emerging Risks and Final Thoughts

I believe that man will not merely endure: he will prevail. He is immortal, not because he alone among creatures has an inexhaustible voice, but because he has a soul, a spirit capable of compassion and sacrifice and endurance.

William Faulkner  
*Nobel Banquet Speech, 1950*

The quote at the beginning of Chapter 8 suggested that scientific truth may be elusive. Recall from Chapter 4 Lord Kelvin's estimate of the age of the earth. My hope is the words in the quote from William Faulkner beginning this chapter will, in the fullness of time, be the truth, and the scientific method will reveal what humankind needs to know to understand and manage emerging risks.

In this chapter, three different areas of emerging risk will be considered—not for any solutions, but to provide some idea of what's ahead. The goal is not to predict the future, but to provide some food for thought about what sorts of problems a risk analyst beginning his/her career in the 21st century can expect. Chapter 8 began with a discussion of “wicked” problems.<sup>1</sup> These are some examples, presented generally with the aim of suggesting the type of problems 21st-century risk analysts will encounter.

### 9.1 RISK FROM EPIGENETIC EFFECTS

Epigenetics refers to alterations in DNA structure, chromosome structure, and gene/protein expression without a change in the DNA sequence. These changes fall into three broad categories—DNA methylation, histone modifications and non-coding microRNAs (miRNAs)—that alter gene expression and nucleosome positioning.<sup>2-4</sup> A comparison of neurodevelopmental effects of arsenic with epigenetic markers was shown in Chapter 5. Epigenetic changes associated with arsenic exposure and possibly linked to disease have been documented for a number of endpoints.<sup>5-14</sup> The mode of action for arsenic is binding to sulfhydryl groups; this event in turn affects coordinated gene expression via Nrf2.<sup>15-18</sup>

Gaps in research, however, need to be filled before epigenetic data can be incorporated into risk assessment.<sup>2</sup> Throughout growth and development, and indeed for the rest of one's lifetime, the epigenome is in a state of constant alteration.<sup>19</sup> Just how much of this dynamic variability needs to be characterized for credible use of epigenetic data in risk assessment remains unknown.

In addition, both the heritability of epigenetic changes and the role of epigenetic changes during development that lead to adult disease need to be clarified. To address the heritability, a comparison of dose-response relationships for transgenerational epigenetic changes to adverse outcomes in multigeneration studies would be required. Because epigenetic changes may also occur during development, distinguishing transgenerational epigenetic patterns from those acquired post-fertilization presents a challenge. Parental patterns of DNA methylation are erased during gamete formation and reset after fertilization.<sup>20</sup> Incomplete erasure of epigenetic markers in gametes provides a biological basis for developmental origins of adult health and disease.

The complexity of epigenetic regulation and the challenge of integrating epigenetics into risk assessment is just beginning to be appreciated. The regulation of gene expression by DNA methylation appears context-dependent.<sup>21</sup> Histone proteins that surround DNA on the chromosomes carry many covalent modifications, and over 100 unique modifications have been identified.<sup>22,23</sup> These patterns form a code or "alphabet" to facilitate an open structure of the chromosome for access to genomic DNA by transcription factors and movement into the transcription factory. Some epigenetic modifications may be repressive and would tend to prevent transcription. The overall pattern of gene expression is responsive to both new stimuli and exposures, but also conditioned by persistent epigenetic modifications that are both inherited and acquired.<sup>24</sup>

Epigenetics also plays a role in the acquisition of the hallmarks of cancer during malignant transformation. Tumor cells often display alterations in DNA methylation patterns and dysregulated developmental programs. These epigenetic changes may represent the biological underpinnings of the hallmarks. For example, histone lysine demethylase enzymes remove methyl groups from the histone proteins and may foster the transcription of cancer-associated genes.

### 9.1.1 Risk Assessment Based on Epigenetics

To assess effects of environmental exposures on epigenetics, specific markers and overall changes in gene expression need to be measured.

Methylation of DNA occurs primarily at cytosine-guanine (CpG) sequences in promoter regions of genes and leads to transcriptional silencing. Several experimental protocols exist for measuring genome-wide methylation as well as at specific loci.<sup>25-29</sup> CpG methylation affects the binding of transcription factors to DNA and thus affects gene expression.<sup>30-35</sup>

Differences in both messenger RNA (mRNA) and microRNAs present in a sample of blood or tissue can be determined using microarray technology.<sup>36,37</sup> Assessing the statistical and biological significance of these results requires expertise in genomics and the specific methods.<sup>38</sup>

Chromatin consists of genomic DNA and histone proteins. The nucleosome is composed of DNA wrapped around histones and proteins. The N-terminal tails of histones interact with DNA, and these interactions can be affected by a variety of histone modifications, including methylation, phosphorylation, acetylation, and others.<sup>39</sup>

Chromatin remodeling allows looping of DNA with the nucleus to allow the transcription complex to attach and to control gene expression. Histone modifications affect remodeling and thus gene expression.<sup>40,41</sup>

A team of academic researchers at the University of North Carolina, government scientists, and consultants led by Dr. Julia Rager of the University of North Carolina used measurements of urinary arsenic and cord blood samples from 59 mother/newborn pairs, part of a pregnancy cohort in Durango, Mexico.<sup>42</sup> Benchmark dose modeling was conducted on five epigenetic markers using quintiles of urinary arsenic as the dose term.<sup>43</sup> The five markers were CpG site methylation, miRNA expression, mRNA expression, and with sets of genes/proteins corresponding to biological functions determined by weighted network correlation analysis with the R package WGCNA.<sup>44</sup> The dose-response analysis was conducted with BMD-Express, a software package maintained by Dr. Scott Auerbach of the National Toxicology Program.<sup>45-47</sup>

Dose-related increases in all the endpoints were observed with urinary arsenic concentration. The BMD and BMDL values were 58 and 45 µg/L urinary arsenic respectively. The weighted network response included biological networks involved in growth signaling.<sup>43</sup>

Epigenetic risk assessment methods are being used to a greater extent in personalized medicine.<sup>48-51</sup> At present, the conceptual framework for using epigenetics within the environmental risk paradigm is still developing.<sup>52-55</sup> Dr. Rager and her co-workers were ahead of their time, and their efforts may end up being the model others use.<sup>9,43</sup>

## 9.2 PHARMACEUTICALS IN THE ENVIRONMENT

Urban environments use lots of water. The waste water is often recycled and purified to be used as drinking water. Since the turn of the century, both pharmaceuticals and illegal drugs have been present at small concentrations in drinking water. Americans fill upward of 4 billion prescriptions for pharmaceuticals each year, almost 13 for every soul living in the US; unsurprisingly, these drugs and their metabolites eventually make their way into the environment.<sup>56</sup>

A five-year effort by the US Geological Survey measured a wide array of substances, including pharmaceuticals, commercial chemicals, estrogenic chemicals, bacteria, and viruses, in 25 drinking water treatment plants. These include common over-the-counter medicines such as acetaminophen and ibuprofen, prescription drugs, including psychoactive benzodiazepines, selective serotonin-norepinephrine reuptake inhibitors and opiates, and illegal drugs.<sup>57</sup> Cocaine and methamphetamine are also found in drinking water sources in the UK.<sup>58</sup>

### **9.2.1 Screening RfDs (sRfDs) for Pharmaceuticals in Drinking Water**

The Minnesota Department of Health (MDH) has been leader on emerging risks for about a decade. MDH recently developed a set of screening reference doses (sRfDs) for 119 pharmaceutical substances. Cancer and endocrine disruption were considered as reasons for applying adjustment/extrapolation factors. Additional information for each drug was obtained from the National Library of Medicine and used to adjust the lowest observed adverse effect level-no observed adverse effect level uncertainty factor (UF) for pregnancy, severe side effects, if the drug was not tested in children, and the presence of FDA “black box” warnings. A duration UF was also used to adjust from short-term use of the drug to assumed chronic exposure via drinking water. The sRfDs were converted to water screening values.

### **9.2.2 Are the Large UFs Sufficient to Account for Serotonin Syndrome?**

When viewed in the comparison to toxicity reference values for environmental chemicals, the sRfDs for active pharmaceuticals appear very conservative with combined uncertainty factors up to 30,000. The exposure to these pharmaceuticals in drinking water, however, occurs in combination with purposeful exposure to a variety of medicines. In addition, mixture effects may occur with active pharmaceuticals, especially anti-depressants. Drinking water in the UK contains citalopram (Celexa) and fluoxetine (Prozac) as well as the stimulants cocaine, methamphetamine, methylene, and mephedrone.<sup>58</sup> Opiates, including codeine, morphine, tramadol, oxycodone, and fentanyl, have been detected, albeit at low levels, in Canadian drinking water.<sup>59</sup>

In combination, these drugs may cause serotonin syndrome, a poorly understood and potentially fatal condition caused by anti-depressant drugs that act to block serotonin reuptake or as direct serotonin receptor agonists. The upshot is an overstimulation of the serotonergic system in the brain, with adverse results, including death. No clinical test is available to diagnose serotonin syndrome and no characteristic signs have been shown to be present postmortem.<sup>60-62</sup> The very large UFs used in the sRfDs may be sufficient to address serotonin syndrome from pharmaceuticals in drinking water, but this particular risk was not explicitly addressed by MDH.

### **9.2.3 An Unrecognized Risk from Drugs in Drinking Water**

Testing of hair for illegal drug residues is often used for monitoring abstinence in child custody situations. Positive tests for cocaine or methamphetamine are tantamount to evidence of use in the minds of many working in child protective services.

The innermost region of the hair follicle is called the bulb and is in direct contact with the blood in the capillaries of the skin. The cells in the bulb undergo cell division to produce daughter cells every one to three days. These cells elongate and move up the follicle to form the hair shaft. There, these cells synthesize the pigment melanin, also found in skin and in the lining of the retina in the eye, and the cells accumulate a sulfur-rich protein called keratin. The cells eventually die, and the hair shaft consists of melanin granules bound in a network of cross-linked keratin fibers.<sup>63</sup>

The drugs analyzed in hair include amphetamines, opiates, and cocaine. The process for hair collection and testing includes cutting a lock of hair, preferably from the posterior vertex region of the scalp, and analyzing a length of 1.5 inches closest to the scalp. Hair grows at approximately 1 cm per month, and the concentration in this length of hair is assumed to represent the average concentration over the past three months.

Recent medical research on melanin indicates that melanin binding may be an important clinical means of drug delivery to the eye.<sup>64</sup> A very recent prediction model of ocular drugs revealed that lipid solubility, the presence of an aromatic ring, and a nitrogen-containing amine group contributed to melanin binding.<sup>65</sup> These same chemical properties are shared by amphetamines, opiates, and cocaine.

These drugs may accumulate in hair due to multiple mechanisms, including external contamination from air or water.<sup>63,66</sup> Not only are decontamination procedures that purport to remove environmental contamination from the hair surface unreliable, but also the use of solvents in these washing procedures may actually cause drug contamination on the hair surface to be incorporated into the inner hair matrix.<sup>66,67</sup>

A positive result of methamphetamine in hair due to showering seems inevitable. What will be the risk that such a finding would be interpreted as illegal usage? This is an example of ontological risk discussed in Chapter 2—risk based on a belief or mindset.

### 9.3 CLIMATE CHANGE

The risk of climate change has been known for years. What humankind is now encountering is the effects of humans in the Anthropocene on climate. These effects include the inland and coastal flooding experienced in the US, more tornados, heat-waves, drought, and other extreme phenomena. What is needed is a means to achieve reduction of harm from weather-associated disasters, and increased resilience by adaptations to the effects of climate change.<sup>68</sup>

Analyzing climate-associated risks will likely require multiple independent sources of data and extrapolation based on a range of scenarios.<sup>69</sup> Obviously, considerable uncertainty exists in such an approach. In addition, the various risks will need to be prioritized in terms of costs and benefits so decision-makers can provide appropriate management actions.<sup>70</sup>

Some thinkers have advocated a shift away from a human-centric worldview and that to fully address the effects of climate change, including mass extinctions, the extent of the human enterprise on earth needs to shrink. The cause has been opined to rest on implicit belief in the superiority of humans to other life forms. Learning to inhabit the earth and to steward the finite resources of this planet may require a new vision of humanity as having equal value to other life forms; only this change in attitude will ensure that the pursuit of scaling back the human enterprise will be successful.<sup>71</sup>

## 9.4 FINAL THOUGHTS

It was threatening to rain the day I completed the draft of this book. Fearing that Boundary Waters Aquatic Center would be closed for the reasons discussed in Chapter 8, I chose another indoor pool in nearby Cobb County for a swim to begin the day. As I got out of my car, thunder rumbled and fat raindrops splatted on the pavement. Once in the pool area, the lifeguard approached me.

“Is it bad out there?” she asked.

“Not too bad,” I told her.

It was a lie. I instantly decided I would give the answer that would keep the pool open and enable me to swim.

Based on the ethics of intention, my lie was immoral.<sup>72</sup> Even knowing the vanishingly tiny risk of lightning, I chose to subject myself and the other swimmers to that risk.

As explained in Chapter 8, many who act in the role of scientist are all too willing to distort scientific findings to serve ulterior purposes, with consequences both large and small. Unfortunately, the actions of a number of so-called scientists have engendered distrust of experts in the mind of public. The thinking is: these are paid experts—they’ll do the bidding of whoever is paying them.

David Zaruk is a professor at Odisee University College in Brussels. His blog is at <https://risk-monger.com>. He delivered a keynote speech at the International Union of Pure and Applied Chemistry global conference on crop protection in May 2019. His take on the precautionary principle is thoughtful and amusing. He always carries an umbrella, and opened it during his address to make the point that carrying an umbrella on a sunny day is precautionary. He points out that precautionary thinking is never wrong—but much of the time, such thinking is not right.

With a precautionary approach, actions are often taken without sufficient knowledge to fully understand the consequences. With “wicked” problems, a precautionary approach and acting without sufficient understanding will almost always lead to detrimental and unanticipated consequences.

Whether “wicked” problems are addressed with active measures or a sea change in attitudes and beliefs, as suggested for climate change, remains to be seen. The most important task for a risk analyst in the 21st century is to refute both probabilistic and precautionary thinking. Your job will be to provide decision tools for societal decision-makers. In this role, never forget that, as a risk analyst, your best asset is your integrity.

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