PART I

CANCER RISK ASSESSMENT, SCIENCE POLICY, AND REGULATORY FRAMEWORKS

CHAPTER 1

CANCER RISK ASSESSMENT

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1.1. CANCER RISK ASSESSMENT

1.1.1. Cancer in the United States

Cancer is a group of diseases that result from abnormal and prolific cellular division. Based on current U.S. National Cancer Institute's Surveillance Epidemiology and End Results (SEER) of cancer prevalence, it is estimated that more than 10 million people were living with cancer in the United States in 2005 (NCI 2008). The American Cancer Society predicts that 1 in 2 males and 1 in 3 females will develop some type of cancer in their lifetime, and that 1 in 4 males and 1 in 5 females is at risk of dying from this disease (NCI 2007a,b). Cancer is undoubtedly a substantial threat to public health.

Understanding the etiology of cancer, identifying methods of prevention or treatment, and determining the carcinogenicity of the chemicals we use in our everyday lives are the objectives of many of our government divisions, academic institutions, and health-care industries. However, for public health agencies charged with quantifying safe levels of exposure to protect public health, these tasks are not simple matters of using biology to inform the standard-setting process; instead, gaps in science must be filled using a number of assumptions that are based both on scientific inferences and policy judgments.

Under Congressional delegation, the broad mission of public health agencies is disease prevention. This includes a wide range of activities from providing education about healthy living to regulating the use and dispersion of agents that are known, or suspected, to cause cancer or other diseases. The basic principle of cancer risk assessment is to characterize both the weight of evidence (WOE) that the agent might be capable of causing cancer and the magnitude of risk, given past, current, or future exposure levels. The fundamental objective is to determine the threshold at which exposure to the agent poses no appreciable risk to humans or, in the absence of mechanistic knowledge, to define an acceptable risk for suspect carcinogens.

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1.1.2. Historical Perspectives of Cancer Risk Assessment

Imagine a time when there was no exposure assessment, no evaluation of dose–response relationships (potency), and no particular attention paid to mechanisms of action to define the relevance of responses in animals to diseases in humans, as well as a time when the science of risk assessment to address environmental carcinogens was not developed. This time existed when the U.S. Environmental Protection Agency (EPA) was created in 1970, and it existed until the first Federal policy to adopt the use of risk assessment and risk management was announced by the Agency in 1976 (Albert et al. 1977; USEPA 1976). This policy was accompanied by the first guidelines for carcinogen risk assessment (USEPA 1976) and the establishment of an Agency group to carry out these assessments (named the Carcinogens Assessment Group, or CAG). The approach was novel at the time; however, it borrowed from the experience of radiation risk assessment, where a common mechanism of action was known and dose–response relationships in humans had been reasonably well characterized. Of course, large knowledge gaps existed. For most agents suspected of causing cancer, evidence was from high-dose studies in animals that relied on two dose levels to define cancer potential for humans who experienced much lower environmental exposures. Although controversial at the time, the science of risk assessment has developed into the internationally accepted approach to evaluate carcinogen risk associated with of exposure to environmental agents, food contaminants, and occupational contaminants. These approaches also have dictated close scrutiny of the scientific principles that lead to improved methods of addressing potency, mechanisms of action, test methods, exposure, and internal dose relationships. This section describes the landmarks and key events in the evolution of this science.

Not long after the EPA was established, it began evaluating carcinogenesis data and translating its findings into public policy. These early decisions spawned the necessity to depart from simple qualitative characterization of tumors in humans or animals to incorporate the reality of exposures at low doses, far below those in the studies, and the potential for harm associated with these low-dose exposures. Because the Agency was newly developed, there was no precedent for regulating carcinogens in the environment.

The early years of the EPA were a time of enormous zeal to cleanse the environment, especially of carcinogens that were thought to be the principal cause of a "cancer epidemic." The Food, Drug, and Cosmetic Act (FDCA) had a provision for regulating intentional food additives to a zero-tolerance level, meaning that evidence of cancer by tumor formation in animals or humans was sufficient cause for banning the agent. The same zero-tolerance policy was attempted for a wide range of environmental agents thought to be potential carcinogens, including three major pesticides: dichlorodiphenyltrichloroethane (DDT), aldrin/dieldrin, and chlordane/heptachlor, although the cancellation of DDT was probably more compelled by ecologic harm (USEPA 1972, 1975). Between 1970 and 1975, the EPA moved to suspend their use. The cancellation of these three pesticides set the zero-tolerance policy in motion and became what was judged to be the Agency's cancer policy. However, it quickly became evident that a zero-tolerance policy was impractical.

For many economically important products, it was impossible to remove all exposure to agents suspected of having the ability to cause cancer (e.g., low-level exposure to benzene, a known human carcinogen, in gasoline). The policy was also highly controversial. Using the qualitative evidence of tumors in animals or humans, attorneys at the EPA had summarized the scientific information needed to characterize an agent as carcinogenic in legal briefs at the conclusions of the hearings to cancel the pesticides listed above. These summary statements were referred to in legal motions as "Cancer Principles." The intent of these statements was to establish the foundation for the EPA's authority to protect public health from exposure to environmental carcinogens. This approach received substantial criticism from the scientific community, parts of the private sector, and the Congress (Anonymous 1976). The criticism was largely based on the fact that the complex field of carcinogenesis could not be reduced to simple summary statements (USEPA 1976). In addition, there was concern that the Agency would take a broad approach to cancer regulation by labeling agents as carcinogenic in humans if they were carcinogenic in animals, treating all agents as if they had equal potency, or regulating without information about exposure and the specific threat of a particular agent.

Given the large number of chemicals to which people are exposed in their everyday lives, there was a substantial need to establish a basis for setting priorities and balancing the risks associated with their use in terms of social and economic factors, as called for by the specific statutes under which public health agencies operated, including the EPA, which had inherited very broad authorities (Anderson 1983). Ultimately, the failure of the zero-tolerance policy led to the development of the risk assessment framework at the EPA. It was not until 1979 that other federal agencies joined the EPA in an effort to establish interagency guidance for conducting carcinogen risk assessments (Albert et al. 1977; IRLG 1979c; USEPA 1976). This initial risk assessment approach was developed to answer two questions (Anderson 1983):

1. How likely is the agent to be a human carcinogen? This step involves evaluating all of the relevant biomedical data to determine the total weight of evidence (WOE). At that time, the WOE was ranked from strongest to weakest in a scientific context. The strongest evidence was obtained from human data that were supported by animal bioassay results. Substantial evidence of carcinogenicity could be obtained from laboratory animal bioassay results showing replication of effects across species related to dose levels, and suggestive evidence could be obtained from weaker associations in animal studies. Other evidence from *in vivo* or *in vitro* studies was also considered.
2. On the assumption that an agent is a human carcinogen, what is the magnitude of its public health impact given current and projected exposures? This step is quantitative in nature and involves establishing a dose–response relationship to extrapolate to low levels of exposure, where environmental exposures generally occur, and evaluating the magnitude of the exposures of interest. Its purpose was to provide regulators a sense of the cancer potency of the agent, and some information about the public health impacts associated with exposures. In this step, risks were bracketed between an upper and lower

bound approaching zero. The upper bounds were expressed both in terms of the individual increased cancer risks in the exposed population and the nationwide impact in terms of the annual increase in cases.

Of particular note: (1) These first guidelines called for revising each risk assessment as better information became available, a goal that has been rarely realized. (2) Gaps in scientific knowledge were to be filled with public health protective assumptions to err on the side of safety, an early application of the precautionary principle.

Over the last several decades, the Agency has sought to extend guidelines for carcinogens to incorporate improvements in our understanding of the cancer process. Because risk assessment necessarily relies on both science and policy judgments, these guidelines are essential to ensure that a consistent approach to risk assessment is taken. The effort to bring consistency to risk assessment is evolving and has produced revisions of guidelines and standard practices (examples of which are shown in Table 1.1). The most fundamental endorsement of the risk assessments

TABLE 1.1. Historical Perspectives of the Development of the Risk Assessment Process

Year	Document	Details
1975	*Quantitative Risk Assessment for Community Exposure to Vinyl Chloride* (Kuzmack and McGaughy 1975)	This was the first risk assessment document to be completed by the EPA.
1976	*Interim Procedures and Guidelines for Health Risks and Economic Impact Assessments of Suspected Carcinogens* (USEPA 1976)	This document communicated the EPA's intent to include "rigorous assessments of health risk and economic impacts" in the regulatory process.
1978	*Hazardous substances summary and full development plan.* United States. Interagency Regulatory Liaison Group (IRLG 1979a)	This document describes laws and legislation regarding hazardous substances and chemicals.
1979	*Publications on toxic substances.* United States. Interagency Regulatory Liaison Group (IRLG 1979b)	This document reports basic facts about toxic substances and describes the publications that are available from many federal agencies.
1980	*Integrated Risk Information System (IRIS)*	This database reports human health effects that may be related to chemicals found in the environment.
1983	*Risk Assessment in the Federal Government: Managing the Process* (NRC 1983)	Commonly referred to as the "Red Book," this document was published by the National Academy of Sciences and described methods for risk assessment in the federal government. The EPA adopted and implemented the risk assessment methods that were outlined in this book.

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TABLE 1.1. *(Continued)*

Year	Document	Details
1984	*Risk Assessment and Management: Framework for Decisionmaking* (USEPA 1984)	Published by the EPA, this document illustrated the strengths and weaknesses of the risk assessment process and emphasized the need to make the process as transparent as possible.
1985	*Chemical Carcinogens: A Review of the Science and Its Associated Principles* (OSTP 1985)	Published by the U.S. Office of Science and Technology Policy (OSTP), this document provides a complete review of the application of epidemiology in carcinogen risk assessment.
1986	*The Risk Assessment Guidelines of 1986a* (USEPA 1986b)	This EPA document provided guidelines for evaluating the human and animal evidence of carcinogenicity, as well as a classification scheme for categorizing the level of risk associated with a particular agent (i.e., limited, inadequate, no data, or no evidence).
1986	*Guidelines for Carcinogen Risk Assessment* (USEPA 1986a)	The purpose of these guidelines was to outline a procedure that EPA scientists could use to assess the cancer risk associated with exposure to chemicals in the environment. This document was also used to inform the public about the process of cancer risk assessment.
1989	*Risk Assessment Guidance for Superfund, Vol. I: Human Health Evaluation Manual (Part A)* (USEPA 1989)	Published by the EPA Office of Solid Waste and Emergency Response (OSWER), this is the first of a series of guidance documents on risk assessment for the Superfund.
1996	*Proposed Guidelines for Carcinogen Risk Assessment* (USEPA 1996)	Because limitations were identified in the 1986 carcinogen risk assessment guidelines, new cancer risk assessment guidelines were set forth that allowed scientists the flexibility to incorporate relevant biological information into the assessment process. The new guidelines were reviewed by the EPA Science Advisory Board (SAB) in 1997. The guidelines were made available for public comment in 2001 and then were reviewed again by the SAB in 2003.
1997	*Exposure Factors Handbook.* U.S. EPA (USEPA 1997)	Published by the EPA National Center for Environmental Assessment (NCEA) within the EPA's Office of Research and Development (ORD), this document provides data on exposure activities and other parameters for assessing exposure to contaminants in the environment. The 1997 handbook updates the 1989 original.

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TABLE 1.1. *(Continued)*

Year	Document	Details
2002	*OSWER Draft Guidance for Evaluating the Vapor Intrusion to Indoor Air Pathway from Groundwater and Soils (Subsurface Vapor Intrusion Guidance)* (USEPA 2002)	Published by the EPA Office of Solid Waste and Emergency Response (OSWER), this document provides guidance for the evaluation of the vapor intrusion exposure pathway.
2003	*World Trade Center Indoor Environment Assessment: Selecting Contaminants of Potential Concern and Setting Health-Based Benchmarks* (USEPA 2003)	This document, published by the Contaminants of Potential Concern (COPC) Committee of the World Trade Center Indoor Air Task Force Working Group, provides guidelines and methodologies for setting health based standards for chemicals in settled indoor dust.
2005	*Guidelines for Cancer Risk Assessment* (USEPA 2005)	The formal guidelines for cancer risk assessment were initially developed in 1986 and were finalized in 2005. After almost two decades of scientific input and progress, the final guidelines were designed to be flexible, with the ability to evolve as scientific advancement occurs.
2008	*Child-Specific Exposure Factors Handbook* (USEPA 2008a)	Published by the National Center for Environmental Assessment (NCEA) within the EPA's Office of Research and Development (ORD), this document supplements the 1997 Exposure Factors Handbook with child-specific data on exposure activities and other parameters for assessing exposure to contaminants in the environment.
2009	*The U.S. Environmental Protection Agency's Strategic Plan for Evaluating the Toxicity of Chemicals* (USEPA 2009)	In response to modern advances in computational and molecular biology, the EPA developed a strategic plan in 2009 to outline an approach for transforming and improving toxicity testing and risk assessment over the next 10 years. The premise of the proposed new plan is that risk assessors should consider how genes, proteins, and small molecules interact in the molecular pathways to maintain cellular function and how exposure to agents in the environment could disrupt these pathways. The strategic plan is built upon three components: (1) toxicity pathway identification and chemical screening prioritization, (2) toxicity pathway-based risk assessment, (3) institutional transition.

that had been practiced at EPA since 1976, where approximately 150 carcinogen risk assessments had been completed in the first eight years, occurred in 1983 when the National Research Council (NRC) of the U.S. National Academies of Science (NAS) endorsed risk assessment as a proper process and defined specific steps for hazard identification, dose–response assessment, exposure assessment, and risk characterization as the risk assessment paradigm (NRC 1983). This endorsement created wider applications of risk assessment, which rapidly expanded across all federal regulatory agencies and beyond to state agencies and international communities. The specifics of this process are described in the following section.

Present-day risk assessment methodologies have an increasing emphasis on physiologically based pharmacokinetics (PBPK) or toxicokinetic models and mode of action (MOA). Such models have been developed to predict exposure levels in target tissues for a large number of agents. PBPK models are especially useful in the risk assessment context because they allow data to be extrapolated across species, dose levels, and routes of exposure.

1.1.3. The Defining Steps in Cancer Risk Assessment

The NAS has developed risk assessment strategies and guidelines that are used by many agencies in cancer risk assessment to answer four fundamental questions: (1) Is the agent a carcinogenic hazard? (2) At what dose does the agent become a carcinogenetic hazard? (3) What is the current and expected extent of human exposure to the agent? (4) What is the estimated disease burden expected from exposure to the agent? The strategies used to answer these questions are divided into four actions (NRC 1983):

- **Hazard Identification.** The total weight of the evidence from epidemiologic, animal, and toxicological studies is evaluated to determine the toxicity and carcinogenicity of an agent. In addition, as scientists begin to understand the process by which healthy cells transform into malignant cells, the use of mechanistic information is becoming more common in risk assessment. This may involve identifying the precursor events that may lead to increased cancer risk, as well as the specific genetic or cellular processes that occur during carcinogenesis.
- **Dose–Response Assessment.** The toxic effect of an agent is dependent upon many factors, including the amount of agent that is ingested, the route of exposure, and the specific endpoint under evaluation. Dose–response assessments are primarily focused on determining the safe dose for human exposure for noncarcinogens or acceptable risk levels for carcinogens. Because thresholds for carcinogen activity could not be defined as had traditionally been the case for noncarcinogens, the first risk assessment guidelines at the EPA relied on a linear, nonthreshold, dose extrapolation model for placing plausible upper bounds on risk; the real risks at low doses were thought to be lower, even approaching zero. Dose–response assessments are generally conducted in animals and use empirical, physiologically based toxicokinetic,

or mechanism-based dose–response modeling techniques. In contrast, safety assessments for noncarcinogens historically relied on (a) establishing a no observed effect level (NOEL) or a lowest observed adverse effect level (LOAEL) in animals and (b) reducing this level by application of various safety or uncertainty factors to arrive at a safe dose for humans. Today, there is a convergence of methods for carcinogens and noncarcinogens, at least academically, to utilize understandings of toxicokinetics and toxicodynamics to arrive at safe exposure levels.

- **Exposure Assessment.** The fate of an agent in the environment and the extent to which humans will be exposed to the agent is determined through exposure assessment. The primary interests in exposure assessments are to determine the magnitude, frequency, and duration of the exposure. This assessment involves determining the environmental fate and transport of the agent, as well as evaluating the routes of potential exposure (i.e., inhalation in the air, ingestion in food or water, and through dermal contact). The most detailed guidance for exposure assessment is found in the EPA's *Risk Assessment Guidance for Superfund*, Volume I (USEPA 1989) and the EPA's *Exposure Factors Handbook* (USEPA 1997).
- **Risk Characterization.** Using both (a) the results of the qualitative hazard identification to express the WOE that an agent poses a cancer risk and (b) the quantitative information obtained from the dose–response modeling together with the results of the exposure assessment, the risk characterization step fundamentally describes the risk associated with exposure to an agent at various levels of exposure for the circumstances of concern.

The fact that there are scientific uncertainties in these steps has long been recognized. While there are no formal methods to fully characterize the uncertainties in the hazard assessment and dose–response stages (USEPA 2005), methodology and mathematical techniques exist for accounting for uncertainty (and variability) in the exposure assessment stages. Monte Carlo risk analysis modeling, for example, is a mathematical tool that can be used to describe the impact of uncertainty in a specific exposure scenario. It provides a probability distribution for each uncertainty parameter in the model and then can calculate thousands of probability scenarios. This tool allows risk assessors to model the unavoidable uncertainties that are inherent in the risk assessment process, including the occasion when conflicting expert opinions needs to be combined (Vose 1997).

The NAS also defined a separate step, *Risk Management*, where the level of acceptable risk is established. For suspected carcinogens, an acceptable risk range of one in a million to one in ten thousand has been chosen by the EPA and most other public health agencies as the acceptable risk range for regulatory purposes, with risk becoming less acceptable as it rises above the presumptively safe level of one in ten thousand (40_CFR_Part_61 1989). In addition, the results of any necessary risk–benefit analyses and scientific uncertainty analyses, as well as other social and economic issues as defined by the enabling statute, may be considered at this stage in the process.

1.1.4. The Mode of Action (MOA)

As described in the *Guidelines for Cancer Risk Assessment* (USEPA 2005, pp. 1–10), the MOA 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." In fact, the severity of effect associated with exposure to an agent largely depends on the interaction between the biology of the organism and the chemical properties of the specific agent (USEPA 2005). In terms of cancer risk assessment, theoretically the potential carcinogen effect of an agent can be identified through modes of action that influence mutagenicity, mitogenesis, inhibition of cell death, cytoxicology, and immune function (USEPA 2005). Conclusions about the MOA for a particular agent are based on the following questions (USEPA 2005): (1) Do animal tests sufficiently support the hypothesized MOA? (2) If the MOA is supported by animal models, is the same action relevant to humans? (3) Are there specific populations or life stages in which humans are more vulnerable to the MOA? This information is included in the final risk assessment narrative that summarizes the total weight of the evidence regarding the potential carcinogenicity of an agent.

Because the MOA is based on physical, chemical, and biological processes, it is possible for an agent to have more than one MOA at different sites within the body. This makes it impossible to generalize the results obtained for one endpoint to other sites within the body. Information on the MOA often includes tumor data in humans, tumor data in animals and observations from *in vitro* test systems, and the structural analogue of the agent (USEPA 2005). As with all components of risk assessment, establishing the MOA of an agent can only be defined with confidence where complete data packages, rather than generic assessments or general knowledge of the agent, provide the foundations. When determining if the MOA observed in animal models is relevant to humans, risk assessors must rely on many sources of information including consideration of the tumor type, the number of studies conducted at each site, and the subgroups evaluated (gender, species, etc.), the metabolic activation and detoxification process observed in the animal model and in humans, the route of exposure, the dose, and the effect of dose and time on the progression of the tumor (see Chapter 13) (USEPA 2005). Only rarely are complete data sets available for defining the MOA. Most often the available information can provide only partial certainty about the MOA and its contribution to the WOE evaluation.

1.1.5. Accounting for Scientific Uncertainty

One of the greatest challenges of risk assessment is to account for and manage the scientific uncertainty associated with each step in the assessment process. Uncertainty is an unavoidable consequence of evaluating the fate of an agent in our dynamic environment and complex human systems. Sources of uncertainty in assessing the carcinogenicity of an agent include: (1) the parameter values resulting from data that are limited or inadequate, (2) the parameter modeling caused by inherent limitation

in the models that are used to evaluate exposures and outcomes, and (3) the completeness of the assessment because of the often infeasible task of exhaustively evaluating all possible components of risk (USEPA 1997). In addition, there is uncertainty associated with applying the results of laboratory animal studies to humans (i.e., interspecies extrapolation), estimating the risk of low-dose ambient exposures from high-dose animal studies (i.e., dose extrapolation), and accounting for the needs of susceptible populations (i.e., intraspecies extrapolation). Given these intrinsic challenges, it may be impossible to guarantee that the best outcome identified in the risk assessment process will actually occur; however, it is imperative that public health decisions are made despite these uncertainties. The consequence of not doing so would be paralysis of the public health and regulatory systems (Bean 1988).

1.2. THE WEIGHT OF EVIDENCE (WOE) FOR DETERMINING CARCINOGENICITY

1.2.1. Epidemiologic Studies

Results from well-conducted epidemiologic studies provide the strongest weight of evidence (WOE) in cancer risk assessment. Epidemiology is the science of understanding the distribution of disease among humans and the factors that increase or decrease the risk of disease incidence (see Chapter 15). Because epidemiologic studies always measure an exposure (i.e., to a toxic agent) and an outcome (i.e., a specific cancer type), they are of great value to the cancer risk assessment process. Nevertheless, most observations in human populations have occurred when populations have been inadvertently exposed at high levels, above those commonly experienced in the environment. Epidemiologic studies are conducted in humans; therefore there are no issues related to species-to-species variation; however, other factors must be considered when estimating how the carcinogen potential of an agent may change when exposures are far lower or when population circumstances are at issue—for example, when lifestyle factors of the individual or population are concurrently assessed. The best evidence comes from well-conducted epidemiologic studies that are sufficiently powered to test a specific hypothesis and are backed up by confirmatory animal studies. However, well-conducted epidemiology studies are available for only a limited number of substances and often have limited uses because of difficulties involved in interpretation.

Unlike animal studies that are conducted in a controlled setting within the laboratory, epidemiologic studies seek to evaluate humans in their natural environments. This is both advantageous and challenging for the risk assessment process. Well-conducted epidemiologic studies will often have many of the following attributes (USEPA 2005): The objectives and the hypothesis are clearly stated, the people included in the study have been properly selected, the exposure has been characterized, the length of the study is long enough to ensure adequate time for the disease to occur, design flaws that may bias the results have been identified and minimized, factors that may confound the relationship between the exposure and the outcome have been properly accounted for, enough people have been enrolled in the study

to detect the desired measure of effect, the data have been collected and analyzed using appropriate methods, and the results have been clearly documented. Because it is possible for one or more of these factors to be inadequate, epidemiologic studies that show no association between exposure to an agent and a cancer outcome do not prove that an agent has no carcinogenic potential. Therefore, the limitations of epidemiologic studies that are used in the risk assessment process must be identified and considered.

The types of epidemiologic studies used by risk assessors include case–control studies, cohort studies, descriptive epidemiologic studies, and case reports:

- Case–control studies enroll people who have the disease (i.e., cases) and people who do not have the disease (i.e., controls) and then look retrospectively to assess the differences in exposure between the two groups. It is possible to determine causality from a well-conducted case–control study; overall evidence of causality is judged as a WOE that takes account of all qualified epidemiologic studies.
- Cohort studies enroll people who have been exposed to the agent of interest and people who have not been exposed to the agent, and then they follow the two groups through time to see which group (if either) has a higher incidence of disease. It is possible to determine causality from a well-conducted cohort study; overall evidence of causality is judged as a WOE that takes account of all qualified epidemiologic studies.
- Descriptive epidemiologic studies do not have a temporal component like case–control or cohort studies. Rather, this type of study evaluates factors that may influence the incidence of a disease, such as demographic or socioeconomic characteristics. It is not possible to determine causality from a descriptive epidemiologic study. Rather, this type of study is often used to generate a hypothesis that can be tested in case–control or cohort studies.
- Case reports are used to describe specific events or outcomes that occurred in a small number of people. It is not possible to determine causality from case reports, but they are useful for identifying unique events, such as the effects of a unique exposure or the incidence of an unusual tumor and for generating hypotheses that may be tested in follow-up, appropriately designed studies.

The premise of epidemiology is to determine if there is an *association* between an exposure and an outcome. However, the goal of risk assessment is to determine if the WOE from all human studies establishes that the agent is known to cause the outcome. In 1965, Sir Bradford Hill developed a list of criteria that is used to help scientists and epidemiologists assess whether the relationship between an exposure and an outcome in epidemiological studies is causal (Hill 1965). Meeting each criterion does not provide a definitive determination of causation, but it does provide substantial information that can be used when the weight of the evidence is evaluated. In addition, the Hill criteria are intended for use in the evaluation of human data, not the combination of human and animal data. As listed below, the EPA has slightly modified the original list that was developed by Hill so it can be used in modern-day risk assessments (USEPA 2005):

1. The association is observed across many different independent studies.
2. The magnitude of the association is large.
3. There is specificity in the observed association such that one exposure leads to one outcome. (*Note*: This is currently believed to be the weakest of all of Hill's criteria.)
4. The exposure precedes the outcome, which leads to a temporal relationship between the two factors.
5. There is a biological gradient that is the result of a strong correlation between the exposure and the outcome.
6. The relationship between the exposure and the outcome is biologically plausible.
7. The relationship between the exposure and the outcome is observed in animal studies or other types of studies.
8. There is experimental evidence of causation from human populations. (*Note*: Given the ethical boundaries associated with using humans in experiments, data from these types of studies are rarely generated.)
9. Information of the structural analogues of an agent can provide information about causality.

In addition, given the complexity of the risk assessment process and the growing amount of scientific literature on this topic, the use of meta-analyses is becoming a necessary skill of risk assessors. Meta-analysis is a valuable statistical technique, in which the potential health effects of an exposure are quantitatively evaluated across the entire body of relevant epidemiologic literature. Meta-analysis differs from a qualitative review of the literature because it is data-driven rather than narrative-based. Conducting a meta-analysis can be a very time-consuming and tedious process, especially when there is a large body of literature available on a specific topic. However, there are many benefits to applying this tool to cancer risk assessment. First, because the results of epidemiologic studies are sometimes conflicting, meta-analysis allows the scientific experts to formally identify sources of heterogeneity across studies. Second, meta-analysis provides researchers with an opportunity to examine selected subgroups of studies and to determine how specific studies influence the overall trend observed in the literature at large. This is especially valuable in cancer risk assessment because factors beyond exposure to the agent may be influencing the risk of cancer. Additional uses of epidemiology information in cancer risk assessments are described in the later part of this book (Chapter 15).

1.2.2. Animal Models

Whole-animal test models are commonly used to determine the potential carcinogenicity of an agent (see Chapter 14). Animal models provide a platform to evaluate cancer outcomes after long-term exposure to the agent at various doses, as well as to identify possible modes of action. Although epidemiologic studies are favored

because they are conducted in human population, data from animal studies are often the primary data available and do provide valuable information to the risk assessment process because they allow the relationship between the agent and the cancer to be evaluated in a highly controlled environment. In addition, because ethical considerations are different for animals from humans, it is possible to learn a great deal about the factors that influence the carcinogenicity of an agent (i.e., detrimental doses and lengths of exposure that increase the risk of tumor initiation and promotion in the chosen laboratory model).

If the outcome of an animal study is the presence of an uncommon tumor type, tumors at multiple anatomical locations within the same animal, development of tumors by more than one route of entry, tumors in multiple species, tumors in both genders, progression of a preneoplastic lesion to a malignant tumor, metastatic disease, unusual tumor response, a high proportion of malignant tumors, or clear evidence of dose-related increases in tumor incidence in replicated studies, then substantial credence is given to the carcinogenic potential of an agent (USEPA 2005). On the contrary, an agent is reasonably deemed as having no carcinogenic potential if no malignancies develop from well-conducted, long-term animal studies in more than two species.

1.2.3. Weight of the Evidence Descriptors

As part of the risk assessment process, the total weight of the evidence from the aforementioned studies is used to determine the agent's carcinogenic potential. In an effort to maintain consistency in the assessment and reporting process, agents are typically categorized in some way. The EPA has defined categories that are very similar to categorical schemes used by the U.S. National Toxicology Program (NTP), the International Agency for Research on Cancer (IARC), and the European Union (EU) (USEPA 2005). The example from EPA is as follows. It is possible for an agent to be classified into more than one group if its association with cancer varies by dose or route of exposure.

- **Carcinogenic to Humans.** There is strong evidence of human carcinogenicity. To meet this classification, there must be evidence of causality from epidemiologic studies. If there is not, an agent can still meet this classification if all of the following conditions are met: (1) There is strong evidence of an association but not enough evidence to show exposure to the agent causes cancer, (2) there is extensive evidence that the agent is carcinogenic to animals, (3) the MOA and precursor have been identified in animals, and (4) there is strong evidence that the key precursor events that initiate the MOA in animals also occur in humans.
- **Likely to Be Carcinogenic to Humans.** There is strong evidence of human carcinogenicity, but the weight of the evidence is not sufficient to meet the conditions of the "Carcinogenic to Humans" category. For example, there is strong evidence to support an association between exposure to the agent and cancer, but epidemiologic causality cannot be confirmed. In this category, the agent has generally been carcinogenic to more than one species of animal.

- **Suggestive Evidence of Carcinogenic Potential.** There is evidence to suggest that an agent is carcinogenic, but the data cannot support strong conclusions about its effect. In this category, there are weak associations (that may or may not be statistically significant) between the agent and the cancer outcome in animal or human studies.
- **Inadequate Information to Assess Carcinogenic Potential.** Agents are categorized into this group if there are inadequate or conflicting data of cancer outcomes associated with exposure to a particular agent.
- **Not Likely to Be Carcinogenic to Humans.** Agents are categorized into this group if there is evidence to suggest that there is no association between exposure to an agent and cancer. In some cases, an agent may be carcinogenic in animals, but the MOA is not similar in humans.

1.3. RISK ASSESSMENT IN THE 21ST CENTURY

1.3.1. Using the Advances in Molecular and Computational Biology

In 2009, the EPA released a strategic plan to use new molecular and computational biology technologies in toxicity testing and risk assessment (USEPA 2009). The goal of the strategic plan is to use knowledge about the toxicity pathway to improve how risk assessments are conducted over the next 10 years. Although the complexity of the human body is well appreciated, specific information about toxicity pathways has been lacking. As a result of scientific and technological advances, valuable information about how genes, proteins, and small molecules interact to form pathways that maintain cellular function is quickly emerging (see Part IV). Understanding the manner in which exposure to agents in the environment disrupt these pathways is of high value to the sustained public health.

The goal of the strategic plan is to replace whole-animal studies with *in vitro* tests in human cell lines. This approach would allow the rapid evaluation of new chemicals, chemical mixtures, different exposure scenarios, and the influence of chemicals on sensitive populations. If successful, this approach will be ideal for areas where data from animal and epidemiologic studies are nearly impossible to obtain and the existing knowledge base is lacking for many substances, such as in the fields of developmental toxicology, neurotoxicology, immunotoxicity, and reproductive toxicity. In the new plan, animal models will be used for evaluating mechanisms and the MOA. The plan is built upon three components (USEPA 2009):

- **Chemical Screening and Prioritization.** There is urgent need for the rapid and cost-efficient screening of chemicals so they can be prioritized for risk assessment. This includes chemicals that are produced in high volumes, toxicants in the air, the drinking water Contaminant Candidate list, and chemicals found at Superfund sites.
- **Toxicity Pathway-Based Risk Assessment.** Current risk assessment strategies are challenged by issues related to species extrapolation, dose extra-

polation, and quantifying cancer risk in susceptible populations. In the new plan, disruptions in the baseline biological processes that are likely associated with toxicity pathways will be identified, and their association with adverse health effects will be measured.

- **Institutional Transition.** Adopting a new paradigm for toxicity testing and risk assessment will require changes to the EPA's operations, organization, and outreach. The EPA is expecting that this transition will likely require more than a decade for full implementation.

1.3.2. Genetic Susceptibility

Carcinogenesis is a complex and multistep process that often cannot be simplified into the basic exposure–outcome matrix. The effect an agent has on cancer risk is dependent upon several factors, including, but not limited to, the nature of the individual who was exposed, the dose the individual received, and the length of the exposure. During the formal risk assessment process, it is relatively straightforward to quantify or model the dose levels and the length of exposure an individual may experience under circumstances with defined parameters. In fact, the exposure assessment process has been well informed by guidelines as well as the availability of exposure factors to be used in determining the average concentration an individual might experience over the applicable duration and frequency of exposure. However, determining the genetic factors that may influence cancer risk and then accounting for these findings during the regulation process is challenging. Furthermore, the role of background genetic factors in cancer causation may be far more important than the role of the agent in question. With the completion of the Human Genome Project (HGP) in 2003, a substantial amount of evidence came to light that illustrated the importance of genetic factors in cancer susceptibility and risk. In fact, a person's genetic background is now considered to be a major factor in determining their risk of developing cancer. Genetic variants in key DNA repair genes and carcinogen metabolism genes have been associated with an increase in risk for some types of cancer.

1.4. APPLICATIONS IN RISK MANAGEMENT

1.4.1. Translating Risk Assessment into Risk Management in the United States

Risk management and public policy decisions related to the regulation of carcinogenic agents are largely based on quantitative risk assessments and qualitative assessments of the biomedical evidence (Anderson 1983). Risk assessment is now commonly used to set priorities, determine if there is residual risk present after the best available technologies have been implemented, balance the risks and benefits of using a carcinogenic agent, set standards and target levels of risk to protect public health, and provide information regarding the urgency of situations where populations have been inadvertently exposed to toxic agents (Anderson 1983).

The determination that an agent has the potential to be labeled a suspect or known human carcinogen does not alone provide the quantitative basis for determining a safe level of exposure. As noted from the early work of the Carcinogen Assessment Group (CAG) at the EPA, there are hundreds of agents that show some evidence of carcinogenic potential; however, the relative potency of these agents has been found to vary enormously (Anderson 1983). In fact, some of the chemicals that have the strongest qualitative evidence of carcinogenicity have a relatively low potency. Consequently, risk managers must be cautious and must consider relative potency in setting quantitative standards.

In the absence of the MOA, the quantification of risk has defaulted to a linear nonthreshold dose–response model to establish a public health protective level of risk. The best-defined approaches for evaluating the risk and setting a level of protective risk have been defined under the EPA programs for cleanup of hazardous waste sites. Given the protective nature of the inference judgments, the outcomes of the risk assessment process are intended to be biased toward public health protection, and consequently they are best used as plausible upper bounds on risk (USEPA 2005). The EPA has commonly used an acceptable range of risk of one in a million to one in ten thousand, becoming presumptively less acceptable as risk rises above this level. However, public health agencies across national and international boundaries may arrive at different levels of acceptable risk as a generic matter or for particular agents, depending upon the application of the precautionary principal. For risk management purposes, low risk defined by the linear nonthreshold model in association with conservatively evaluated exposure can define, with a reasonable degree of confidence, when a risk to public health is acceptable and not of concern as a causal agent of disease. However, because these approaches rely partly on science and partly on inference-based public health protective assumptions, they cannot be used to determine causality. Therefore, it is inappropriate to imply that associated levels of exposure are causally related to disease occurrence when the acceptable risk ranges used by public health agencies to quantify standards for exposure and remediation are marginally exceeded (USEPA 2008b).

1.4.2. International Risk Management

In the United States, the science of risk assessment has evolved out of the necessity to make public health decisions in the face of scientific uncertainty. Risk assessment methodologies have been established over the past three decades, and their applications have impacted virtually every aspect of public health and environmental protection in many countries. An example of the far-reaching applications of risk assessment can be found in the World Trade Organization (WTO) Agreement on Sanitary and Phytosanitary (SPS) (Anderson and St. Hilaire 2004; Measures 1994). This agreement requires counties to either (1) adopt the harmonized international standards or (2) use standards based on risk assessment, scientific principles, and scientific evidence if they choose to adopt stricter regulations than the international standards (GATT 1947; Howse 2000; Measures 1994). The WTO provides a platform for resolving discrepancies that arise over the appropriateness of national

standards that are more restrictive than other national or international standards. As of July 2008, the WTO had 153 members (www.wto.org).

In 2007 the regulation on Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) was enacted in an effort to improve the framework in which chemicals are regulated in the EU. REACH requires industry to be responsible for the assessment and management of risks that may be posed by chemicals, as well as to provide the necessary safety information to their users. The overall goal of REACH is to enhance the manner in which public health and the environment are protected from the risks that are associated with the use of synthetic chemicals. It requires that companies work together to complete the registration requirements for all substances that are made in or imported into the EU. REACH requires participation in the Substance Information Exchange Forum (SIEF), which obligates companies to share information from vertebrate studies. In addition, REACH promotes the framework of "One Substance, One Registration" (OSOR), which minimizes the administrative issues that can be associated with this type of regulation. REACH has also established parameters for submitting chemical safety reports that encourage the collection, evaluation, and dissemination of all data based on the elements of risk assessment and public health protection (Environment_Directorate-General_of_the_European_Commission 2009).

Most developed countries have developed their own guidelines and practices for risk assessment. The Society for Risk Analysis and its flagship journal, *Risk Analysis: An International Journal*, serve as an academic forum to share the rapidly advancing sciences in the field. Also, the importance of these sciences and their applications and development is found in the curricula of most major universities.

1.4.3. Risk–Benefit Analysis

Determining the level of risk associated with an agent may not be the only factor that is evaluated when determining when, how, and where the agent will be used. Risk–benefit analyses may play various roles in risk management, to determine if the risk of an agent outweighs its benefits. The enabling statutory language and a variety of other social and economic factors play roles in risk–benefit analysis. Generally speaking, the risk associated with an agent will be tolerated at a higher level if the agent poses substantial benefit (and vice versa). The U.S. Food and Drug Administration (FDA), the U.S. Occupational Safety and Health Administration (OSHA), and the EPA use risk–benefit analyses as permitted by the applicable statute to determine the standard of regulation for a given agent. For example, if the contraindication for a specific type of heart medication is liver cancer in 1 per 10,000 individuals, the risk associated with its use will likely be deemed as more acceptable if the drug reduces the mortality associated with heart attack by 80% than if it reduces mortality associated with heart attack by only 10%.

The EPA's regulation of pesticides is governed by the Federal Insecticide, Fungicide, and Rodenticide Act (FIRFA). Because there are public health benefits associated with controlling pests as well as risk associated with the chemicals used for this purpose, FIRFA requires that the EPA balance the risk and benefits of an agent when determining how it will be regulated. Resulting decisions include

quantifying the risk of disease in the general population that is associated with exposure to the agent after normal use, the risk of disease experienced by the applicators of the agent, and comparative risk for a substitute agent, if available.

The challenge of risk–benefit analyses is to ensure that all costs are accounted for at the social and environmental levels. In addition, one must consider risks and benefits at both the individual and population levels. Certainly, the level of risk that a person is willing to accept is a private and personal decision.

1.4.4. Risk Acceptance and Risk Communication

Information obtained from risk assessments is used to aid public health officials in developing management decisions. However, the public will often view the risks associated with an agent differently than will the scientific experts, even after costly and time-consuming risk assessment efforts have been implemented. These discrepancies may be attributable to difference in how the public and scientific communities define risk, or they may stem from the fundamental lack of trust the public has toward the risk assessment process (Slovic 1991). Regardless, risk perception is an important topic that invariably must be considered before the implementation of regulations or public health management decisions.

The manner in which an individual or different cultures perceive risk is often influenced by demographic, psychological, social, or political factors (Slovic 1991). The perception of risk can vary *between* and *within* individuals, such that two people may perceive the risk of the same agent differently, and a single person may view the risk of an agent differently depending on the current events in their life. Research in this area has consistently revealed many issues that are known to affect how risk is perceived, including (Asante-Duah 2002b): Are exposures to the risk factor voluntary or involuntary? Are the potential or known effects of exposure to the risk factor immediate or delayed? Is the risk factor natural or manmade? Can the risk factor be controlled? If it is controllable, how does the individual perceive their control over the risk factor? Is the type of risk factor new to the individual or are they familiar with it? Are there benefits associated with the risk factor? Are the consequences of exposure to the risk factor manageable or catastrophic? Is the individual exposed to similar risk factors? Are the effects of the risk factor reversible? Are there alternatives to the risk factor? Does the individual view the distribution of the risk factor as equitable within the population? Is exposure to the risk factor continuous or intermittent? Are the consequences associated with exposure to the risk factor tangible?

Understanding and considering these issues is a challenging but essential component of risk management. However, effective risk communication is central to the successful implementation and acceptance of management actions. Risk communication often takes shape in the form of written communication (i.e., newsletters, public notices, warning labels) or verbal communication (i.e., focus groups, public meetings, workshops) (Asante-Duah 2002a). In terms of cancer risk assessment, effective risk communication strategies include, but are not limited to: involving all stakeholders and the public early in the decision-making process; taking the necessary steps to ensure that there is a two-way dialogue between the scientific experts

and the interested parties; anticipating and preparing for the mitigation of controversy; delivering clear, honest, and factual information about the risk factors; and implementing a system to evaluate how all parties perceived the risk communication efforts (Asante-Duah 2002a).

The precautionary nature of risk management decisions made by public health authorities can approach a zero risk tolerance that is not based on the outcome of the risk assessment process or the certainty of the data that underlie the assessment process but rather on social and political influences. The original purpose of risk assessment was to separate important from less important risks and provide a basis for making decisions to protect the public health. With the adoption of risk assessment and risk management as a process for making public health decisions, the concept of achieving zero risk for suspect carcinogens was abandoned as a workable, achievable policy.

The important role of risk assessment is to inform the public health decision process so that responsible decisions in the interest of public health can be made. Extreme application of the precautionary principle, whether motivated by public expectations or regulatory desire to achieve ever lower risk, can lead to a virtual zero tolerance policy; it is the role of risk assessment founded on scientific principles to advise the reasonableness of these policy decisions.

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