CHAPTER ONE

INTRODUCTION TO RISK ASSESSMENT IN PUBLIC HEALTH

Mark Robson
Fred Ellerbusch

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

—JOKE TOLD AT AN EPA RISK ASSESSMENT MEETING

Learning Objectives

Students who complete this chapter will be able to

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

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

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

Where to Begin?

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

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

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

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

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

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

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

What Is Risk?

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

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

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

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

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

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

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

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

ing lines and the result is—nothing. The behaviors that result in environmental risks associated with entanglements continue because we are focused on perception rather than reality. When the lack of environmental literacy is combined with priority setting, the results can lead to the funding of programs that may not represent the greatest opportunities for risk reduction.

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

Acceptable Risk

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

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

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

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

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

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

Risk Assessment Is Not New

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

The ancient Greeks believed that estimating risk was possible.

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

New Risks Arising from Common Public Health Practices

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

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

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

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

Risk in Context

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

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

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

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

Thought Questions

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

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Further Reading

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- Kammen, D., and Hassenzahl, D. *Should We Risk It? Exploring Environmental, Health, and Technological Problem Solving.* Princeton, N.J.: Princeton University Press, 1999.

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CHAPTER TWO

THE RISK ASSESSMENT–RISK MANAGEMENT PARADIGM

Gilbert S. Omenn

Learning Objectives

Students who complete this chapter will be able to

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

Definition of Risk

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

Historical Perspectives

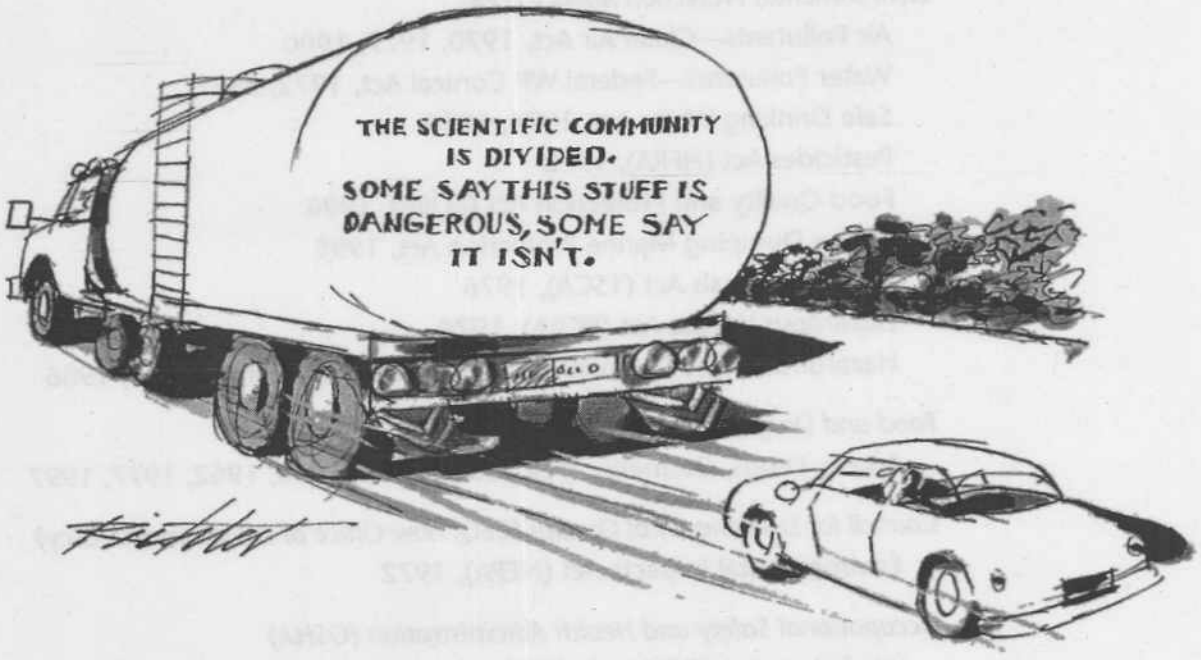
Over the past 30 years public health scientists and policy makers have developed and applied systematic approaches to understanding and evaluating the extent of exposures to environmental agents, the nature of potential hazards to health, the variation in susceptibility to such adverse effects, and the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

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

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

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

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



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

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

The Red Book

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

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

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

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

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

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

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

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

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

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

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

The Objectives of Risk Assessment: Statutes and Programs

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

EXHIBIT 2.2. OBJECTIVES OF RISK ASSESSMENT.

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

Biological End Points

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

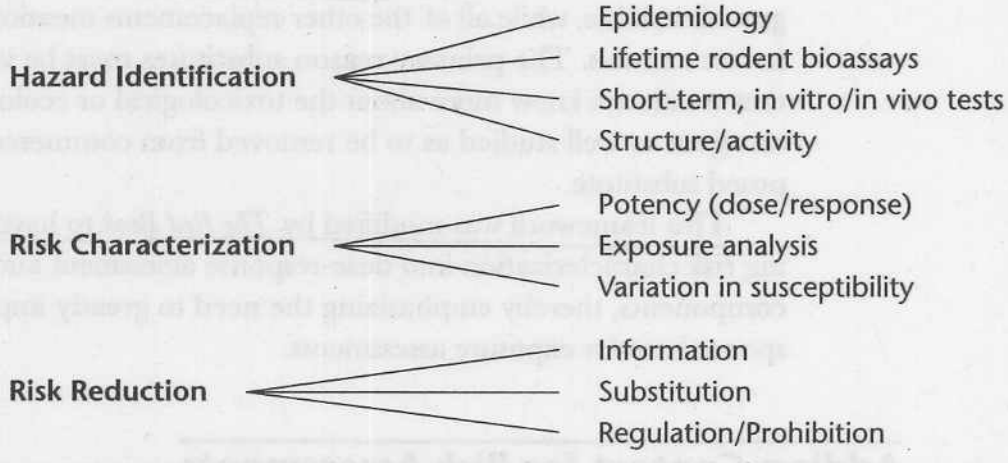
A Framework for Regulatory Decision Making

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

EXHIBIT 2.3. BIOLOGICAL END POINTS.

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

FIGURE 2.2. FRAMEWORK FOR REGULATORY DECISION MAKING.



Source: Calkins and others (1980).

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

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

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

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

Adding Context for Risk Assessments

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

EXHIBIT 2.4. BUILDING INFORMATION ABOUT CONTEXT.

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

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

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

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

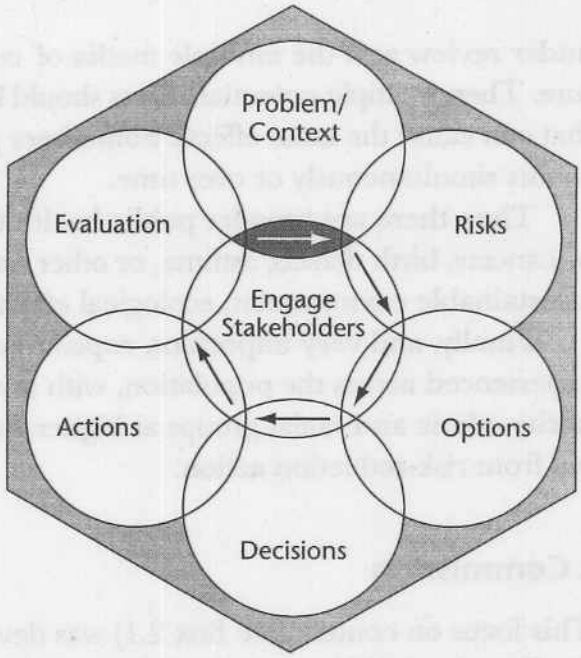
The Risk Commission

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

BOX 2.1. CONTEXT.

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

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



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

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

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

Special Challenges for Risk Assessment of Chemicals

Data and Testing

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

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

Extrapolation

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

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

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

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

Variation and Uncertainty

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

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

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

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

Emerging Contributions from Eco-Genetics

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

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

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

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

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

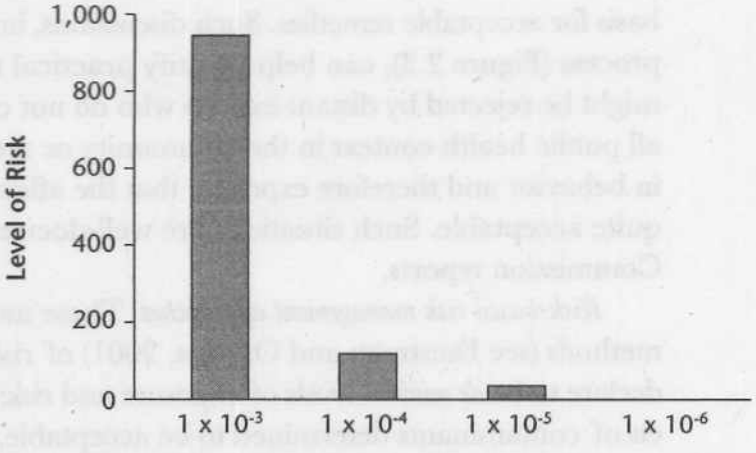
Risk Management–Risk Communication Approaches

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

EXHIBIT 2.5. ESSENTIAL COMPONENTS FOR RISK REDUCTION.

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

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



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

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

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

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

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

EXHIBIT 2.6. VARIOUS RISK MANAGEMENT AND RISK COMMUNICATION APPROACHES.

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

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

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

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

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

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

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

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

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

Thought Questions

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

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