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NIOSH Practices in Occupational Risk Assessment

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Foreword

The Occupational Safety and Health Act of 1970 [29 USC 15], through delegation of functions by the Secretary of Health and Human Services, mandates the National Institute for Occupational Safety and Health (NIOSH) to …"develop criteria dealing with toxic materials and harmful physical agents, which will describe exposure levels that are safe for various periods of employment…" [29 USC 669 (a) (3)]. Critical in developing these recommended criteria is assessment of the risk of adverse health effects that workers might experience given exposure to occupational hazards. The foundation for making these recommendations is quantitative risk assessment (QRA). NIOSH QRA is a science-based process that identifies workplace hazards, assesses the response to exposure of those hazards, and characterizes the associated health risks to inform risk management decisions.

NIOSH has over 30 years of experience conducting risk assessment. The methods used are consistent with National Research Council 1983 and 2009 guidance, which is the dominant benchmark in the field. The field of modern risk assessment, established by a broad range of legislation, has been highly productive in addressing issues of health, safety, and the environment. However, over the last few decades the science behind risk assessment has evolved and the utility, impact, and credibility of risk assessments have been challenged. To address these issues, it is important to have a transparent process by which risk assessments are conducted. This document describes the process that NIOSH uses to conduct QRA.

There is a pressing need for risk assessment, particularly of chemical substances. Over 50 million U.S. workers are exposed to hazardous chemicals in the course of their work each year, either by skin contact or by inhaling vapors, gas, dust, or fumes. Toxic chemicals encountered in the workplace pose a wide range of health hazards to workers. Health effects may include irritation, sensitization, respiratory disease, cancer, and cardiovascular, immunological, and reproductive disorders. NIOSH conducts risk assessment when there is limited direct information to make a determination of a safe level of exposure for workers in order to prevent disease, injury, or death. Given limited information, assumptions in NIOSH risk assessment generally favor worker protection. This document and the resultant guidance, such as occupational exposure limits, should provide useful information to all stakeholders who use risk assessment information in the management of occupational hazards.

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Abstract

Exposure to on-the-job health hazards is a problem faced by workers worldwide. Unlike safety hazards that may lead to injury, health hazards can lead to various types of illness. For example, exposures to some chemicals used in work processes may cause immediate sensory irritation (e.g., stinging or burning eyes, dry throat, cough); in other cases, workplace chemicals may cause cancer in workers many years after exposure. There are millions of U.S. workers exposed to chemicals in their work each year. In order to make recommendations for working safely in the presence of chemical hazards, the National Institute for Occupational Safety and Health (NIOSH) conducts risk assessments. In simple terms, risk assessment is a way of relating a hazard, like a toxic chemical in the air, to potential health risks associated with exposure to that hazard. Risk assessment allows NIOSH to make recommendations for controlling exposures in the workplace to reduce health risks.

This document describes the process and logic NIOSH uses to conduct risk assessments, including the following steps:

- Determining what type of hazard is associated with a chemical or other agent;
- Collating the scientific evidence indicating whether the chemical or other agent causes illness or injury;
- Evaluating the scientific data and determining how much exposure to the chemical or other agent would be harmful to workers; and
- Carefully considering all relevant evidence to make the best, scientifically supported decisions.

NIOSH researchers publish risk assessments in peer-reviewed scientific journals and in NIOSH-numbered documents. NIOSH-numbered publications also provide recommendations aimed to improve worker safety and health that stem from risk assessment.

Executive Summary

Introduction

Occupational health risks describe the potential and severity of adverse effects in workers from their exposure to workplace hazards. Herein, *adverse effects* refer to health effects that are changes in the morphology, physiology, growth, development, reproduction, or life span of an organism, system, or population that result in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences [IPCS 2004]. Safeguards, derived from a combination of scientific assessment, engineering, and best management practices, mitigate these risks. Risk assessment is an important tool for informed decision-making on workplace safeguards when there are limited data on risks. Since the 1990s, quantitative risk assessments conducted by the National Institute for Occupational Safety and Health (NIOSH) have buttressed recommendations on limiting chemical exposures and some other workplace hazards. The need for these recommendations is critical given estimates that over 50 million U.S. workers report frequent exposure to chemicals at work each year [Calvert et al. 2013]*.

This report describes the underlying science and general approach NIOSH researchers use in conducting high quality, scientifically sound quantitative assessments of the risks associated with these workplace hazards. It focuses on chemical risk assessment practices; however, some of these practices have benefitted NIOSH assessments of other workplace hazards, such as ionizing radiation and noise. The report informs NIOSH risk assessors, other scientists, stakeholders, and the public on the NIOSH risk assessment process. It is one of many routine exchanges between NIOSH, its stakeholders, and the risk assessment community, both home and abroad, which act to ensure best practices in risk assessment supporting worker protection.

Risk Assessment Process

NIOSH risk assessments are typically carried out by a multidisciplinary team of epidemiologists, toxicologists, biostatisticians, industrial hygienists, and other exposure scientists (e.g., health physicists and chemists), hereafter referred to as risk assessors. NIOSH risk assessments are often conducted in response to investigations prompted by persons who are at risk (e.g., affected workers), risk managers (e.g., employers, regulators), or risk assessors, alone or in combination, who need information on the probability and severity of potential workplace hazards. NIOSH then develops a risk assessment plan containing two key components: (1) a conceptual model that identifies the hazard (sources, stressors, and pathways), persons potentially at risk, and apparent adverse effects; and (2) an analysis plan (work plan) that outlines the analytic components (i.e., data and methods) and interpretative approaches

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*Correspondence with authors (Calvert et al., 2013), who confirmed that about one third of workers participating in the 2010 National Health Interview Survey reported either "frequent occupational skin contact with chemicals" in their main current job over the past year or "frequent occupational exposure to vapors, gas, dust, or fumes" at their longest-held job.

(e.g., risk metrics) to be used. This approach is consistent with recommendations by the National Research Council (NRC) of the National Academies [NRC 2009]. Planning helps to ensure that the risk assessment applies the best scientific methods available, applies the highest-quality evidence, and addresses the needs of the decision-makers (risk managers). Initial plans comprise preliminary information that is subject to change as more information becomes available; therefore, plans may evolve throughout the risk assessment process.

NIOSH risk assessments determine the relationship between the occupational exposure and adverse effects leading to the development of a reference value, either a recommended exposure limit (REL) or a risk management level for carcinogens (RML-CA), to be used to guide exposure control. Data permitting, this determination is preferred to be quantitative. The quantitative risk assessment uses three major components of the risk assessment process that are completed sequentially: hazard identification, dose-response assessment, and risk characterization (Figure 1). Hazard identification is the systematic process for assessing the weight of evidence on whether an agent of interest causes an adverse effect in exposed workers. The findings from hazard identification are characteristic descriptions and information on the exposures of interest, any important cofactors (e.g., other risk factors, moderating factors, mediating factors, or confounders); modes and mechanisms of action; and conditions (e.g., pre-existing diseases) under which changes in exposures change the probabilities or timing of adverse effects. These data are prerequisites for conducting the dose-response assessment. The term *dose-response* is broadly defined as the relationship between the amount of an agent administered to, taken up by, or absorbed by an organism, system, or population and the change developed in that organism, system, or population in reaction to the agent. In NIOSH quantitative risk assessment, the dose-response is generally expressed as the conditional probability of the adverse effect in exposed workers at different levels of occupational exposure, given assumed levels for other direct causes of the adverse effect. In practice, the terms *exposure* and *dose* have been expressed in many ways over time and are often used interchangeably. By strict interpretation, exposure refers to contact between an agent (e.g., hazardous substance) and a target (e.g., human lung tissue), and dose is the amount of the agent administered to, taken up by, or absorbed by the target [IPCS 2004]. The dose-response assessment provides estimates of the dose-risk relationship for use in the third component of risk assessment, namely, risk characterization. Risk characterization is the qualitative and, wherever possible, quantitative determination of the probability of occurrence, including attendant uncertainties, of known and potential adverse effects in workers under defined conditions of exposure to an agent [IPCS 2004]. It reflects the culmination of the planning, problem formulation, and analysis phases of risk assessment to integrate the science of hazard identification and dose-response assessment with risk policy (e.g., target risks). NIOSH uses the output from risk characterization (i.e., a description of risk estimates and attendant uncertainties) in combination with information on available technology (e.g., analytic feasibility) to establish a sound basis for NIOSH recommendations. These recommendations inform decision-makers who are responsible for managing workplace risk. Figure 1 shows the components of risk assessment and their relationship with risk management.

NIOSH risk assessments follow the traditional NRC risk assessment steps except that NIOSH does not use the exposure assessment step [NRC 1983; NRC 2009]. In a risk assessment, exposure assessment is the process of estimating or measuring the magnitude, frequency, and duration of exposure to an agent, along with the number and characteristics of the population exposed [IPCS 2004; NRC 2009]. The exposure assessment is driven by
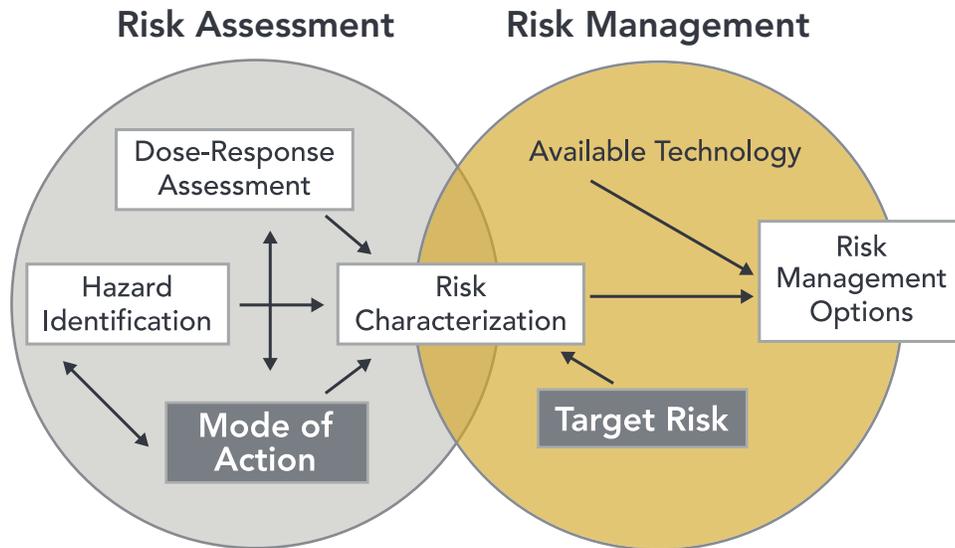
Figure 1. NIOSH risk assessment and risk management processes.

the needs of environmental risk assessments which require information on the extent of human exposure to be able to project population risks and overall disease burdens in risk characterization.

In contrast, NIOSH uses the information from the first two steps of the risk assessment to estimate health risks of individuals from the agent at various levels of exposure. This forms the risk basis for occupational exposure limits for use in risk management. The NIOSH mission, as stated in the Occupational Safety and Health Act, is "…to describe exposure levels that are safe for various periods of employment, including but not limited to the exposure levels at which **no employee** (*emphasis added*) will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience" [29 USC 669 (a)(3)]. Therefore, the extent of exposure described as exposure assessment in the NRC formulation and the at-risk population are implicit.

Similarly defined approaches are used by the Occupational Safety and Health Administration (OSHA) in determining Permissible Exposure Limits (PELs), and in the Integrated Risk Information System (IRIS) implemented by the U.S. Environmental Protection Agency (EPA). The EPA's IRIS comprises two of the four steps (hazard identification and dose-response assessment) described by the NRC. The omission of a formal *exposure assessment* step does not preclude the evaluation of exposure data that are pertinent to other risk assessment steps. For example, the quality of exposure data from observational studies is a common concern in hazard identification and dose-response assessment.

Hazard Identification

Hazard identification is typically the lengthiest component of the risk assessment process. Identifying hazards requires knowledge of both the agent and the adverse effect. Furthermore, NIOSH risk assessors approach hazard identification in terms of supporting quantification of the dose-risk relationship; therefore, its findings are intended to define the

population at risk, the agent, the adverse effect(s) of interest, and any cofactors (e.g., effect modifiers, confounders, or other sources of uncertainty) in sufficient detail to conduct sound quantitative dose-response analyses. Consistent with systematic review principles, the general framework for gathering and evaluating relevant human and animal study data consists of five basic steps: (1) define the causal questions of interest and develop criteria for study (data) selection; (2) develop literature search protocol and conduct search; (3) review, identify, and select relevant information; (4) evaluate and integrate evidence across studies; and (5) synthesize and interpret findings [Rhomberg et al. 2013]. The paths to meeting these steps can vary widely with the specific scientific context. In general, risk assessors judge the weight of evidence in study evaluation by using multiple factors—such as strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy—as first posited by Sir Austin Bradford Hill [1965]. For synthesis and interpretation, risk assessors consider the following factors:

- The design and conduct of studies providing data for risk assessment:
  - Are study results generalizable and relevant to the risk assessment problem?
  - Are results reproducible?
  - Was confirmation or refutation of findings attempted?
  - What factors may jeopardize external validity of the results?

- The characterization of exposure, dose, and adverse effect:
  - What is the utility of the study data for hazard identification?
  - Will these data be suitable for inclusion in the database for the dose-response assessment?
  - What are the sources of measurement error and their potential effects on the dose-response association?

- The degree of data certainty and strength of findings in support of hazard identification:
  - Have researchers used sound statistical methods?
  - Are results robust under alternative assumptions?
  - Have results been over- or misinterpreted?
  - How likely are findings due to chance, bias, residual confounding, or other sources relevant to internal validity of the study?

To improve efficiency, NIOSH often uses hazard identification by other agencies, such as the U.S. National Toxicology Program (NTP), EPA, OSHA, the Mine Safety and Health Administration (MSHA), the Agency for Toxic Substances and Disease Registry (ATSDR), the European Chemical Agency (ECHA), and the International Agency for Research on Cancer (IARC). These agencies have a long history of identifying hazards by using sound and transparent methodologies. Information on hazard identification is also available in the literature.

Relevant data primarily stem from human epidemiologic and animal toxicologic studies. Ideally, the direct estimation of risk from human data is always preferred to using data from experimental animal studies, because: (1) data reflecting actual exposures and responses within the population of interest are inherently superior for risk assessment; and

(2) the uncertainty in extrapolating data from animal toxicologic studies to predicting human risks can be much larger than that in well-designed epidemiologic studies [Hertz-Picciotto et al. 1995; Smith 1988; Stayner et al. 1999]. Although some epidemiologic data may arise from experimental designs, most information pertinent to risk assessment stems from observational studies of working populations (e.g., cohort and case-control studies). Human data are not without limitations; therefore, risk assessments tend to rely on a combination of human epidemiologic and animal toxicologic data for hazard identification and dose-response analyses. In fact, human studies tend to provide evidence of an association between exposure and disease, which can guide the choice of agents, exposure routes, and pathological endpoints for examination in toxicological studies that may contribute greatest to quantifying risks.

In environmental risk assessments, exposure assessment is considered a separate step for assessing the likelihood of exposure for estimating population risks and/or disease burden. In contrast, NIOSH risk assessments, as described herein, estimate the risks to a hypothetical working population from a known exposure. Although exposure probabilities are not typically calculated, dose-response analyses include exposure information; therefore, NIOSH systematically assesses the availability, magnitude, and validity of exposure data used in relevant studies as a part of hazard identification and applies this information, as applicable, in the dose-response assessment.

Dose-response Assessment

The second component of NIOSH risk assessment is the dose-response assessment. Given exposure and outcomes of interest, the aim of the dose-response assessment is to obtain reliable and valid estimates of the point of departure (PoD) in a cause-and-effect relationship for effects with a response threshold, or the risk at levels of exposure (e.g., the risk per unit dose) for non-threshold effects. Here, the PoD refers to a point on the dose-response curve that is established from experimental or observational data that corresponds to a level of no (or low) effect without substantial extrapolation. These estimates are essential to risk characterization.

NIOSH generally obtains dose-response estimates via statistical models constructed to provide the conditional expectation of the dependent variable (the adverse effect) given one or more explanatory variables, but at least including the variable describing the agent exposure of interest. Model input data stem from toxicologic and/or epidemiologic investigations identified and assessed in hazard identification. Because different model specifications can lead to different estimates, a key step in dose-response analysis is model selection. Clearly, it is preferable to base model selection on biologic plausibility, although a strong advantage of one model among several plausible models is rarely evident. Furthermore, data from most studies are imperfect and potentially incomplete. In lieu of available statistical techniques and algorithms designed to deal with data imperfections, the risk assessor may have to rely on assumptions based on scientific judgment.

Thus, another important part of the dose-response assessment is sensitivity analysis. In a sensitivity analysis, risk assessors quantitatively evaluate plausible alternative risk assessment strategies, defaults, and assumptions for their impact on risk estimates. In addition to providing a measure of analysis robustness, sensitivity analyses aid the risk manager by providing a range of plausible estimates of the dose-risk relationship.

Risk Characterization

The final step in NIOSH risk assessment is risk characterization. It is the translation of information from hazard identification and dose-response assessment into a basis, completely or in part, for recommendations on limiting workplace exposure. The framework of NIOSH risk characterization centers on a choice between two distinct approaches, based primarily on the evidence supporting the absence or presence of an impairment threshold. For effects with a response threshold, NIOSH typically adjusts the PoD in dose-response analysis by using factors that account for natural heterogeneity (e.g., interspecies variability or interindividual variability) to arrive at an estimate of a safe dose. Here the term *safe* implies that excess risk at this exposure level is absent or negligible. NIOSH used this approach in its risk assessment of nonmalignant pulmonary effects from exposures to carbon nanotubes and nanofibers [NIOSH 2013b]. In contrast, consider a causal agent that is neither necessary nor sufficient to cause disease (e.g., cancer). In this case, cause and effect is best described as a relationship between the probability of disease and the dose level that is absent of a dose threshold. Cancer from low-dose ionizing radiation is a classic example of an effect generally considered having residual risk at any level of dose. In a NIOSH risk assessment of radon exposure and lung cancer in uranium miners [NIOSH 1987], a safe level of ionizing radiation exposure was not assured; therefore, residual lung cancer risk under select exposure scenarios was estimated with probabilistic means. When effects appear to be without a response threshold, NIOSH obtains quantitative estimates of low-dose risk by model-based extrapolation of the risk at doses below the observed data. To illustrate, probabilistic models have been used by NIOSH to estimate the dose that would cause a lifetime excess cancer risk of 1 in 1000 from occupational exposure to hexavalent chromium [NIOSH 2013a] and titanium dioxide [NIOSH 2011]. There are instances in which the risk characterization approach is less dependent on a determination of whether the process has a threshold. For example, the response threshold may reside far below the observable range in dose-response analyses and may vary widely among exposed individuals. Under this condition, NIOSH may opt for assessing lifetime risks based on model extrapolation. Similarly, an effect that is generally considered stochastic (e.g., cancer) may be indirectly caused by exposure through a precursor effect (e.g., inflammation) residing on the causal pathway that has a threshold. If this is the only important pathway present, then a safe level of exposure is more likely (i.e., a level below inflammation).

An important consideration of risk-based characterization is the selection of a target risk, which is a single level of risk broadly considered tolerable, given reasonable and practical risk management. There are multiple methods and principles available for establishing risk acceptance criteria, and the adopted methods and principles will undoubtedly influence the choice of target risk. Thus, risk acceptance (or tolerance) criteria are more likely to be unique to the situation at hand rather than be pre-defined [Rodrigues et al. 2014; Vanem 2012]. Nevertheless, NIOSH has established a target risk level for non-threshold carcinogens of one excess case per 10,000 workers continuously exposed over a 45-year working lifetime [NIOSH 2017]. This level is a starting point for initiating a risk management process. The setting of target risk levels for other outcomes is a fundamental component of risk management; therefore, actions are primarily the responsibility of the decision-makers and not the risk assessor. As such, a detailed discussion on the various risk management principles in play for determining these levels is beyond the scope of this report, although discussions are available in several published reports [Aven 2016; HSE 2001; Rodrigues et al. 2014; Tchiehe and Gauthier 2017; Vanem 2012]. Finally, health risk is but one aspect

typically needed to derive a target risk level, given that risk tolerance can depend on the combination of individual, societal, economic, and environmental impacts. Although employers in managing risks may consider these other factors, NIOSH quantitative risk assessment is solely focused on characterizing health risks.

Conclusions

The identification and quantification of occupational risk are paramount to worker protection. NIOSH has a long, rich history of systematically assessing workplace hazards and communicating recommendations aimed to mitigate associated risks. As such, most recognize NIOSH as a leader in occupational risk assessment and often seek its expertise in this field. This report aids others in their understanding of the NIOSH risk assessment process. To this end, the report describes the NIOSH approach to addressing hazard identification, dose-response analyses, and risk characterization, including demonstrated examples of NIOSH risk assessments.

Above all, the NIOSH approach stresses careful attention to the aims of the risk assessment throughout the assessment process. It is important to thoroughly investigate the robustness of key assumptions and provide transparency for both the main analysis and analyses of alternative modeling strategies and defaults. Maintaining mindfulness of the intended audience is of utmost importance; therefore, NIOSH risk assessors endeavor to follow the guiding principles of transparency, clarity, consistency, and reasonableness when conducting risk assessment (Table 1).

Table 1. Guiding principles of NIOSH risk assessments

Principle	Description	Criteria for risk characterization
Transparency	Explicitness is essential in the risk assessment process.	Use a risk analysis plan.
		Describe assessment approach, assumptions, extrapolations and use of models.
		Describe plausible alternative assumptions. Identify data gaps.
		Distinguish science from policy.
		Describe uncertainty.
		Describe relative strength of assessment.
Clarity	The assessment itself is free from obscure language and is easy to understand.	Be brief and concise.
		Use plain English (avoid jargon).
		Avoid technical terms.
		Use simple tables, graphics, and equations.

(Continued)

Table 1 (Continued). Guiding principles of NIOSH risk assessments

Principle	Description	Criteria for risk characterization
Consistency	The risk assessment conclusions harmonize with those in other risk assessments and with other NIOSH actions.	Use this technical report. Follow NIOSH policies on technical writing and peer review. Place assessment in context with similar risk assessments.
Reasonableness	The risk assessment uses sound science and sensible judgment.	Use review by peers. Use best available scientific information. Use good judgment.

Adapted from the *EPA Risk Characterization Handbook* [Fowle and Dearfield 2000].

Risk assessment science is continuously evolving. Methods currently under development may provide additional, powerful tools to assess risks to workers based on very limited data. Validation of these new approaches is a critical need. In efforts to stay abreast of the science, NIOSH will continue to embrace new methodologies, but it will do so with appropriate caution and deliberate evaluation of new techniques and approaches.

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1 Background

In their highly cited article, Kaplan and Garrick [1981] first posited that an analysis of risk is an effort to answer three questions:

1. What can happen?

2. How likely is it that it will happen?

3. What are the consequences if it does happen?

Thus, the hazard (the potential source of harm) imposes risk (the likelihood of hazard causing harm) that is a function of both opportunity (likelihood) and consequence, as generally expressed by the following equation:

$$Risk = f(hazard,\ consequence,\ opportunity)$$

Risk is omnipresent and diverse in the human experience; therefore, steps are necessary to manage the many kinds of risks in our daily lives, such as business risk, social risk, political risk, and occupational risk. To illustrate, the risk function for health risk associated with hazardous exposure is:

$$Risk = f(target,\ exposure,\ toxicity,\ opportunity)$$

Where:

- The target is the biological entity (e.g., an organ, an individual, or a population) that is exposed,

- Exposure is contact between the agent (a chemical, biological, or physical entity) and the target,

- Toxicity is the deleterious biological effects (i.e., the adverse effects) elicited by the agent, and

- Opportunity is the likelihood of cause and effect.

In this example, the target and the exposure form the hazard, while toxicity represents the consequence.

Occupational risk is the potential and severity of adverse health effects in workers from their exposure to workplace hazards. In this context, the adverse effect is simply a specified unfavorable change

in health status of a worker from known exposure. Safeguards, carefully derived from scientific assessment and best practices, reduce occupational risks. Risk assessment is an important tool for informed decision-making on workplace safeguards when there are limited data on risks. For example, risk assessment provides the scientific underpinnings to authoritative recommendations, such as occupational exposure limits (OELs). Risk assessment conducted by the National Institute for Occupational Safety and Health (NIOSH) provides the foundation for Recommended Exposure Limits (RELs) and Risk Management Limits for Carcinogens (RML-CAs) for chemicals and other workplace hazards, such as ionizing radiation and noise.

NIOSH first considered the need to quantify occupational risks when standards for benzene exposure promulgated by the Occupational Safety and Health Administration (OSHA) were challenged in the 1980s, resulting in the well-cited Supreme Court decision "Industrial Union Department, AFL-CIO v. American Petroleum Institute, 448 U.S. 607 [1980]," hereafter referred to as the *Benzene Decision*. That decision essentially established a need to quantify the risk from occupational exposure as a basis for exposure limits. In response, NIOSH developed a "Risk Assessment Team," which later expanded to a "Risk Assessment Activity." This team of toxicologists, epidemiologists, exposure scientists, and statisticians provided quantitative risk assessments for radon [Hornung and Meinhardt 1987; NIOSH 1987]; ethylene glycol monomethyl ether, ethylene glycol monoethyl ether, and their acetates [NIOSH 1991]; cadmium [Stayner et al. 1992a; Stayner et al. 1992b]; 1,3-butadiene [Dankovic et al. 1993]; and coal dust [Kuempel et al. 1997]. In 1995, the Risk Assessment Activity was formally organized. Since that time, NIOSH staff have conducted quantitative risk assessments for a wide variety of agents, including diesel exhaust

[Stayner et al. 1998], 1,3-butadiene [Stayner et al. 2000], asbestos [Stayner et al. 1997], silica [Park et al. 2002; Rice et al. 2001], noise (with and without co-exposure to carbon monoxide) [NIOSH 1998], titanium dioxide [NIOSH 2011], hexavalent chromium [NIOSH 2013a], carbon nanotubes and nanofibers [NIOSH 2013b], diacetyl and 2,3-pentanedione [NIOSH 2016], manganese in welding fume [Park and Berg 2018; Park et al. 2009], toluene diisocyanate [Daniels 2018], and metalworking fluids [Park 2018] (Table 1-1).

In general, risk assessment is a process in which NIOSH characterizes the risk of adverse health effects from workplace hazards by using information from hazard identification (exposure and outcome) and dose-response assessment. This evaluation determines whether an exposed population is at greater-than-expected risk of adverse effects, such as disease (cancer or non-cancer) or injury. Once the hazard is identified, the magnitude and nature of its associated risk can be explored further, using either qualitative or quantitative approaches. Qualitative risk assessments are descriptive and indicate whether an adverse effect is likely or unlikely under specified conditions of exposure. Quantitative risk assessments provide numerical estimates of risks based on mathematical modeling. For example, a quantitative risk assessment may relate conditions of workplace exposure to an estimate of increased lifetime risk of a disease or injury.

Quantitative risk assessments require (1) data on exposures relevant to the adverse effect of interest; (2) data on the adverse effect associated with the exposure of interest; and (3) a mathematical model describing that dose-response relationship. The list of completed risk assessments shown in Table 1-1 clearly indicates the preference for directly estimating worker risks using data from human studies compared to experimental animal studies. Risk assessments based on epidemiologic, population-based studies have real-world relevance to workers, but they generally suffer from limitations inherent to study design and available data. Risk assessments based on experimental animal data provide detailed information on the dose-response relationships;

however, there is often concern about the validity of extrapolating animal-based risk assessments to humans, who generally have much lower and more variable exposures. The integration of mechanistic, animal, and human data is important for developing a thorough understanding of the risks.

The risk assessment process has become increasingly complex over the past several decades. In occupational safety and health regulation, the need to quantify risk became apparent with the *Benzene Decision*, which established that OSHA could not issue a standard without demonstrating a significant risk of material health impairment. The ruling allowed (but did not require) numerical criteria to be used to determine whether a risk is "significant." As a result, risk assessment became standard practice in OSHA rulemaking for health standards, and quantitative risk assessments are now preferred whenever data, modeling techniques, and biological understanding are adequate to support their development. NIOSH has adopted many of the same risk assessment practices as OSHA in order to keep the analyses relevant and meaningful within OSHA's regulatory context.

1.1 NIOSH Risk Assessment History

Historically, NIOSH employed a variety of methods to establish recommendations intended to prevent adverse effects in workers. NIOSH considered the health effects associated with experimental or observed exposure concentrations and applied a safety factor to ensure that even the most susceptible individual would be generally protected from a hazard. One major exception was in addressing issues of carcinogenicity. When evaluating carcinogens, NIOSH typically assumed that no exposure could be considered safe. This led to RELs for carcinogens that were not numerical, but directed employers to keep exposures as low as feasible [Fairchild 1976].

In its first decades, NIOSH was largely uncertain about the utility of dose-response modeling, especially for carcinogens. In 1982, NIOSH commented

Table 1-1. Examples of NIOSH quantitative risk assessments (in chronologic order)

Agent	Adverse Effect[*]	Dose-response Assessment[†]	Risk Characterization	Reference
Radon	Lung cancer	Epidemiologic, Cox proportional hazards regression	Extrapolation, excess lifetime risk, target risk unspecified	[Hornung and Meinhardt 1987; NIOSH 1987]
EGME, EGEE, EGMEA, EGEEA	Reproduction, developmental, hematotoxic effects	Toxicologic, NOAEL and LOAEL assessments	PoD/UF	[NIOSH 1991]
Cadmium	Lung cancer	Epidemiologic, Poisson and CPH regression, additive relative rate function	Extrapolation, excess lifetime risk, target risk unspecified	[Park et al. 2012; Stayner et al. 1992a; Stayner et al. 1992b]
1,3-butadiene	Leukemia	Toxicologic, Weibull time-to-tumor regression model, animal to human extrapolation, epidemiologic and toxicologic literature review	Extrapolation, excess lifetime risk, target risk unspecified	[Dankovic et al. 1993]
Asbestos	Lung cancer, asbestosis	Epidemiologic, Poisson regression, additive relative rate function (cancer), power function (asbestosis)	Extrapolation, excess lifetime risk, target risk unspecified	[Stayner et al. 2000] [Stayner et al. 1997]
Coal mine dust	Coal workers' pneumoconiosis, progressive massive fibrosis, pulmonary dysfunction	Epidemiologic, logistic and multiple linear regression	Extrapolation, excess lifetime risk, target risk unspecified	[Kuempel et al. 1997]
Diesel exhaust	Lung cancer	Toxicologic and epidemiologic (review)	Extrapolation, excess lifetime risk, target risk unspecified	[Stayner et al. 1998]
Silica	Lung cancer	Epidemiologic, Poisson regression, additive relative rate function	Extrapolation, excess lifetime risk, target risk unspecified	[Rice et al. 2001]

(Continued)

Table 1-1. Examples of NIOSH quantitative risk assessments (in chronologic order)

Agent	Adverse Effect[*]	Dose-response Assessment[†]	Risk Characterization	Reference
Silica	Non-malignant lung disease	Epidemiologic, Poisson regression, additive relative rate function	Extrapolation, excess lifetime risk, target risk unspecified	[Park et al. 2002]
Noise	Material hearing impairment	Epidemiologic, logistic regression	Extrapolation, excess lifetime risk with no target risk level specified	[NIOSH 1998; Prince et al. 2003]
Hexavalent chromium	Lung cancer	Epidemiologic, Poisson regression linear ERR model	Extrapolation, excess lifetime risk, 10^{-3} target risk	[NIOSH 2013a; Park et al. 2004]
Titanium dioxide	Lung cancer	Toxicologic, nonlinear extrapolation, BMD model averaging, quantal endpoint	Extrapolation, excess lifetime risk, 10^{-3} target risk	[NIOSH 2011]
Carbon nanotubes and nanofibers	Non-malignant adverse lung effects	Toxicologic, NOAEL and BMD assessments	PoD/UF	[NIOSH 2013b]
Diacetyl and 2,3-pentanedione	Pulmonary dysfunction	Epidemiologic, linear extrapolation, multiple regression, Poisson regression	Extrapolation, excess lifetime risk, 10^{-3} target risk	[NIOSH 2016; Park and Gilbert 2018]
Toluene diisocyanate	Asthma	Epidemiologic, Poisson regression linear ERR model, and BMD	PoD/UF and extrapolation, excess lifetime risk, 10^{-3} target risk	[Daniels 2018]
Manganese	Neurobehavioral impairment	Epidemiologic, BMD	Extrapolation, excess prevalence, target risk unspecified	[Park and Berg 2018; Park et al. 2009]
Metalworking fluids	Cancer (multiple sites)	Epidemiologic, Poisson regression linear ERR model	Extrapolation, excess lifetime risk, 10^{-3} target risk	[Park 2018]

[*]Analyses may have considered multiple adverse effects. The adverse effect shown is the primary effect examined.
[†]The dose-response assessment refers to the primary source supporting final models and/or recommendations on risk-based exposure limits.

Abbreviations: BMD, benchmark dose; EGEE, ethylene glycol monoethyl ether; EGEEA, ethylene glycol monoethyl ether acetate; EGMEA, ethylene glycol monomethyl ether; EGMEA, ethylene glycol monomethyl ether acetate; ERR, excess relative rate; LOAEL, lowest observable adverse effect level; NOAEL, no observable adverse effect level; CPH, Cox proportional hazards; PoD, point of departure; UF, uncertainty factor.

to OSHA on an Advance Notice of Proposed Rule-making on the Identification, Classification and Regulation of Potential Occupational Carcinogens [NIOSH 1982]:

> *Because our understanding of the mechanism of carcinogenicity is incomplete, our use of mathematical models to predict its outcome must be employed with extreme caution. To select a model or models from among the many choices and to have them incorporated into Administration policy will not resolve those issues.*

However, just a few years later, NIOSH engaged in quantitative risk assessment. As cited in 1986 NIOSH testimony on OSHA's Proposed Rule on Occupational Exposure to Benzene [NIOSH 1986a], NIOSH drew on the *Benzene Decision*, which focused on significant risk of material impairment of health, and United Steelworkers of America v. Marshall, 647 F. 2d 1189 (D.C. Cir. [1980]), cert, denied 101 S. Ct. 3148 [1981], hereafter referred to as the *Lead Decision*, to conclude:

> *These two decisions provided the impetus for the inclusion of a quantitative risk assessment effort in the standards recommending program of NIOSH* [NIOSH 1986a].

The first reference to quantitative risk assessment in NIOSH policy statements was in the 1986 NIOSH testimony to OSHA recommending 0.1 ppm as a permissible exposure limit (PEL) for benzene, based largely on findings from a NIOSH risk assessment using epidemiologic data [Rinsky et al. 1987]. Risks at 0.1 ppm were determined to be around one excess cancer per 1000 workers over a working lifetime. However, this initial risk-based REL was never incorporated into an updated Criteria Document for benzene, and later documentation referred to the limit of quantification (LOQ) of the analytical method (also around 0.1 ppm at the time) as the basis of the 0.1 ppm REL [NIOSH 1988]. Here, the LOQ is the amount or concentration of the analyte at which quantitative results can be reported with a high degree of confidence, which is based on assay-specific acceptance criteria [NIOSH 1995b].

In 1986, although NIOSH did not conduct its own risk assessment for formaldehyde, NIOSH testified that the OSHA risk assessment for formaldehyde was acceptable [NIOSH 1986b]. This risk assessment used animal bioassay data to estimate the human cancer risk of 3.46 cases per 1000 workers exposed over a working lifetime at the proposed PEL of 3 ppm. However, the NIOSH REL of 0.016 ppm as an 8-hour time-weighted average (TWA) was based on the lowest concentration that was considered quantifiable at the time.

In 1987, NIOSH published its first Criteria Document to include a quantitative risk assessment: *Criteria for a Recommended Standard for Occupational Exposure to Radon* [NIOSH 1987]. The risk assessment was based on epidemiologic data on excess lung cancer in underground uranium miners exposed to radon [Hornung and Meinhardt 1987]. The risk assessment found that continuous exposure to radon progeny concentrations of one Working Level Month (WLM) annually over a working lifetime corresponded to 5–10 excess lung cancers per 1000 miners. The risk from radon exposure versus the feasibility of controlling exposures was a point of discussion in the document. The REL was ultimately based on the limits of control technology at the time; however, NIOSH also communicated risks at this level, which supported additional recommendations for continued control technology development.

NIOSH risk assessments during the 1990s largely incorporated data from well-designed occupational epidemiologic studies that had become a mainstay of the Institute's field studies program. Epidemiological risk assessments of lung cancer in humans were conducted for cadmium, chrysotile asbestos, and diesel exhaust [Stayner et al. 1998; Stayner et al. 1997; Stayner et al. 1992a; Steenland et al. 1998]. Cancer as a result of worker exposures to ethylene oxide was also examined [Steenland et al. 2003]. NIOSH also conducted worker-based risk assessments for various lung function measures after coal dust exposure and for hearing loss after noise exposure [NIOSH 1995a; Prince et al. 2003]. In addition, although not a complete risk

assessment, physiologically based pharmacokinetic (PBPK) modeling was used for dose estimation in a worker study of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) exposure [Lawson et al. 2004]. Animal-based risk assessments were conducted to predict human risks in the absence of sufficient human data. Toxicologic-based examples include assessments of 1,3-butadiene and cancer at various sites in the mouse and rat, and assessments of glycol ethers and reproductive effects in the mouse, rat, and rabbit [Dankovic et al. 1993; NIOSH 1991; Stayner et al. 2000].

In the 2000s and beyond, the need for quantitative risk estimates preferentially based on epidemiologic data resulted in risk assessments becoming increasingly complex. Advances in risk assessment have included innovations in reconstructing past exposures in epidemiological studies, expansion of statistical modeling techniques, increased understanding of the role of particle dosimetry issues in risk assessment, and exploration of dose-response modeling for non-cancer health endpoints. Advancements such as new techniques in statistical modeling methods to account for survivor bias in human studies, the incorporation of genetics and genomics into risk assessment, and the potential for using quantitative structure activity relationships for risk assessment pose many challenges and opportunities for the future [Buckley et al. 2015; Comber et al. 2003; Schulte et al. 2015; Weitzel et al. 2011].

2 Purpose and Scope

Quantitative risk assessment is a foundation of authoritative recommendations. NIOSH conducts high quality, scientifically sound quantitative assessments of workplace hazards as input for developing its Criteria Documents, including establishing the basis for RELs and alternative forms of authoritative recommendations, such as hazard banding. This document describes the underlying science and general approach used by NIOSH researchers when conducting risk assessments, defined as the (preferably quantitative) determination of the relationship between the predicted exposure and adverse effects in workers. This information is intended for scientists, stakeholders, and the public to improve their understanding of the NIOSH risk assessment process. Every risk assessment is unique; therefore, situations may arise which require steps that are not specifically addressed in this report. Furthermore, discussions on NIOSH risk management and risk communication practices that typically follow the completion of its risk assessments are beyond the scope of this report. In particular, exposure assessment, as described by the National Research Council (NRC) [NRC 1983], may improve risk management practices by identifying and assessing efficiencies of feasible control options. Although important to the NIOSH mission of protecting workers, these activities are outside the scope of this document.

In developing its program, NIOSH benefitted from seminal reports by the NRC, which lay the foundation for modern risk assessment [NRC 1983; NRC 2009]. The NRC paradigm identified four major steps: hazard identification, dose-response assessment, exposure assessment, and risk characterization. This basic construct is used throughout the risk assessment community; however, some authoritative bodies have described the process using different terms and groupings of steps. For

example, the Integrated Risk Information System (IRIS) includes the first two steps of the NRC risk assessment process. Also, the International Organization for Standardization (ISO) describes risk assessment as an overall process comprising three steps, namely, risk identification, risk analysis, and risk evaluation, which best correspond to hazard identification, dose-response assessment, and risk characterization of the NRC paradigm [ISO 2018]. Similarly, three NRC steps (hazard identification, dose response assessment, and risk characterization) are most applicable to NIOSH risk assessment, as shown in Figure 2-1.

1. *Hazard identification* is the identification of the type and nature of adverse effects that an agent has an inherent capacity to cause in an organism, system, or population [IPCS 2004]. An adverse effect is defined as the specified change in the morphology, physiology, growth, development, reproduction, or life span of an organism, system, or population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences [IPCS 2004]. Hazard identification is the initial stage of the risk assessment. The products from hazard identification are characteristic descriptions and data on the exposure of interest; any important cofactors (e.g., other risk factors, moderating factors, mediating factors, confounders, or colliders); modes and mechanisms of action; and conditions (e.g., pre-existing diseases) under which changes in exposures change the probabilities or timing of adverse effects. Preferably, these data are suitable for quantifying the dose-response relationship. Therefore, hazard identification is the necessary antecedent to dose-response assessment.

2. *Dose-response assessment* is an analysis of the dose-response association between exposure
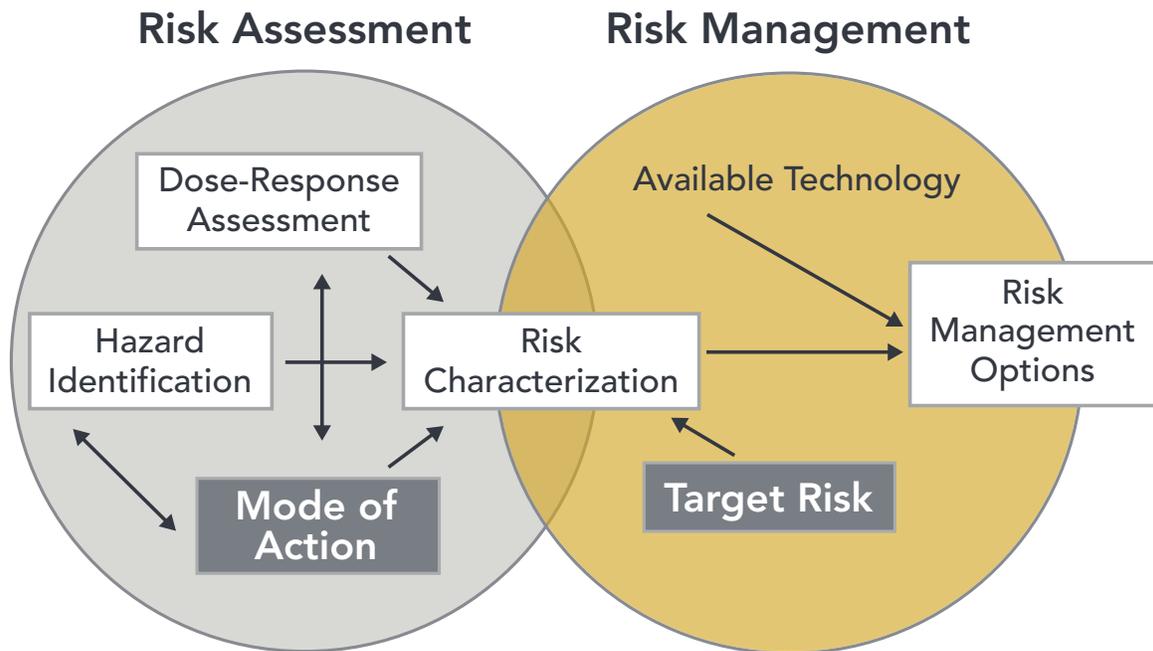
Figure 2-1. NIOSH risk assessment and risk management processes.

to the agent and adverse effects. The term *dose-response* is broadly defined as the relationship between the amount of an agent administered to, taken up by, or absorbed by an organism, system, or population and the change developed in that organism, system, or population in reaction to the agent [IPCS 2004]. In NIOSH risk assessment, the dose-response is typically described as the conditional probability of the adverse effect (i.e., the response) in exposed workers at different levels of occupational exposure to a hazardous agent, given assumed levels for other direct causes of the adverse effect. The meanings of the terms *exposure* and *dose* have been expressed in many different ways over time, and these terms are often used interchangeably (see section 4.3.3.1). Desired products of the dose-response assessment are estimates of the risk per unit dose having reasonable statistical properties for use in quantitative risk characterization. In lieu of sufficient data for quantification, the dose-response may be qualitatively described.

3. *Risk characterization* is the qualitative and, wherever possible, quantitative determination, including

attendant uncertainties, of the probability of occurrence of known and potential adverse effects of an agent in workers under defined exposure conditions [IPCS 2004]. It reflects the integration of the sciences from the two preceding steps (i.e., hazard identification and dose-response assessment) with additional information necessary to complete the basis for the REL or other supported recommendation. Some of this information may be based on risk assessment/management policy rather than science; therefore, risk characterization is also a component of the risk management process.

NIOSH risk assessments do not include all the steps outlined in the NRC paradigm. A NIOSH risk assessment does not include the exposure assessment step. Exposure assessment is the process of estimating or measuring the magnitude, frequency, and duration of exposure to an agent, along with the number and characteristics of the population exposed. Traditionally, exposure assessment provides information on sources, pathways, and routes of exposure necessary to be used in conjunction with dose-response information to project whole

population risks. For an environmental risk assessment, exposure assessment is critical to consider the likelihood and severity of exposure in assessing whole population risk.

In contrast, NIOSH uses the information from the first two steps of the risk assessment to estimate health risks to the individual from the agent at various levels of exposure. This forms the risk basis for RELs for use in risk management. The NIOSH objective, as stated in Section 20(a)(3) of the Occupational Safety and Health Act of 1970, is "... to describe exposure levels that are safe for various periods of employment, including but not limited to the exposure levels at which **no employee** [emphasis added] will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience." Thus, the risks of concern to NIOSH cover the range of exposures as experienced by each worker, and are not considered generally as a population risk.

Nevertheless, exposure information is used for dose-response analyses; therefore, the quality of exposure data ultimately used to describe the dose-response relationship must be evaluated as a component of hazard identification. Thus, this document describes exposure methods and measures (see section 4.3.3), including sources of bias (see section 4.3.4), in Chapter 4.0. Additional information on measurement error is available in Appendix B.

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3 Risk Assessment Plan (Problem Formulation)

There can be many paths to initiating a risk assessment. NIOSH risk assessments have begun after concerns were raised by workers, employers, regulators, and lawmakers. Risk assessments can follow anecdotal evidence on emerging occupational health issues or systematic examination of signs and symptoms of occupational disease. Factors contributing to a decision to conduct a risk assessment usually include broad information on the availability and use of the agent, numbers of workers at risk, exposure pathways, the type and severity of effects, general mitigation options, and alternatives to risk assessment. Consideration of these factors usually evolves over time. For example, early case reports of bronchiolitis obliterans in popcorn plant workers [Kreiss et al. 2002] motivated several preliminary health assessments that ultimately led to a formal quantitative assessment of pulmonary disease risk from exposure to diacetyl and 2,3-pentanedione that formed the risk basis for a REL [NIOSH 2016].

In general, a risk assessment has two distinct initiating stages: (1) planning and scoping and (2) problem formulation (Figure 3-1) [NRC 2009].

Planning and Scoping

What are the occupational risks?

Are current safeguards (e.g., REL) adequate to protect workers?

What technical assessments are needed to evaluate risk and management options?

What conditions affect safeguards and the level of analysis required?

What resources are available to conduct the assessment?

Risk Managers and Stakeholders

Problem Formulation

Integrate available data

Conceptual model

Analysis plan

Risk Assessment

Hazard Identification

Dose-Response

Risk Characterization

Risk Managers and Risk Assessors

Figure 3-1. The interrelationships between planning and scoping, problem formulation, and risk assessment.

Planning and scoping typically involve a dialogue between stakeholders and risk managers (with support from risk assessors) on the hazards and potential risk mitigation strategies, including conceptualizing the need, purpose, structure, and content of a risk assessment to aid in decision-making. Problem formulation occurs from communication between risk managers and risk assessors (with support of stakeholders) on the technical design of the risk assessment, which uses the broad concepts developed in planning and scoping. Although planning and scoping provide input into problem formulation and therefore are initiated first, the activities in both stages will likely progress concurrently.

The planning and scoping stage is described as a deliberative process that is intended to assist decision-makers in defining a risk-related problem [NRC 2009]. Planning and scoping begin with an acknowledgment that risk assessment is the appropriate decision-making tool. In practice, planning and scoping usually begin with discussions among risk managers and stakeholders on a certain health risk. These discussions may involve risk assessors in a supportive role. In general, the planning and scoping stage (1) identifies the occupational health concern, (2) assesses whether existing safeguards are appropriate or what additional information is needed to inform decision-making, and (3) determines the resources needed to conduct the risk assessment. The product is a statement describing the specific concerns the risk assessment will address and the resources needed to do so.

At the outset of problem formulation, NIOSH investigators develop a risk assessment plan that contains two critical components: (1) a conceptual model that identifies the hazard (sources, stressors, and pathways), persons at risk, and potential adverse effects for analysis; and (2) an analysis plan (work plan) that outlines the analytic components (i.e., data and methods) and interpretative approaches (e.g., risk metrics) to be used [NRC 2009]. The conceptual model guides decisions on data needs, and the analysis plan matches elements of the conceptual model with a proposed analytic approach. The two overarching principles in developing the plan are (1) to ensure that the risk assessment uses the best scientific methods and the highest-quality evidence and (2) to address the needs of the decision-makers (risk managers). Thus, in the problem formulation stage, it is imperative to be mindful that the risk assessment serves both scientific and communicative needs. This is best accomplished by including input from both scientists and decision-makers in the design of the risk assessment plan, if practical. For complex risk assessments, the analysis plans and conceptual models may benefit from peer review.

One way to formulate the risk assessment plan is to use a series of questions that the risk assessment is intended to address, such as this partial list of some examples:

- What agents are involved?

- Who is potentially at risk?

- What are the characteristics of the potential adverse effects caused by the hazard?

- What types of data support or inform the risk assessment process?

- What dose-response data will be included? For example, what criteria determine the acceptability of experimental animal data with inhalation as route of exposure?

- How will exposure be expressed (e.g., inhaled dose, absorbed dose, or air concentration)? What are the reasonable alternative expressions, and how would using those alternatives change the risk assessment?

- How are the health effects defined and measured? Are health effects aggregated (e.g., all cancer)? If aggregated, how would using alternative aggregation strategies alter the risk assessment?

- What evidence of a dose-response association is available? What types of causal mechanisms are likely to be involved?

- How should one deal with the background (control) incidence of different effects? Are the processes producing the observed health effects

in control animals (or unexposed populations) likely to interact with processes by which the hazard of interest causes these effects, or should the toxic mechanisms be treated as if they were independent of background processes?

- How should one evaluate important sources of uncertainty in the risk assessment? Are there any reasonable anticipated adjustments to the exposure or health effect based on mechanism, metabolism, potential confounding factors, other exposures, or other factors? What is the anticipated impact of uncertainty on the risk assessment findings?

- How will the final risks be expressed, and if quantitative analysis is done, what target risk levels are used? What is the support for those decisions, and are there reasonable alternatives? If yes, how would using those alternatives affect the risk assessment?

- What is the timeframe for completing the assessment?

The above list of questions may be applicable in many risk assessments; however, the list is not comprehensive. Each risk assessment will require its own set of questions to explore.

As necessary, the risk assessor refers to the plan throughout all aspects of the risk assessment. Appropriate plans include enough detail so that another risk assessor could reproduce the analysis. Risk assessment plans are living documents. If circumstances dictate changes are necessary, then risk assessors should revise their plans by clearly indicating the changes made, along with a justification for the revision. This helps to document decisions made throughout the course of the risk assessment.

The development of a written risk assessment plan is a relatively new addition to the NIOSH risk assessment process. Up to this point, NIOSH risk assessments published in Criteria Documents or Current Intelligence Bulletins have not included a formal written plan.

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4 Hazard Identification

The first step in occupational risk assessment is hazard identification, which is the process of characterizing the nature and strength of the evidence of causation, hereafter referred to as the weight of evidence (WoE), between an agent of interest (e.g., benzene) and an adverse effect (e.g., leukemia) in exposed workers. In this way, hazard identification is pursuing a causal explanation, which is a cognitive goal of identifying disease mechanisms and detecting causal factors [Russo and Williamson 2007]. Ideally, this evidence will serve as input to the dose-response assessment to support quantitative risk assessment. Evaluating the WoE generally requires a systematic approach to critically assess and interpret the body of scientific information (i.e., a systematic review). This information stems primarily from epidemiologic studies of humans and animal toxicology, with mechanistic data providing a reinforcing role. Human data sources are preferred for quantifying occupational risks; however, hazard identification has at times relied solely on animal data or a combination of human and animal data. When used in combination, either data source may take a supportive role in the risk assessment, along with complementary mechanistic data.

In a recent survey aimed to identify best practices in WoE analyses, investigators reviewed approximately 50 WoE frameworks from academia, the federal government, international bodies/organizations, consortia, and others (such as consulting firms, industry toxicology research groups, and military organizations). Although specific methods differed, the general framework of an acceptable approach to gathering and evaluating relevant human and animal study data consists of five basic steps: (1) define the causal questions of interest and develop criteria for study (data) selection; (2) develop literature search protocol and conduct search; (3) review, identify, and select relevant information;

(4) evaluate and integrate evidence across studies; and (5) synthesize and interpret findings [Rhomberg et al. 2013]. The paths to meeting these steps can vary widely with the specific scientific context of the risk assessment; therefore, precise methods for assessing WoE cannot be prescribed without understanding the individual context, although general guidelines are provided herein and are also available elsewhere [Higgins and Green 2008; NRC 1983; NRC 2014; NTP 2015a; NTP 2015b; Rhomberg et al. 2013; WHO 2000]. As such, risk assessors strive to develop and describe their approach in sufficient detail to ensure a transparent and defendable standard of WoE is met for their evaluation [Weed 2005]. To accomplish this, NIOSH risk assessors may develop systematic review protocols for evaluating data quality and synthesizing evidential information. As discussed in a recent NIOSH-commissioned report on systematic reviews [Hempel et al. 2016], these protocols incorporate best practices to accomplish the following:

- Assess all human and animal data relevant to mode of action, their human relevance, and dose-response.

- Evaluate the types of data that have been considered.

- Trace the reasoning by which the data bear on the evaluation of the assessment question.

- Consider alternative modes of action and develop a biological story for each plausible mode of action/outcome combination.

- Consider the relevance, response, and predictivity of the outcomes and use other knowledge (e.g., biological pathways) to inform the relevance determinations.

- Integrate data across all lines of evidence so that the interpretation of one will inform the interpretation of others (e.g., if the proposed

mode of action were true, determine what observable consequences it should have across lines of evidence).

- Clearly present the WoE findings and explore ways to measure and communicate different magnitudes of WoE and different degrees of plausibility of explanations and their risk-assessment consequences.

In conducting the systematic review, risk assessors consider the internal and external validity of the research, as it relates to the risk assessment. Internal validity is the degree to which study findings are free from bias. External validity is the degree to which study findings may apply, be generalized, or be transported to the population or groups of interests (i.e., workers) that did not participate in the study. Broadly, risk assessors consider the following factors:

- The design and conduct of studies providing data for risk assessment. Are study results generalizable and relevant to the risk assessment problem? Are results reproducible (have they been confirmed or refuted)? What factors may jeopardize external validity of the results?

- The characterization of exposure, dose, and adverse effect. What is the utility of the study data for integration and evaluation across studies? Will these data be suitable for inclusion in the database for the dose-response assessment? What are the sources of measurement error and their potential effects on the dose-response association?

- The degree of data certainty and strength of findings in support of hazard identification. Have sound statistical methods been used? Are models correctly specified? Are results robust under alternative assumptions? Have results been misinterpreted? How likely are findings due to chance, bias, residual confounding, or other sources relevant to internal validity of the study? (See Appendix B.)

In practice, to inform their assessments, NIOSH risk assessors have sometimes relied on hazard identification by other agencies, such as the U.S. National Toxicology Program (NTP), the U.S. Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), the Mine Safety and Health Administration (MSHA), the Agency for Toxic Substances and Disease Registry (ATSDR), the European Chemicals Agency (ECHA), and the International Agency for Research on Cancer (IARC). These agencies have a long history of hazard identification using sound, transparent methodologies. The NIOSH Chemical Carcinogen Policy [2017] provides additional information on the use of available cancer hazard assessments. Hazards have also been identified by recent research that has not been reviewed and synthesized by these agencies. This occurs most often in cases where emerging hazards have been identified or when new information on an existing hazard becomes available. In all cases, NIOSH risk assessors evaluate, integrate, and synthesize the existing evidence to characterize the hazard for dose-response analyses and risk characterization. This is accomplished by using best practices of the many frameworks established for hazard identification. These practices are discussed in comprehensive reviews [Higgins and Green 2008; NRC 1983; Rhomberg et al. 2013], recent commentaries [Howard et al. 2017; Woodruff and Sutton 2014], and technical reports [EPA 2018a; NRC 2014; NTP 2015a; NTP 2015b; WHO 2000]. In addition, tools for conducting and assessing systematic reviews are available to NIOSH risk assessors, such as AMSTAR and a recent report commissioned by NIOSH as an aid for conducting systematic reviews [Hempel et al. 2016]. Historically, NIOSH risk assessors have utilized thorough literature reviews as the foundation for risk assessments. This new report on systematic reviews will serve as an important resource to guide future reviews.

In summary, NIOSH risk assessors are mindful that the term *hazard* is defined as the inherent property of an agent (or situation) having the potential to cause an adverse effect when an organism, system, or population is exposed to that agent. Thus, identifying hazards requires knowledge of both the agent

and the adverse effect. Furthermore, NIOSH risk assessors approach hazard identification in terms of supporting the next step in the risk assessment. Therefore, data must sufficiently define dimensions of the population at risk, the agent, the adverse effect(s) of interest, and any cofactors (e.g., effect modifiers, confounders, or other sources of uncertainty), knowledge of which is necessary for conducting sound quantitative dose-response analyses.

4.1 Hill's Views on Causation

Observed associations are typically evaluated by NIOSH against multiple factors to assess WoE. The framework used to make an assessment is likely to be specific to the problem at hand; however, there are numerous WoE frameworks available to the risk assessor for planning an approach [Rhomberg et al. 2013]. Perhaps the most widely known WoE framework was introduced by Sir Austin Bradford Hill [1965], who proposed nine heuristic aspects of association commonly referred to as the "Bradford Hill criteria." These aspects comprise strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy. However, using these aspects to weight data is but one approach; Hill cautioned against the use of his views as a set of definitive rules on causality and acknowledged that many additional factors may be equally if not more important to WoE. Similar concerns have surfaced in several contemporary critical assessments of Hill's views [Fedak et al. 2015; Hofler 2005; Howick et al. 2009; Ioannidis 2016; Phillips and Goodman 2004; Thygesen et al. 2005]. Thus, the term *guidelines* is preferred to *criteria*, as posited by Howick et al. [2009]. More information on the formulation of Hill's guidelines, including critical assessments of their use in causal inference, is available in the assessments referenced above and in seminal epidemiologic texts [Checkoway et al. 2004; Rothman et al. 2008]. The guidelines are briefly described below.

1. **Strength** of association refers to the magnitude and statistical precision of the observed association, whereby a strong association is less likely to be influenced by unmeasured confounders, other sources of bias, or chance alone. Thus, this aspect addresses the feasibility of statistical inference. A strong association is neither necessary nor sufficient for a causal relationship. For example, the association between cardiovascular disease and smoking is considered relatively weak; however, it is also considered causal. Conversely, an effect estimate achieving statistical significance provides little evidence of causality without due consideration of other aspects, such as underlying statistical methods, biologic plausibility, and reproducibility of results.

2. **Consistency** refers to the reproducibility of similar effects in different populations (studies). Generally, evidence from a series of studies reporting similar effects is weighted more than findings from a single study. Like strength of association, consistency also addresses the feasibility of statistical inference, because increased homogeneity across studies is evidence against poor internal validity. Nevertheless, consistency is neither necessary nor sufficient for a causal relationship.

3. **Specificity**, in Hill's view, is the simple premise that an association is more likely to be causal if it is observed between one cause and one effect. Of course, specificity is reliant on the definitions of the cause (exposure) and effect (disease). In practice, epidemiologic examinations tend to involve complex exposures and multifactorial diseases with similar pathways; therefore, highly specific agent-disease associations are seldom observed. For this reason, many consider specificity to be of little importance for causal inference in most settings.

4. **Temporality** refers to the general acceptance that the cause (exposure) must precede the effect (disease) in time. This is the only criterion that is considered necessary for a causal relationship. Thus, study designs that

firmly maintain the temporal progression from cause to effect are far more persuasive in causal inference.

5. *Biological gradient* refers to the observed presence of a dose-risk relationship (i.e., dose-response). Typically, this is defined as a monotonic trend in disease frequency with increasing levels of exposure. Studies designed to examine dose-response trends are more persuasive for causal inference. Nonetheless, the absence of a monotonic biologic gradient does not preclude the existence of a causal relationship. This aspect of Hill's guidelines is the focus of NIOSH quantitative risk assessment, which is exploited by the dose-response modeling described in Section 5.0.

6. *Plausibility* refers to a measure of biologic reasonableness for explaining the agent-disease association. The guideline is largely a function of the current understanding on toxicity and disease etiology. It is important to synthesize evidence from a wide array of animal and human studies to assess the plausibility of an association between contributing causes and complex diseases. Toxicological data from experimental animal studies can be particularly useful for assessing biological plausibility. For example, if an agent causes toxicity in animals similar to that observed in humans, then this is strong evidence of biological plausibility.

7. *Coherence* is related to plausibility; it implies that the interpretation of a causal association agrees with known disease etiology. Of course, coherence relies on current knowledge, which is always subject to change. Hill stated that the absence of coherent information should not be considered as evidence against causation. In contrast, the presence of conflicting information is counter to causality. The risk assessor must judge whether the conflict is true (thus potentially negating a cause-and-effect relationship) or false, because of study errors or misinterpretation.

8. *Experiment* refers to evidence of a successful intervention; that is, removing (or reducing) the cause results in the disappearance (or attenuation) of the effect. This is sometimes referred to as evidence of manipulative causation. For example, lower lung cancer rates have followed patterns of decreased smoking. This observation supports the hypothesis that lung cancer is caused by smoking. Hill considered this criterion as "… the strongest support for the causal hypothesis." However, evidence from interventions is rarely available to risk assessors.

9. *Analogy* is related to plausibility; if a causal association is apparent with an agent, then the standard of evidence is lessened for similar agents by analogy. For example, human data on the toxicity of diacetyl are believed informative on risks from exposures to the chemically similar agent 2,3-pentanedione, for which human data are unavailable.

Although Hill's guidelines are still in wide use [Wakeford 2015], there have been many advances in science since their introduction. In response, several authors have made efforts to modernize these guidelines [Becker et al. 2015; Cox 2018; Fedak et al. 2015; Hofler 2005; Howick et al. 2009; Weed 2018], while others have found their continued use in causal inference limited [Ioannidis 2016]. Cox [2018] recently updated and strengthened Hill's views, including suggested statistical tools, in the context of modern causal discovery principles and methods. These methods are aimed toward drawing valid causal conclusions that better inform decision makers on risk management approaches. In general, modern causal discovery recognizes the interplay in the network of causal mechanisms that explain the complex dose-risk relationship typical in most diseases. In particular, manipulative causal analysis is used to infer disease probabilities under changing exposure conditions (i.e., intervention) while holding other factors fixed (e.g., how does a change in exposure level change the probability of the adverse effect?) [Pearl 2010]. Clearly, manipulative causation informs decision analysis supporting

risk management, which usually assumes that decision variables have values that can be manipulated by decision-makers to help choose an effective risk mitigation course [Cox 2018]. In contrast, associative causation, which assesses causality on the basis of measures of association (e.g., relative risk and odds ratios) and WoE criteria, is directed more towards identifying potential causes (i.e., affording a causal explanation, as posited by Russo and Williamson [2007]) rather than assessing the effectiveness of interventions. Of the two approaches, associative causation is found most often in observational data, and causation is often interpreted based on Hill's guidelines or similar qualitative WoE criteria.

Regardless of the actual framework used, risk assessors are encouraged to apply Hill's guidelines, or a derivative of these guidelines, to the data integration step of hazard identification, using them not as a checklist or simple measure of WoE but to uncover patterns in the data that support scientific inference on causality [Hempel et al. 2016; Rhomberg et al. 2013]. Finally, it should be clear that neither approach is sufficient to empirically validate causal discovery, given limitations in available data [Cox 2018; Oates et al. 2016]; therefore, some judgement (and accompanying uncertainty) on hazard identification is necessary.

4.2 Adverse Effects

Adverse effects in workers—sometimes referred to as the adverse health effect(s), outcome of interest, or simply the response—must be clearly defined in the population at risk and comparative populations, such as control groups or the general population. NIOSH risk assessors affirm that case definitions and ascertainment methods used in candidate epidemiologic studies are adequate for risk assessment. When considering cancer and non-cancer adverse effects or biomarkers for those effects, it is important to understand the progression of disease and select a measurable adverse effect as early in the process or with the least severity of effect as possible. Ideally, an empirically

observable endpoint that is clearly a key event or precursor to the adverse effect of interest should be targeted for risk assessment, but the strength of association between the exposure and outcome and the potential for confounding are important to consider. Furthermore, an agent may involve multiple adverse effects. Frequently, risk assessors have limited evaluations to the most sensitive effect by examining multiple effects separately and then choosing the effect offering the greatest risk per unit exposure. However, recent efforts have shifted toward a more holistic approach of estimating aggregate risks from the combined effects of exposures to one or more agents.

4.2.1 Cancer

Cancer is a term used to describe over 100 different diseases in which abnormal cells divide without control and can invade nearby tissues [Ruddon 2007; Schottenfeld and Fraumeni Jr 2006]. Given this broad definition, there are many possible characterizations of cancer as an adverse effect used in epidemiologic studies, ranging from all cancers combined to a precise classification of a primary malignant tumor. In dose-response analyses, studies showing specific adverse effects are superior to those showing the effects of all cancers combined, given varying etiologies among types of cancer; however, specificity of the adverse effect may come at a cost of statistical imprecision, given the rarity of most individual cancers. Moreover, most occupational studies have examined mortality data from death certificates, which often lack desired cancer specificity. Therefore, human studies have infrequently examined specific malignancies (e.g., lung adenocarcinoma). Instead, cause-specific cancer endpoints are typically constructed by grouping multiple tumors that share common traits (e.g., lung cancer, respiratory cancers, and solid tumors).

It is important to consider the potential effects of a heterogeneous grouping on the dose-response. For example, ionizing radiation is a known leukemogen; however, strong evidence of chronic lymphocytic leukemia (CLL) radiogenicity is lacking [Linet

et al. 2007; Silver et al. 2007]. This has led some expert committees to conclude that CLL is nonradiogenic [NRC 1990; UNSCEAR 2000]. If CLL is not associated with ionizing radiation, then combining it with radiogenic leukemias will act to attenuate the dose-response between the grouped outcome and exposure; therefore, most studies have excluded CLL from the leukemia grouping.[†] Group definitions can vary between studies and even within a study because of changes in diagnostic criteria over time. When combining data for hazard identification and subsequent dose-response analyses, the risk assessor considers the compatibility of the adverse effect definition between studies.

4.2.1.1 Carcinogenesis

The mechanisms of carcinogenesis are rapidly becoming an important aspect of hazard identification. Human carcinogenesis is a multistage process that can involve numerous mechanisms causing various biological changes leading to tumorigenesis. These mechanisms can vary widely by agent; therefore, risk assessors systematically assess available mechanistic data to appropriately characterize the dose-risk relationship and evaluate the overall carcinogenic hazard of an agent. IARC has identified the following characteristics of human carcinogens that are useful in a systematic strategy of assessing mechanistic data for hazard identification [IARC 2019; Smith et al. 2016]:

- The agent acts as an *electrophile* either directly or after metabolic activation. Electrophiles are electron-seeking molecules that commonly form addition products (adducts) with cellular macromolecules including DNA, RNA, lipids, and proteins.

- The agent is *genotoxic*, i.e., it induces DNA damage that may or may not result in mutation. A genotoxic agent that induces mutations is termed mutagenic.

- The agent alters DNA repair or causes genomic instability.

- The agent induces epigenetic alterations. The term *epigenetic* refers to stable changes in gene expression and chromatin organization that are independent of the DNA sequence that can be mitotically inherited over cell divisions.

- The agent induces *oxidative stress*, i.e., an imbalance between formation of reactive oxygen and/or nitrogen species and their detoxification.

- The agent induces chronic inflammation.

- The agent is immunosuppressive. Immunosuppression is a reduction in the capacity of the immune system to respond effectively to foreign antigens.

- The agent modulates receptor-mediated effects.

- The agent causes immortalization. The agent disrupts normal cellular replicative senescence to cause unlimited proliferation.

- The agent alters cell proliferation, cell death, or nutrient supply.

Most carcinogens demonstrate more than one of these traits. Assessing mechanistic data requires three basic steps: (1) identify relevant information, (2) screen and organize mechanistic data, and (3) synthesize mechanistic information (e.g., develop adverse-outcome pathways). In this way, the IARC approach provides a foundation for carcinogen classification (i.e., hazard identification); however, mechanistic data can also inform choices made in risk characterization, such as estimating the response expected at low doses.

4.2.2 Non-cancer

For non-cancer risk assessment, it is important to evaluate issues of severity, reversibility, progression to more serious conditions, and other pertinent issues. NIOSH has typically conducted quantitative risk assessment on non-cancer adverse effects by assuming chronic exposure (see Table 1-1). There may be instances where the effects after short-term or intermediate-length exposure are determined to

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[†]The research on CLL radiogenicity is inconsistent; however, in 2011 after a review of the literature and consultation with subject matter experts, NIOSH recommended that CLL be considered radiogenic for purposes of compensating workers covered under the Energy Employee Occupational Illness Compensation Program Act (EEOICPA).

be critically important. In those cases, the risk assessor must evaluate and document the impact of the exposure in the context of a shorter-term exposure duration and any longer-term sequelae.

With respect to assessing risk persistence, a key question is whether the observed pathophysiologic change defined as the endpoint of interest is reversible with cessation of exposure. Unfortunately, data are often insufficient to answer this question; therefore, irreversibility is typically assumed as a worst-case scenario until evidence to the contrary becomes available. Two examples of NIOSH risk assessments illustrate this issue. First, NIOSH examined Parkinson's disease–like symptoms and manganism resulting from manganese exposure in welders [Park et al. 2009]. The NIOSH risk assessment quantified the relationship between manganese exposures in confined-space welding and cognitive deficits in working memory or verbal IQ. However, the information was insufficient to conclude whether the risk of exposure-related neurobehavioral deficits persisted after cessation of exposure. Without the data, NIOSH conservatively assumed that excess risk accrued with exposure and persisted afterward. Similarly, a risk assessment of diacetyl exposure and the development of bronchiolitis obliterans used multiple definitions of pulmonary dysfunction as a case-surrogate for the onset of the condition [NIOSH 2016]. Again, risk accumulation and persistence were assumed in lieu of contrary information. In both risk assessments, the assumption of irreversible adverse effects had large impact on estimates of lifetime risk per unit exposure.

4.3 Human Data

NIOSH risk assessors prefer the direct estimation of risk from human data. In practice, however, risk assessments usually must rely on a combination of human and animal data for hazard identification and dose-response analyses. This is because both data sources are imperfect; human data tend to be vulnerable to potential biases from confounding factors, and there is large uncertainty in extrapolating

risk in animals to humans. It is common for human data to be weighted more than animal data for hazard identification, but to be less informative on dose-response. In those instances, human studies provide evidence of an association between exposure and disease, which can guide the choice of agents, exposure routes, and pathological endpoints for examination in animal toxicology studies that might contribute greatest to quantifying risks.

4.3.1 Epidemiologic Study Design

Figure 4-1 shows a hierarchy of epidemiologic study designs, ordered by the potential contribution to WoE. Human data for WoE assessment may originate from experimental or observational studies. Regarding the former, study participants are intentionally exposed to an agent under controlled experimental conditions. In this context, the term *controlled* refers to design parameters intended to minimize the effects of factors other than the exposure condition on the measured response [NASEM 2017]. These studies are sometimes referred to as clinical studies, human challenge studies, or controlled human exposure studies. Adherence to a strict experimental design is a trait of controlled human exposure studies that lessens the potential for major biases; therefore, these data tend to be well suited to hazard identification and dose-response analyses. As explained previously (see Hill's guidelines), experimental designs with exposure intervention can provide strong support for causal inference. However, human experimental data on exposures to hazardous agents are sparse for obvious ethical reasons; therefore, observational studies tend to be the most important information source for directly addressing the dose-risk relationship in humans and are the focus of the discussion on epidemiologic study design.

Observational studies can be further classified as either analytic (e.g., longitudinal and cross-sectional studies) or descriptive (e.g., case reports, case series, and ecologic studies), the latter being the least informative for risk assessment. Detailed descriptions
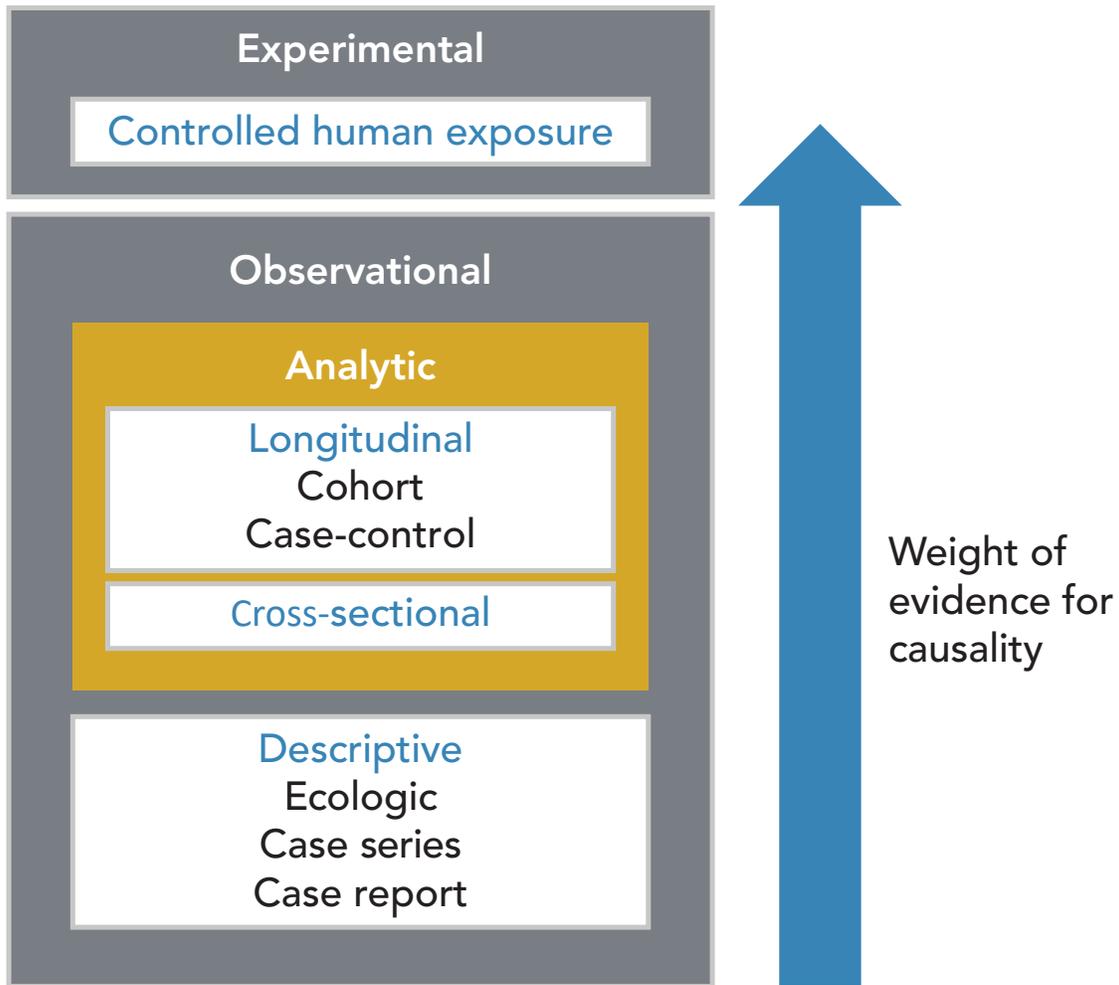
Figure 4-1. Hierarchy of human epidemiologic studies.

of epidemiologic study designs are available in seminal texts [Breslow and Day 1980; Breslow and Day 1987; Checkoway et al. 2004; Rothman et al. 2008].

Of observational research types, longitudinal analytic studies (e.g., cohort or panel studies) are most useful with respect to WoE. These studies follow the exposure and health status of each individual in a study sample or population over time. An important strength of this design is its ability to measure temporal changes in exposure and outcome at the individual level. Thus, this study design allows for direct examination of the dose-response. Cohort studies are the most common source of human data in NIOSH risk assessment. A cohort

comprises a group of individuals who share some defining characteristics, who are followed in time. Data can be collected prospectively; however, most occupational cohort studies are historical, using data that span a time prior to initiation of the study. A disadvantage of a cohort study is that it requires the recruitment of many participants who must be observed over a long period for examining rare outcomes (e.g., cancers); therefore, a detailed accounting of individual exposures for everyone in the study group may be impractical.

Measures of association can vary in cohort studies. If comparisons are made between the study population and an external referent (e.g., the U.S.

population), common measures of association are the standardized mortality ratio (SMR) or standardized incidence (morbidity) ratio (SIR) [Rothman et al. 2008]. These measures are simply the ratio of the observed number of cases to the number of expected cases, where the number of expected cases is calculated based on disease rates observed in the referent population that are standardized by characteristics (e.g., age, race, gender, and calendar period) in the study population. Trends in SMRs by categories of exposures can offer crude dose-response information; however, because of indirect standardization methods, comparisons of SMR are vulnerable to bias due to differences (e.g., differences in age, gender, and race) in comparison groups. Internal comparisons (comparisons made within the study population) offer better dose-response data than SMR and SIR analyses. Measures of association from internal comparisons include trends across standardized rates by exposure categories or risk measures from dose-response regression models. Risk measures can be expressed on a relative scale, such as hazard ratios (HRs), rate (or risk) ratio (RR), or excess relative risk (ERR), or in terms of risk differences, such as attributable risk or excess absolute risk (EAR).

A case-control (or case-referent) study compares exposure among persons with the outcome of interest (i.e., cases) to exposures among persons preferably drawn from the same population (controls). Thus, the reduction in study size saves time and expense relative to a cohort study. This design is particularly useful when examining rare adverse effects. Cases can be enumerated at a point in time (prevalent cases) or over a period (incident cases). An important consideration is the number of matched controls per case. In the absence of a dose-response relationship, reasonable asymptotic relative efficiency is achieved with few controls [Breslow et al. 1983; Goldstein and Langholz 1992; Ury 1975]. However, the actual relative efficiency decreases as the strength of the exposure–response increases and as the skewness of the exposure distribution increases [Bertke et al. 2013]. The standard

effect measure of the case-control study is the odds ratio (OR), which approximates the risk ratio (relative risk) if the disease is rare.

A special instance of a case-control study is one that is nested within a specified cohort. This design retains many of the analytic advantages of the large cohort while reducing the number of subjects needing exposure estimates. Thus, a nested case-control study allows for improvements in exposure data that can lead to better information on dose-response. As in cohort studies, a nested design also allows for precise treatment of the timescale; therefore, measures of association related to events per unit person-time can be estimated by means of dose-response regression modeling (e.g., HR, RR, and ERR).

A cross-sectional study (e.g., survey) examines the frequency or level of an attribute (e.g., exposure and/or adverse effect) in a defined population at a particular point in time. This design is often used to examine the prevalence of nonfatal diseases or symptoms that typically do not rapidly lead to employment termination (e.g., mild decreases in lung function, changes in blood pressure, pre-clinical biomarkers of early effect, and skin irritation). This design is a poor choice for examining diseases that are rare or periodic. Because cross-sectional studies are based on prevalent cases, this design has limited value for examining etiologic relationships. Other disadvantages are the lack of information on temporal sequence between cause and effect and the potential for selection bias from health-related employment termination that took place prior to recruitment into the study.

Epidemiologic studies that are conducted with observation at the group level (e.g., plant, city, county, or nation) instead of the individual level are called ecologic or aggregate studies [Rothman et al. 2008]. These studies can involve a single cross-sectional survey or repeated measures (i.e., time-trend design). Ecologic studies may be a practical alternative to individual-level studies when exposures and disease are relatively homogeneous within a population but differ between populations, or when

individual exposure estimates are not possible. Within-group heterogeneity is a likely condition; therefore, extrapolation to the individual level is not feasible. Thus, an association at the group level does not imply the same association at the individual level. This limitation is known as the ecologic fallacy. Another major limitation is that these studies lack the ability for adequate control of confounding. For these reasons, ecologic studies have limited value in assessing causal associations. Nevertheless, ecologic studies may provide descriptive information on differences in populations that may be suggestive of a potential cause-and-effect relationship. This information can be used to support findings from analytic studies.

Other descriptive study reports, such as case reports and case series, provide information on symptomology, disease history, diagnostic features, and outcomes for one or more subjects under observation. The term *case report* refers to a description of a person with a disease, whereas *case series* refers to a series of related case reports that were typically collected at a specific practice, clinic, or hospital over a defined time. Like cross-sectional studies, routine data studies are of limited value for examining etiologic relationships but may initiate larger investigations that are better designed to inform on causation. In addition, these studies are purposed for identifying emerging trends in adverse health, high-risk populations, and unrecognized hazards; therefore, they can be an important data source for hazard identification in risk assessment. Case reports can be very informative on rare diseases when exposures are well defined. For example, 4,4′-methylenebis(2-chloroaniline) (MBOCA) is considered carcinogenic in humans (IARC Group 1) because of sufficient evidence in experimental animals and strong mechanistic evidence; however, evidence in humans was deemed inadequate [IARC 2012]. Liu et al. [2005] reported on a 52-year-old non-smoking male patient with bladder cancer who was significantly exposed to MBOCA while employed as a chemical worker for 14 years. Reconstruction of his past exposures yielded no other exposures to bladder carcinogens.

Thus, this case study provided direct evidence of MBOCA potentially acting as a human bladder carcinogen.

Data may also be available as summaries, such as integrative reviews [Cooper 1982; Jackson 1980], meta-analyses [Thacker 1988], and pooled studies [Blettner et al. 1999; Checkoway 1991; Friedenreich 1993]. For these study designs, an overarching goal is to reconcile inconsistent results among multiple studies to infer generalizations. Research integration can be accomplished qualitatively or quantitatively, depending on the approach. Given a set of relevant published observational studies, an integrative review gathers information to provide a qualitative assessment of the evidence in narrative form. These reviews are timely and inexpensive; however, findings are vulnerable to publication bias and the subjective judgement of the reviewer. For example, risk assessors should be wary of judgements based mostly on a tally of observed positive or negative associations [Greenland 1987].

A meta-analysis is an extension of the integrative review that analytically combines the published information to provide a quantitative synthesis across the literature, usually in the form of a summary effect measure. Although they are quantitative, summary effect measures rely on consistency in the data, design, and conduct of the studies selected for meta-analysis; therefore, methods used to select studies and address heterogeneity are an important consideration for the risk assessor. Given that these studies also rely on published data, there is a potential for publication bias.

In contrast to meta-analyses, pooled studies are the reanalysis of individual data from multiple studies [Friedenreich 1993]. Pooling allows for a consistent definition of study variables, improved examination of confounding and effect modification, and superior statistical modeling of the dose-response. These studies can include unpublished data; therefore, the potential for publication bias can be reduced. A potential drawback of pooling is that it may disregard characteristics (e.g., differences in unmeasured risk factors) of the individual

study populations being combined, which may bias summary risk estimates or lead to spurious results [Bravata and Olkin 2001]. As in meta-analysis, superior pooled studies are designed to select data (or studies) using criteria that reduce the potential for bias and include methods to assess and account for residual heterogeneity. Pooled studies are less common because they tend to be more expensive and time-consuming and can require considerable coordination between study centers.

When assessing human studies for WoE, NIOSH risk assessors often use available checklists of study design and analysis criteria that have been widely vetted. For example, clinical research has greatly improved under the Consolidated Standards of Reporting Trials (CONSORT) statement, which includes a 22-item checklist and flow diagram [Moher et al. 2001]. Similar checklists are available for meta-analyses of clinical trials and observational studies [Moher et al. 1999; Stroup et al. 2000]. The checklists developed under the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) initiative are useful tools for assessing the strengths and weaknesses of stand-alone observational studies [von Elm et al. 2007]. STROBE provides separate checklists for cohort, case-control, and cross-sectional studies. Also, for longitudinal studies, risk assessors are encouraged to use the checklist offered by Tooth et al. [2005]. This checklist consists of 33 questions on study design and analysis criteria. This and similar checklists may augment the systemic approach to assessing WoE; however, they should be viewed only as potentially useful tools among many. Given that each risk assessment is unique, reliance solely on published checklists should be avoided.

In summary, most human data used in NIOSH occupational risk assessments are drawn from observational studies and (preferably) from longitudinal studies of working populations. These data include information on disease status from registries, death certificates, medical records, diagnostic exams, or self-reports (i.e., questionnaires). Exposure data sources include personal or ambient measurements, modeling, constructed proxies (e.g., job-exposure matrices), self-reports, or any combination of these. Risk assessors must fully understand the nature and limitations of the data in studies selected for risk assessment.

4.3.2 Health Effect Data

Mortality is a common endpoint in epidemiologic studies. Cause of death information stems primarily from death certificates, which can provide information on multiple causes of death. Typically, the underlying cause of death (UCOD) is preferred, given longstanding and well-accepted use in public health, although some studies examined multiple causes to increase the number of available cases, especially for rare outcomes. The UCOD is defined as the disease or injury that initiated the train of events leading directly to death, or the circumstances of the accident or violence that produced the fatal injury [WHO 1977]. Although the unidimensional UCOD is conceptually easy to understand, it does not consider other important contributors to death that may also be listed on the death certificate. This is especially true for complex chronic illnesses, which are typically characterized by multiple contributing causes. To make better use of available information, multiple causes of death (MCOD) data have become an appealing alternative in some studies [Chamblee and Evans 1982; Israel et al. 1986; Redelings et al. 2007].

For study purposes, death causes are usually translated to codes from the International Classification of Diseases (ICD). Coding death certificates is a highly specialized and interpretive process that is nearly always conducted only by a qualified nosologist. Agreement between nosologists tends to be high, but some disagreement and errors in coding are unavoidable, as are inaccuracies in the death certificates themselves. For example, the UCOD recorded on death certificates have differed upwards of 20% to 40% when compared with autopsy conclusions [Cameron and McGoogan 1981; Engel et al. 1980; Maudsley and Williams 1996; Sehdev and Hutchins 2001]. Coding sequence errors in translating information from the death certificate are

also likely. In both cases, the effects of these errors may be offset in analyses using MCOD data.

Morbidity data are typically abstracted from either disease registries or medical records. Obtaining morbidity information is generally more difficult than obtaining mortality data, given there are few reportable diseases (e.g., cancer) and most U.S. disease registries have originated more recently than mortality databases. Cancer registries are perhaps the most informative, given that nearly all states have had registries for acquiring data since the early 1990s. Cancer incidence data are generally considered superior to mortality data, because of improved diagnostic information in registries and greater discovery of highly survivable cancers. In addition, incidence data are less susceptible to survival effects (e.g., competing risks and healthy worker survivor effects) in dose-response analyses, although incidence data are more susceptible to screening bias.

The United States lacks a national cancer incidence database; studies of U.S. workers require matching to multiple state cancer registries. The number of cases depends on whether workers leave the covered area during the observation period. Therefore, interstate migration can be an important source of underascertainment. For example, retirement patterns suggest that interstate migration rates for retirees are upwards of 5% [Cowper et al. 2000]. Localized migration rates can be much higher. In a study of cancer among U.S. firefighters in Chicago, Philadelphia, and San Francisco, registry data were obtained for over 16% of cases via linkage to eight other states, with nearly 7% from Florida alone [Daniels et al. 2014]. Acquiring data from multiple state cancer registries can be onerous, costly, and time-consuming. Furthermore, U.S. disease registries may have limitations due to several factors, such as poor coverage, underreporting of some diseases (e.g., melanoma), no reporting of others (e.g., basal cell carcinoma), duplicate reporting among multiple databases (e.g., neighboring state cancer registries), varying data acquisition procedures across databases, and a relatively short time span since registry inception. Although morbidity data

can be generally superior in analyses, longitudinal studies of chronic work-related illnesses, including cancer, have primarily relied on mortality data.

Most researchers have preferred registries to medical charts, when practical (e.g., for a cancer study), given that registries are generally less resource intensive and data are less affected by losses due to death or follow-up. However, ascertainment from registries can be quite poor for some cancers that are underreported, such as melanoma treated in private clinics [Cockburn et al. 2008] or not reported (e.g., basal and squamous cell carcinomas, excluding genital sites). A viable (and potentially superior) option to registry linkage is to combine self-reported data with medical verification. These methods, sometimes referred to as "medical follow-back" [Schubauer-Berigan et al. 2015] and "active follow-up" [Pinsky et al. 2016], generally involve four steps: (1) administer questionnaires to identify prospective cases, (2) determine whereabouts of relevant medical records for case confirmation, (3) obtain consent and obtain access to the records, and (4) verify diagnosis and other characteristics. These methods also provide for gathering information on important covariates that is not available in disease registries. An example of this design is the recent NIOSH study of breast cancer incidence in a cohort of U.S. flight attendants [Schubauer-Berigan et al. 2015]. For this study, researchers verified the cases that were first identified by self (or proxy) by contacting the physician, hospital, or other health care organization in which the cancer diagnosis was made and obtaining supporting documentation of the diagnosis.

Data on adverse effects may be self-reported alone or stem from expert diagnosis. For example, study data may originate from members (or proxies) of the population at risk who have reported specific symptoms or diagnosed conditions that may be regarded as caused by the exposure of interest. These data are vulnerable to errors from inaccurate recall [Atkinson et al. 2016; Howell et al. 2015; Wallace and Kohatsu 2008], which may be attenuated somewhat by using medical information to confirm a reported diagnosis (e.g., Schubauer-Berigan et al.

[2015]). Expert assessment of signs or diagnoses requires uniform application of an adverse effect definition by knowledgeable evaluators. Evaluators should be blinded to the study subjects' exposure status when assessing health effects to reduce the potential for evaluator bias.

A recent example of using expert assessment in a NIOSH risk assessment is found in the criteria document supporting the REL for diacetyl and 2,3-pentanedione [NIOSH 2016]. In that study, researchers quantitatively assessed the effects of diacetyl and 2,3-pentanedione exposures on pulmonary function, using spirometry data and defined case definitions based on expert assessments of forced expiratory volume (FEV) and forced vital capacity (FVC). These case definitions were used in models quantifying the dose-response relationship between diacetyl exposures and changes in pulmonary function. The models also included data gathered by using a medical questionnaire to collect self-reported information on respiratory health, dermal symptoms, allergies, smoking habits, coexposures, and protective equipment used.

4.3.3 Exposure Methods and Measures

The National Research Council has defined exposure science as the collection and analysis of quantitative and qualitative information needed to understand the contact between the receptors (e.g., workers) and the physical, chemical, or biologic stressor [NRC 2012]. Exposure science plays a critical role in (1) systematically assessing the availability, magnitude, and validity of exposure data as a part of hazard identification and (2) providing input to dose-response analyses (e.g., explanatory variables in dose-response regression models). As such, the evaluation of exposure methods and measures supporting NIOSH risk assessment focuses on the methods used in informative studies to estimate or measure exposure, and a synthesis of exposure information for use in dose-response analyses. In particular, the risk assessor must evaluate the likelihood of potential bias in the

dose-response resulting from exposure misclassification or misspecification (see Appendix B).

Ideally, the dose-response relationship between an adverse effect and an agent is quantified by using complete exposure histories on each subject in the affected population. Of course, ideal conditions are rarely present in observational studies of working populations. Therefore, exposure assessors face many challenges such as these:

- The reliance on data from previous studies or employer information that is suboptimal for risk assessment purposes.

- A lack of sensitive, specific, precise, accurate measurements of worker exposures. Exposure values are often derived indirectly from employment information (job titles and employment) and other proxy sources (e.g., other research, industrial hygiene data, process records, and institutional knowledge).

- Incomplete information on exposure or other risk factors that could influence effect measures. For example, exposures that occur while a worker was employed elsewhere (i.e., outside of studied facilities) are rarely known.

- Temporal and spatial variation in occupational characteristics (e.g., tasks, chemical inventories, and engineering controls). These can result in wide-ranging interindividual and intraindividual variation in exposure, differences which can add to the uncertainty in exposure indices.

- Industry settings that involve complex exposures to combinations of hazardous agents rather than a single agent of interest. Health effects from exposures to an agent may be entangled with effects from other agents. Furthermore, the combined effects of a mixture of agents (i.e., cumulative risk) may differ from the additive effect of separate exposures to these agents.

Because of the evolution of workplace hazard controls, present day exposures to hazardous agents tend to be lower than in earlier times, resulting in

less evident exposure-related adverse effects. Thus, there is increased need for the most informative exposure estimates for quantifying a correspondingly smaller attributable risk. As such, the field of exposure science is rapidly progressing to meet the demand for improved methods for estimating exposures. Many of these methods are summarized in several works on occupational epidemiology and risk assessment [Checkoway et al. 2004; EPA 1992; Nieuwenhuijsen 2010; NRC 1983; White et al. 2008].

The quality of exposure information in observational studies is often limited by data availability. When considering data for the purpose of occupational risk assessment, the risk assessor generally weights available information by the hierarchy shown in Table 4-1. This order supports a general preference of individual exposure estimates over group estimates and quantitative values over exposure classes. Thus, exposure information ranges from individual exposure estimates derived from personal monitoring (most precise), to exposure status that is dichotomously assigned (least precise).

4.3.3.1 Exposure Indices

Exposure is typically quantified directly or indirectly in terms of either exposure or dose [NRC 2012; White et al. 2008]. The metrics derived are sometimes referred to as exposure indices [Checkoway and Rice 1992; Loomis et al. 1999; Nieuwenhuijsen 2010]. The terms *dose* and *exposure* have been

used interchangeably in risk assessment; however, a distinction between these terms is generally recognized [IPCS 2004; Kriebel et al. 2007; NRC 2012; Paustenbach 2000]. Exposure refers to contact between an agent and a target. Contact takes place at an exposure surface over an exposure period. Dose is the total amount of an agent administered to, taken up by, or absorbed by an organism, system, or population. Thus, dose is also the amount of agent that enters a target after crossing an exposure surface [IPCS 2004]. Strict adherence to the distinction between dose and exposure relies on the choice of target and exposure surface, and dose estimation may require a complete accounting of various physiologic and metabolic systems that modify the amount deposited into the chosen human target. In practice, the choice of exposure or dose metrics depends on the aims of the candidate study, which may or may not align with the needs of the risk assessment. Therefore, NIOSH risk assessors consider how the choice affects the WoE provided by the study during hazard identification and, if data are selected for dose-response analyses, what additional steps (if any) are needed to convert the quantity used in the dose-response analysis to the quantity needed for a suitable REL.

Exposure indices can be expressed in many ways by using information on three basic dimensions: intensity (e.g., concentration, mass), duration (e.g., hours, days), and frequency (e.g., times per day)

Table 4-1. Types of exposure data in occupational epidemiologic studies (adapted from Checkoway et al. [2004])

Type of Data	Dose Approximation
Quantified personal measurements on all workers	Most Precise
Quantified area- or job-specific measurement data	
Ordinal ranking jobs and tasks (e.g., JEMs, SEGs, using exposure categories)	
Duration of employment in the industry	
Ever/never employed in the industry	Least Precise

Abbreviations: JEM, job-exposure matrix; SEG, similar exposure group.

[Nieuwenhuijsen 2010; White et al. 2008]. Indices may include each dimension separately or in combination, such as assessing ionizing radiation exposure as a time-integrated dose (e.g., lifetime dose equivalent measured in sievert [Sv]) or a time-averaged dose (dose equivalent rate measured in Sv per hour) [Checkoway and Rice 1992; Kriebel et al. 2007]. Ideally, the choice of metric is determined from adequate information on which metrics (if any) best predict risk. In lieu of this information, the characteristics of the adverse effect might imply the most appropriate choice. For example, exposure indices used to examine acute toxicity effects are typically based on short-term or instantaneous intensity (e.g., peak airborne concentration), whereas cumulative dose (i.e., the time integral of exposure intensity) is generally preferred for chronic effects in which biologic damage appears proportional to the delivered dose quantity (e.g., silica and chronic silicosis or ionizing radiation and cancer) [Checkoway and Rice 1992; Rappaport 1991]. As another example, an adverse effect may be reversible by elimination of toxic agents from the body over time. In this instance, a measure of the amount of the hazardous agent residing in the body (i.e., body burden) might be preferred.

Body burdens are a metric of internal exposure and are typically determined via biomonitoring methods that measure the hazardous agent, its metabolites, or other reaction products in a biologic matrix (e.g., human tissues, saliva, blood, or excreta) [Needham et al. 2007]. Pharmacokinetic models can also be used to estimate body burdens. Thus, an understanding of the underlying biological mechanism related to the outcome of interest is important for index selection. If an understanding of the expected response is lacking, then it may be necessary to assess the dose-response by examining multiple indices [Blair and Stewart 1992]. In this case, the choice of the best index is based on its validity and reliability, as well as its utility in subsequent dose-response analyses.

Summary (aggregate) exposure metrics (e.g., average, geometric mean, or peak exposures) are often used to assign group-level exposure indices in the absence of individual data. Clearly, the choice of summary metrics can have a marked effect on results from dose-response analyses. Often, the choice is limited to published results that may not be best suited for risk characterization. For example, exposure distributions of most occupational agents tend to be right-skewed, and geometric mean values are used in many studies as a measure of central tendency. Although these measures may be appropriate for the intended purpose, the choice was likely made without consideration of a subsequent use in describing population risk. It has been shown that the appropriate group assignment for risk characterization is largely dependent on the expected shape of the dose-response, regardless of the underlying exposure distribution [Crump 1998; Seixas et al. 1988]. In most situations, the anticipated response increases with dose; therefore, the arithmetic mean (i.e., average) provides a better approximation for assessing population risk [Crump 1998].

4.3.3.2 Direct Assessment Methods

Direct methods of assessing exposure refer to obtaining direct measurements of the agent of interest (e.g., airborne concentrations) or biomarkers of exposure [Checkoway et al. 2004; Nieuwenhuijsen 2010; NRC 1991]. These data are generally the most informative in risk assessment and are preferably collected from measurements at the individual level, although group assignment is also possible. Information from personal monitoring is likely to provide the most accurate estimate of individual exposure. Personal monitoring can be conducted by using direct reading devices and breathing-zone air samples; by using *in vivo* (e.g., whole body radiation counter) measurements; or by using biomarkers of the agent of interest, its metabolites, or its effects (e.g., chromosome aberrations from ionizing radiation exposure) in biologic media such as blood, hair, excreta, sputum, sweat, or exhaled breath [Nieuwenhuijsen 2010; White et al. 2008]. Ideally, exposure data stem from monitoring during tasks that are representative of the occupation of each worker and over an adequate period to

inform the exposure distribution. For example, many workers employed in the nuclear industry have worn personal radiation dosimeters in radiation areas throughout their careers, beginning as early as the late 1940s. However, personal monitoring of ionizing radiation exposure is the exception; limitations in logistics, costs, and technology have excluded widespread use of personal monitoring in most other industries.

In most epidemiologic studies, the direct measurement of individual exposure is not practical given large numbers of study participants; therefore, a common approach is to use group-level measurements [Checkoway et al. 2004]. Group-level measurements pertain to either (1) measurements from personal monitoring of a worker or a sample of workers who represent a group with similar exposure or (2) ambient measurements in work areas occupied by a group with similar exposure. A summary measure of exposure is assigned to each member of the similar-exposure group; thus, estimates rely on the underlying assumption of similar exposure level and variation among persons within the similar-exposure group. Group measurements are a source of Berkson error and may result in shared error (see Appendix B). The effects of these errors on risk estimates should be evaluated in the risk assessment whenever practical.

Ambient (stationary or area) measurements are further limited by the required translation to individual exposure [Nieuwenhuijsen 2010]. For example, measurements from a fixed air sampler placed between the exposure source and the exposed person may tend to overestimate the individual exposure. Furthermore, sampling plans are often designed to describe maximum exposures for regulatory compliance purposes. Hence, exposure estimates from such sampling plans would be susceptible to overestimation. Risk assessors consider the potential for exposure misclassification resulting from the design and conduct of ambient exposure measurements that are subsequently used in risk assessment. Regarding group assignments based on personal monitoring, exposure estimates are strengthened by increased sample sizes and the

use of repeat measures that enable an assessment of between- and within-worker variability. NIOSH risk assessors consider sample size and the availability of repeat measures when assessing the validity of group assigned exposures from personal monitoring data.

4.3.3.3 Indirect Assessment Methods

There often are few historical industrial hygiene monitoring data available for most hazards; therefore, indirect methods of exposure estimation are commonplace in occupational studies. Exposure estimates can be derived indirectly from proxy measures, questionnaires, expert judgement, job-exposure matrices (JEMs), statistical models, or any combination of these sources. Several comprehensive reviews on data sources, assessment methods, uncertainties, and validation techniques are available to risk assessors [Kauppinen 1994; Seixas and Checkoway 1995; Stewart et al. 1996; Teschke et al. 2002].

4.3.3.3.1 Self-Report or Proxy Respondent Data

When data are obtained directly from individual study participants or indirectly from proxy responses to a study interview or questionnaire, assessments are subject to bias from recall that has been influenced by case status (i.e., recall bias). The literature is abundant with reports examining the validity and reliability of exposure estimation methods using self- or proxy-reported data [Ahlborg Jr 1990; Baumgarten et al. 1983; Benke et al. 2001; Bond et al. 1988; Bourbonnais et al. 1988; Fritschi et al. 1996; Joffe 1992; Nieuwenhuijsen 2010; Stewart et al. 1987; Teschke et al. 1994].

4.3.3.3.2 Job Exposure Matrix

A JEM is widely used by NIOSH for estimating exposure indices, whereby a job, which is defined by relevant employment information (e.g., job title, task, department, and plant), is systematically linked to an exposure level. Noteworthy early JEM examples involve assessments of exposures to silica, asbestos, and solvents [Dement et al. 1983;

Eisen et al. 1984; Gardner et al. 1986; Rice et al. 1984; Rinsky et al. 1987; Seixas et al. 1997; Stewart et al. 1986]. JEMs have been used to identify similar exposure groups, to provide individual qualitative and quantitative exposure estimates, and in conjunction with algorithms and statistical models, to fill in gaps in exposure information during time periods when monitoring data were unavailable [Coughlin and Chiazze 1990; Dement et al. 1983; Eisen et al. 1984; Hallock et al. 1994; Hornung et al. 1994; Seixas et al. 1997; Woskie et al. 1988].

In its simplest form, the JEM is a table with rows and columns characterizing occupation and exposure, respectively. Thus, each cell represents an estimate of the exposure for individuals linked to an occupation. Strata for occupation and exposure are optimized to increase estimate precision while reflecting the exposure gradient, which is necessary for dose-response analyses. Of course, there is still a large potential for exposure misclassification in a two-dimensional JEM. This misclassification can be reduced by adding dimensions. Contemporary JEMs typically describe exposures along four axes, comprising strata for the agent, job or task, time, and location.

NIOSH risk assessors evaluate the quality of source data and methods used in the JEM to reduce exposure misclassification. Given the JEM's reliance on employer-provided information, the completeness, accuracy, and scale of these data are typically scrutinized. These data fall into two categories corresponding to the primary dimensions: (1) individual employment information used to establish task, time, and location of the worker and (2) process information and plant industrial hygiene data used to assess the exposure potential (i.e., agent). Worker data often stem from personnel records, medical histories, or questionnaires. Exposure data often include job descriptions, chemical inventories, monitoring data, and incident and accident reports. Information on exposure modifiers is likely found in plant records on engineering controls, administrative policies, and personal protective equipment use. Employer-provided information is rarely complete; therefore, JEMs are sometimes augmented by data from other sources (e.g., new measurement data, statistical models, and other JEMs). For example, industrial hygiene data from routine sampling that began in the 1980s may have supported exposure estimates for previous decades. In this case, the risk assessor assesses the methods used to extend estimates to unmonitored periods.

In some instances, data are available from other sources (e.g., measurement data, statistical models, and other JEMs) that can be used to assess the quality of the JEM and/or quantify the magnitude of potential misclassification. For example, consider a cohort study that estimated exposure by using personnel records and ambient air measurements but had personal monitoring data available on a subset of the study population. These monitoring data could then be used as a standard for comparison to study estimates and be a means to calibrate the JEM.

The exposure information in the epidemiologic report is likely to be brief and have limited use for assessing data completeness. Fortunately, superior JEMs are often documented in separate detailed reports that are available in the literature or can be found in study records. For example, exposure estimates for a cohort mortality study of beryllium-processing workers in multiple plants [Schubauer-Berigan et al. 2011] relied on data from three separately published JEMs [Chen 2001; Couch et al. 2011; Sanderson et al. 2001] for dose-response analyses that were subsequently used in quantitative risk assessment for developing permissible exposure levels [Schubauer-Berigan et al. 2017]. When JEM data are not published, risk assessors are encouraged to contact investigators for additional documentation needed to assess the quality of the exposure data supporting study findings.

4.3.3.3.3 Expert Assessment

Employment information and/or self-reported data are often used in tandem with expert judgement by industrial hygienists, chemists, engineers, and other professionals to estimate exposure [Nieuwenhuijsen 2010; Teschke et al. 2002]. It is generally thought

that experts, having a better understanding of exposure mechanisms because of their training, can more accurately estimate exposures than can the workers themselves. Furthermore, if the experts are kept blind to case status, the potential for information bias is reduced. Nevertheless, it may be impractical for experts to become suitably familiar with all exposure conditions over the period of interest without detailed information from employer records and the affected workforce. Another disadvantage of expert judgment is an inherent inconsistency among experts, given relatively unstructured opinions about the exposure that have developed from varying levels of training and experience. In preferred studies using expert judgement, reliability is typically assessed by comparing estimates from two or more experts [Benke et al. 1997; Kromhout et al. 1987; Ramachandran et al. 2003; t' Mannetje et al. 2003; Van Wendel De Joode et al. 2005a]. When available, comparisons with measurement data are preferred for assessing validity [Benke et al. 1997; Tielemans et al. 1999; Van Wendel De Joode et al. 2005b].

4.3.4 Factors Compromising Internal Validity

An important consideration not listed among Hill's viewpoints is refutation of alternative explanations of study findings. An important source of spurious results in research findings is systematic error (i.e., bias). Bias is defined as a deviation of the results or inferences from the truth, or processes leading to that deviation [Gail and Benichou 2000]. Study designs are typically evaluated by risk assessors to ensure that candidate epidemiologic studies are absent of major systematic errors. Common sources of systematic errors can be classified into four general forms:

- Selection bias, resulting from procedures used to select participants into or out of the study or that inherently occurs as part of the normal occupational setting (e.g., healthy worker survivor bias effects described below).

- Information bias, resulting from misclassification of the study participants' disease or exposure status.

- Confounding, which is a mixing of the effects from the exposure of interest with the effects of other measured or unmeasured factors (confounders) on the risk of the adverse effect. Insufficient accounting for confounding factors can lead to biased risk estimates.

- Healthy worker effects, which are a combination of selection and confounding biases resulting from relationships between heath status, employment, and exposure. This source of potential bias is restricted to observational studies of working populations.

On the basis of these general forms, risk assessors must answer the following questions:

1. Is there any evidence suggesting a potential for a strong selection bias that may fully explain the observed findings?

2. Is there any evidence supporting the potential for a strong information bias that may fully explain the observed findings?

3. Could the findings of the study be attributed to confounding by other risk factors, either because of inadequate control (residual confounding) or because of lack of control?

4. Are there plausible alternative explanations that may fully account for the observed findings?

5. In lieu of bias, how likely are the study findings to have resulted from chance?

These questions describe the potential for a strong bias or imprecise findings that may invalidate risk estimates. Ideally, the risk assessment relies on study results that are not attributable to bias or chance; therefore, a positive response to any of the questions above is generally grounds for removal of the study from further consideration. The term *strong* is used to describe an unacceptable bias by its degree; therefore, it implies that a small distortion of the effect relative to its reported size (i.e., a potential weak bias) may not be disqualifying

for risk assessment purposes. However, the potential for a bias that may only partially explain study findings still requires evaluation for proper use in risk assessment. To aid in responding to these questions, risk assessors are encouraged to review Appendix B of this report, which provides specific information on potential biases common in human risk assessment.

Bias can occur in any stage of the research, including the literature review, study design, data collection, analysis, interpretation of results, and publication. When reviewing studies for validity, risk assessors avoid using a "guilty until proven innocent" approach, whereby one assumes that the study design and analysis are inadequate unless enough information to the contrary is provided by the study authors. Instead, the risk assessor evaluates the potential impact of study limitations and omissions on findings for determining WoE [Zaccai 2004]. Although Appendix B provides some discussion on specific types of biases that may be encountered, for additional information risk assessors may consult several highly cited articles [Arrighi and Hertz-Picciotto 1994; Delgado-Rodríguez and Llorca 2004; Greenland et al. 1999; Grimes and Schulz 2002; Sackett 1979] and epidemiologic texts [Breslow and Day 1980; Breslow and Day 1987; Checkoway et al. 2004; Gail and Benichou 2000; Rothman et al. 2008].

4.4 Laboratory Animal Data

Data from human studies are often inadequate to fulfill hazard identification; therefore, risk assessors use toxicological information from bioassays in animals, either alone or in combination with information from human studies. As noted by Cohen et al. [2004], using animal data as the basis for human risk requires two fundamental assumptions: (1) the findings in the animal study are relevant to humans (interspecies extrapolation) and (2) the doses used in the animal bioassay are relevant for estimating risk at human exposure levels (dose extrapolation). In general, animal studies predict human health risks well [Allen et al. 1988;

Crump et al. 1989; Griffin 1986]. For example, in its recent report on tumor site concordance, IARC confirmed that the induction of cancer in experimental animals is relevant to the identification of a carcinogenic hazard to humans, given that all human carcinogens that have been adequately tested in animals have also been shown to cause cancer in animals [IARC 2019]. Nevertheless, tumor site concordance is not assured or even routinely observed. For example, there are four agents for which there is sufficient evidence for breast cancer in humans and seven agents for which there is sufficient evidence for breast cancer in experimental animals, but only one of these agents causes breast cancer in both humans and animals [IARC 2019]. NIOSH recognizes that differences exist between species because of the unique inherent physiological and biochemical mechanisms in each species [Homburger 1987] and because exposure conditions in animal models can differ greatly from the work environment. Moreover, humans lack the homogeneity observed among inbred experimental animals. Collectively, these differences may lead to false-positive or -negative assay findings [Ennever and Lave 2003; Ettlin and Prentice 2002; Haseman and Elwell 1996].

As in human studies, not all animal studies are equally useful. Some studies are limited by virtue of their sample size, experimental design, methods, and the interpretation of the results by authors. It is very important that the toxicity evaluation of a substance be based on information from well-conducted studies. Evaluation of the quality and reliability of individual animal toxicity studies requires consideration of factors associated with a study's hypothesis, design, methods, execution, analysis, and interpretation [Hothorn 2014; Klimisch et al. 1997; Lu and Kacew 2002; NTP 2015a; NTP 2015c; Salem and Katz 2014].

4.4.1 Relevance and Appropriateness of the Animal Model

A relevant and appropriate animal model of human disease is one that includes a living organism in which normative biology or behavior can be studied,

or in which a spontaneous or induced pathological process can be investigated, and in which the phenomenon in one or more respects resembles the same phenomenon in humans [NRC 1981]. The term *relevance* refers to the comparability of the observations in animals to those in humans. Clearly, a preferred model is one in which the phenomenon of interest is observed equally in both animals and humans. In practice, the degree of direct comparability can be low, which is a limitation in animal studies. Limited comparability does not preclude the use of animal information in human risk assessment. In fact, animal studies may provide the best dose-response information to support human risk assessment. The term *appropriateness* refers to factors that support the choice of animal model for risk assessment, depending on the scientific questions to be addressed. These factors can include animal life span; genetic homogeneity; specific anatomical, physiological, or behavioral attributes; the frequency of the effect of interest and its background occurrence; and availability (supply and cost) [Hedrich and Bullock 2004; Krinke 2000; NRC 1981].

Understanding the mode of action (MoA) of a chemical helps to establish the best animal model for use in the toxicity testing and risk assessment (MoA is further described in Section 4.4.2.2). For example, male rats are not a useful model for evaluating the risk of kidney cancer from gasoline exposure in humans [Baetcke et al. 1991]. The MoA for kidney cancer in male rats from gasoline exposure (and various other chemicals, as described later for d-limonene exposure) involves the presence of alpha-2u-globulin protein. This protein combines with the metabolites of gasoline, which can eventually induce kidney tumors. Humans, female rats, and mice do not have this protein. From everything known to date, the presence of alpha-2u-globulin is necessary for the development of kidney tumors; therefore, no excess kidney cancer has been observed in exposed mice or female rats.

For test compounds that depend on a metabolite to produce an adverse effect in the animal (for example, epoxide formation for some carcinogens), the most appropriate animal species is often the one that has the closest similarity to humans with respect to relevant metabolic processes involved in toxicity [Bogaards et al. 2000; Martignoni et al. 2006; Nilsson et al. 2012; Panchal and Brown 2011]. Sometimes other factors besides metabolism are important in selecting an appropriate animal model. For example, an adequate number of test animals are needed to ensure that a study has adequate statistical power to detect an adverse effect. Therefore, if rhesus monkeys are most metabolically similar to humans, but only small numbers of these animals were used in the experiment and the toxicologic response was equivocal, then the rhesus monkey may not be the best animal model for the risk assessment.

Ideally, animal studies used in human risk assessment should be performed in animals of appropriate age (adult versus newborn), of both sexes, and with a health status (e.g., pregnant versus nonpregnant) that corresponds to human exposure and toxicity. The study should take into consideration the appropriate duration and pattern of exposure (acute versus chronic; single exposure versus repeated administration) to simulate human occupational exposure.

Often, a test compound will have data from several animal studies. The information on test animals should include species, strain, sex, age, and number of animals per group from any individual study. Ideally, an animal model with the most valid biological rationale (e.g., similar pharmacokinetic profiles) should be selected as the animal model most relevant to humans. However, in some cases no such closely relevant model exists. In such cases, the animal model that is most sensitive (i.e., showing a toxic effect at the lowest administered dose after dosimetric adjustments are performed) is often used [Barnes and Dourson 1988].

4.4.2 Animal Toxicologic Study Design

Animals most often used in bioassays are rat, mouse, guinea pig, hamster, rabbit, monkey, and dog. Codified U.S. EPA guidelines for conducting animal toxicity studies are available [Health Effects Testing

Guidelines, 40 CFR 798]. International guidelines are provided by the Organisation for Economic Co-operation and Development (OECD), in the OECD Guidelines for the Testing of Chemicals, Section 4, Health Effects, Tests 403, 412, 413, and 452 for inhalation exposure studies [OECD 2009; OECD 2018b; OECD 2018c; OECD 2018d] and Tests 402, 404, 410, 411, and 429 for dermal toxicity studies [OECD 1981a; OECD 1981b; OECD 2010; OECD 2015; OECD 2017]. These guidelines provide recommendations on physical parameters of test substances and testing conditions; on laboratory animals (e.g., species, number, sex, age, and condition); and on gross pathology, histopathology, and clinical, biochemical, hematological, ophthalmological, and urinary excretion tests to be included in the study. It is generally recommended to conduct toxicity tests for each test compound in at least two species, typically rats and mice [Bingham et al. 2001; Salem and Katz 2014]. In addition to improving consistency between studies, these test guidelines can be useful for evaluating WoE among studies, where deviations from these guidelines can indicate potential weaknesses.

NIOSH considers that for an experimental animal study to be useful for human risk assessment, its design should be sufficiently documented to include information on study aims and hypotheses tested; reasons for selecting the animal model used; species, strain, weight/age, sex, and source of animal used; details of each experiment performed, including its design and number of animals used; exposure, including dose, route, schedule, and duration; and statistical methods [EPA 1994]. This information may be found in a study protocol or in the methods section of the study report. Superior studies provide enough documentation of the methods to replicate findings. Combined with a clear and thorough presentation of findings, the study design information is a valuable resource for judging WoE. It is also often helpful if individual animal data are made available for additional analysis.

Studies should include enough test animals and dosing groups to support statistical analysis. The type of study conducted (acute, sub-chronic, or chronic) provides insight into the number of animals and dose groups needed. For example, chronic animal bioassays (2-year studies in mice and rats) typically involve 50 animals per sex per species per dose. These types of studies are useful for collecting information on carcinogenicity and other health effects that require chronic exposure. Sub-chronic studies, on the other hand (90-day studies in mice and rats) typically use fewer animals per species per sex per dose and are typically used to detect non-cancer, organ system health endpoints such as pulmonary inflammation, liver toxicity, and kidney toxicity. The toxicology study guidelines referenced in this section provide more detailed information on studies with adequate numbers and dose groups.

Datasets from studies adhering to good laboratory practices (GLP) [OECD 2005] and to internationally accepted test guidelines (e.g., OECD, EPA, and EU) are preferred as candidates for risk assessment. In addition, studies with sufficient details on methods, analysis, and results that have been peer-reviewed are often acceptable [Klimisch et al. 1997].

4.4.2.1 Exposure Information

Exposure conditions play a vital role in the experimental design of animal toxicity studies. Determination of the dose that reached the test animal in a study is a complex process. This involves using proper methods for the generation, characterization, and delivery of a test compound [EPA 1994]. NIOSH has established the following criteria to assess the suitability of animal toxicologic studies for risk assessment purposes.

Ideally, the study should clearly define the physicochemical characteristics of the substance used, such as purity, stability, pH, partition coefficient, vapor pressure, particle size and distribution, breathing zone concentration, and vehicle. The concentration of the test compound should be reported as means and variances. The exposure concentration, type of exposure (e.g., vapor or aerosol), administration route, exposure schedule, and exposure duration should be clearly described.

For an inhalation study, the information should include a description of the generation and characterization technology used (e.g., chamber design, type, dimensions, uniformity of distribution, source of air, generating system, air conditioning, and exhaust treatment) [Nelson 1992; Wong 2007]. The number of air changes, air flow rate, oxygen content, temperature, and relative humidity are exposure chamber characteristics that should be monitored and reported as means and variances. The description of the characterization method(s) should also include frequency of measurement, calibration of the measurement instrument, frequency of the calibration, and other quality assurance elements [Barrow 1989; Chen and John 2001; Moss and Cheng 1989; Wong 1999].

The various inhalation exposure techniques include whole body, head only, nose only, intra-tracheal instillation, and oropharyngeal aspiration [Driscoll et al. 2000; Phalen 1997; Sahu and Casciano 2009; Wong 2007]. Factors such as safe and efficient generation, amount of material, test compound stability, exposure duration, and the measurements desired influence the selection of an exposure technique for a study design. For instance, in chronic inhalation exposure studies, whole-body exposure of laboratory animals in cages is the most common method, whereas nose-only exposures are most often used for short-duration particle exposures. However, it should be noted that several factors such as heat, stress, and anesthesia could affect the biological patterns of the animal, potentially influencing results [Hughes et al. 1982; Mete et al. 2012; Overmyer et al. 2015; Stratmann et al. 2010; Suvrathan et al. 2010]. Due consideration of these issues should be included in detail in the data analysis to ensure appropriate comparisons.

Test agents may affect lung ventilation, function, uptake, clearance mechanisms (e.g., mucociliary clearance), and retention of the dose. Particle overloading in the lungs of test animals, especially rats and mice—a well-known outcome of particle exposures at higher concentrations and/or longer duration—should also be evaluated [EPA 1994; Morfeld et al. 2015; Morrow 1988; Oberdörster

1995; Oberdörster 1997; Olin 2000; Pauluhn 2014]. Overloading results in aggregated alveolar macrophages (AMs) engorged with phagocytized dust particles. These AMs release an array of mediators, resulting in various inflammatory responses and tissue injury [EPA 1994; Kanj et al. 2005; Laskin and Pendino 1995]. Overloading is characterized by a dose-dependent decrease in the rate of particle clearance from the lungs; thus, first-order clearance kinetics would underestimate the retained particle dose in the overloaded rat. Overloading can be addressed in quantitative risk assessment by using dosimetry models that account for higher-order kinetics to estimate the retained particle dose in rodents and humans. The nature and severity of rat lung responses to particle overload are less certain than the lung responses in humans at equivalent doses; however, without overloading, rats would not reach the equivalent mass lung doses that have been observed in workers in dusty jobs [Kuempel et al. 2014; Morfeld et al. 2015; Olin 2000; Pauluhn 2014]. Comparison of the particle burdens in the lungs of test animals to the particle burdens expected in the lungs of occupationally exposed humans is useful in evaluating whether the experimental study in question is relevant to occupational health risk assessment. Sections 5.6.2.5 and 5.6.2.7 provide additional information on lung clearance kinetics of particles in rodents and humans.

Animal studies have different durations (acute, subchronic, and chronic) and frequencies of exposure (single, intermittent, and continuous). Study variations help to identify the hazard associated with a given test compound, but not all of them may be appropriate for quantitative risk assessment, depending on the human exposure of concern.

Appropriate control groups of unexposed (e.g., air-only controls in inhalation studies) and/or vehicle-exposed animals should be included in the study. The control group(s) should be treated similarly to the chemically treated group, except that the control group should not receive any of the test compounds [Hayes 2008; Salem and Katz 2014]. In addition, historical control data can also be used to evaluate the differences between control and treated

groups. In general, historical control data should be submitted from the same laboratory and should be from animals of the same age and strain generated during the 5 years preceding the current study [OECD 2018d].

Most often, animal bioassays expose animals to higher doses of a chemical than those common in human exposure [Klaassen et al. 2013]. Sometimes the animal doses are comparable to occupational exposures, but often they are significantly higher (see Section 5.6.2.8 for more details). Toxicity observed at high doses may or may not occur at lower doses. Therefore, animal studies should always be evaluated in the context of dose-response relationships. Doses for vapor exposure are usually provided in units of parts per million (ppm) or milligrams per cubic meter (mg/m^3), and doses for airborne particle exposures are usually provided as the mass concentration (mg/m^3) and aerodynamic particle size (e.g., mass median aerodynamic diameter, MMAD). Number concentration is also reported for airborne particles or fibers. The size and shape of particles determine the region in the respiratory system in which particles are deposited (see Section 5.6.2.2 for more details). Care should be taken to ensure that particle morphology under test conditions reflects human exposure patterns. The physicochemical properties of a particle determine whether it will be dissolved in the blood or removed by clearance mechanisms.

In dermal exposure, the contact area, absorption, concentration of the chemical, contact frequency, retention time, and penetration potential contribute to the dermal toxicity [Marquart et al. 2003; Poet and McDougal 2002; Schuhmacher-Wolz et al. 2003; van Ravenzwaay and Leibold 2004].

4.4.2.2 Consideration of Mode of Action and Adverse Outcome Pathways

Typically, when conducting risk assessment to inform the development of a REL, NIOSH evaluates health effects that may be experienced by humans or that may be related to health effects experienced by humans, as evidenced by the results of human and animal studies. Once the constellation of health effects under consideration has been established, the risk assessor critically evaluates the health effects to determine which effect(s) are of interest. In doing so, the risk assessor clearly explains the rationale for selection of the health effects and their relevance to human health.

As part of its hazard identification, NIOSH evaluates MoA and adverse outcome pathway (AOP) information to determine whether evidence is adequate to establish that the events leading to adverse effects in animals are unlikely to operate in humans. An AOP is a construct portraying the sequence of events between a direct molecular initiating event and the adverse effect relevant to risk assessment [Ankley et al. 2010]. Whenever information is available to describe the MoA or the AOP, NIOSH uses this information to evaluate the dose-response information. MoA is generally thought of as the underlying biochemical interactions that lead to the expression of the adverse effect. Full information on the MoA is rarely available. MoA refers to the general processes and key events that are involved in the toxicity of a chemical. MoA analysis includes review of physical, chemical, and biological information on the substance [Boobis et al. 2006; Boobis et al. 2008].

It is sometimes observed that humans have a different sensitivity to a test compound than experimental animals do [Lasagna 1987]. In addition, there are cases where the MoA or adverse effect identified in an animal model is not relevant to human health. The case of d-limonene exposure causing kidney tumors in male rats, but not in female rats or either sex of mice, is one example. The male rat kidney tumors have been linked to a metabolite of d-limonene binding to the protein, alpha-2u-globulin, leading to toxicity, cellular regeneration, and tumor formation. Humans have no functionally similar protein; therefore, this MoA does not appear to operate in humans, and the male kidney tumors do not indicate a human cancer risk. Cohen et al. [2004] summarize this case and others. In their report, the authors describe a framework

for evaluating the relevance of chemically induced animal tumors to humans.

An understanding of the MoA of the toxic agent can help define which data are most appropriate for consideration. The EPA has described MoA framework initially for cancer risk assessment in the *Guidelines for Carcinogen Risk Assessment* 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 [EPA 2005]. Examples of possible modes of carcinogenic action include "…mutagenicity, mitogenesis, inhibition of cell death, cytotoxicity with reparative cell proliferation, and immunologic suppression." Later the MoA framework concept was expanded to assess risk for non-cancer endpoints [Bogdanffy et al. 2001; Julien et al. 2009; Lochner et al. 2005; Seed et al. 2005]. The substance may induce adverse effects by more than one MoA in a single tissue or at different sites. Therefore, a single MoA for an endpoint may or may not apply to all other health endpoints.

An expanded MoA framework focuses on the WoE establishing the MoA in animals and whether the key events identified in animals are plausible in humans, and it considers kinetic and dynamic factors to determine whether the MoA is plausible in humans. To use the MoA framework, the risk assessor asks the following questions (Figure 4-2):

- *Is the WoE sufficient to establish the MoA in animals?* The first step in considering the relevance of MoA information to human health is having sufficient MoA information on the animal species for the health effect of interest. The default position is that the health effects observed in animals are relevant to humans. As stated in Seed et al. [2005], "[W]hen data are insufficient to confidently characterize an MoA for test animals, the animal tumor data are presumed to be relevant to humans and a complete risk assessment is necessary."

- *Are key events in the animal MoA plausible in humans?* To evaluate whether the MoA is relevant to humans, there must be sufficient

information available regarding the potential for the key events identified in the animal MoA to operate in humans. For example, a key enzymatic pathway observed in the animal should also be present in humans or, if the exact enzymatic pathway is not present, then determine if there are pathways that serve a similar or identical function. If there is insufficient information in humans to characterize the relevant pathways, as described above, then the animal data are presumed to be relevant to humans and a complete risk assessment is necessary. However, if there is clear evidence that the relevant pathways do not operate in humans, then the risk assessor should assume that the observed effects in animals are not relevant for humans for this endpoint. Unless it is known that all the health effects observed in animals derive from a common MoA, this analysis needs to be conducted separately for all health effects under consideration for risk assessment.

- *If we take into account kinetic and dynamic factors, as well as life stages, then are key events in the animal MoA still plausible in humans?* This step requires quantitative information on the relative kinetic and dynamic factors that would influence risk in humans and animals, as well as consideration of life stages of potential exposure in humans. For example, consider the case in which the MoA has been identified in animals, involving toxicant metabolism by a specific enzymatic pathway found in both animals and humans; however, there is a high rate of metabolism by this pathway in the rodent that is not evident in humans. In addition, humans have a competing enzymatic pathway that metabolizes the toxicant much more rapidly. Thorough analysis of the kinetics indicates the potential human toxicity via this MoA is, in fact, very low, suggesting the conclusion that there is no need to conduct a risk assessment for this endpoint. The same type of analysis could be conducted when considering potential exposures during specific life stages, if that is deemed a critical variable.

AOPs are structured representations of biological events leading to an adverse effect. AOPs are
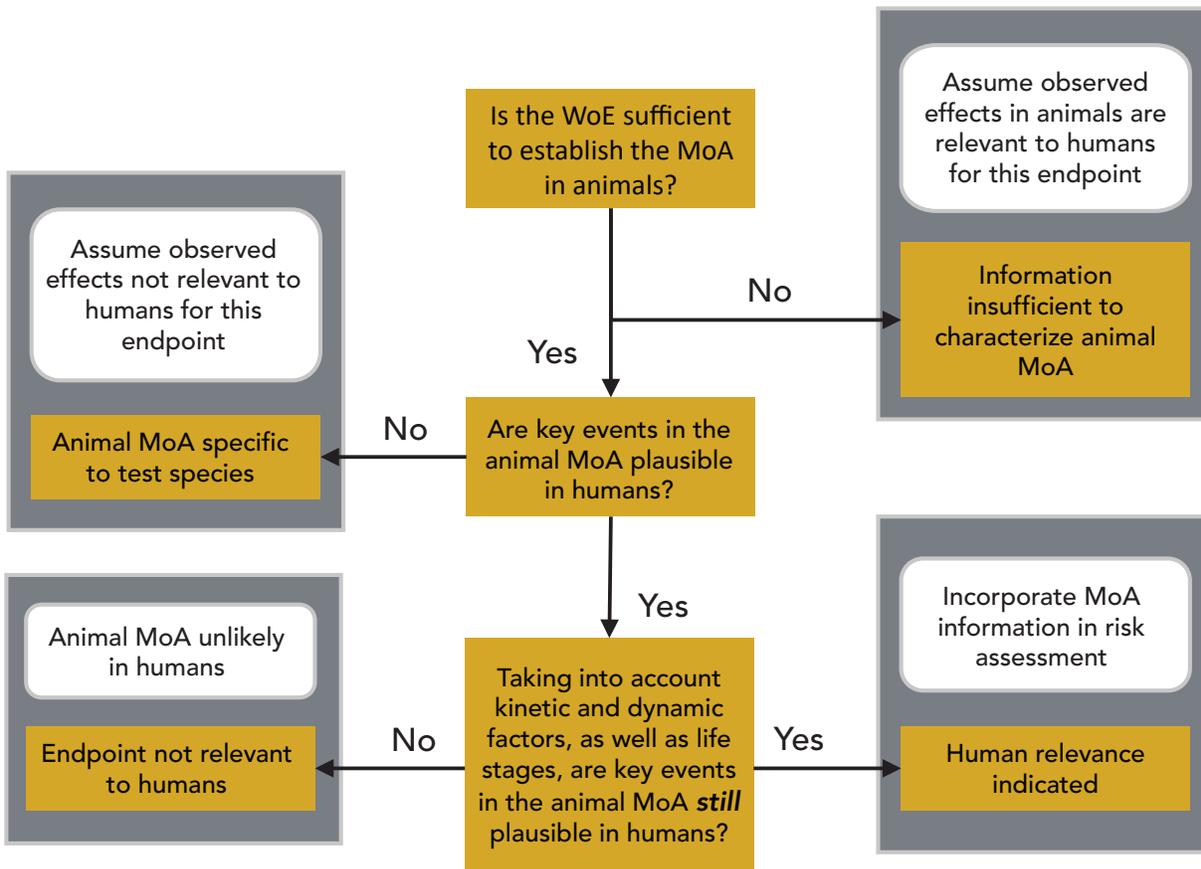
Figure 4-2. Framework for Mode of Action (MoA) assessment (adapted from Seed et al. [2005])

flexible frameworks that can include linking relationships that are causal, mechanistic, inferential, or correlation based [Ankley et al. 2010]. AOPs have been established for several chemical groups. In an AOP, a structured sequential chain of events is constructed with all available scientific information. For example, a chain of events might entail a toxicant exposure causing a molecular initiating event, which then leads to a series of key events causing the adverse outcome of interest. Information on key events in AOPs, the biochemical mechanism of action, or the processes involved in the presumed MoA could give insight into the toxicity of chemicals, including the characteristics of the dose-response (see Appendix C for more information on AOPs).

4.4.2.3 Selecting the Adverse Effect of Interest

Ideally, the dose-response relationship is demonstrable. The observed effects should be directly related to the magnitude of exposure to the test compounds and not influenced by concurrent exposure to other compounds or already existing health conditions [Lewis et al. 2002]. In general, the recommended list of hematology, clinical biochemistry, and histopathological examinations to be evaluated in the laboratory studies are given in several guidelines [Crissman et al. 2004; OECD 2009; OECD 2018b; OECD 2018c; OECD 2018d; Weingand et al. 1996]. NIOSH risk assessors refer to these guidelines, as applicable, for a better understanding and evaluation of the study.

Preferably, the histopathological examinations should be of all tissues for all treated doses and control groups and all tissues from animals. However, many published studies, excluding the NTP studies, employ histopathological examination only for the target endpoints, which although somewhat limited in scope still may be useful for risk assessment. In addition, quantitative histopathological measures of response (e.g., dichotomous or ordinal categories of the occurrence and severity of an adverse response) are necessary to use these data in dose-response modeling.

A special consideration is the appropriateness of selecting early biomarkers, precursor effects, and critical molecular/cellular changes in lieu of the adverse effect anticipated in humans. An example of this is evaluating inflammatory markers that lead to secondary genotoxicity and ultimately cancer after exposure to inhaled particulates. Cancer is of direct and relatable interest to human health. Moreover, for poorly soluble, low-toxicity particulates, the MoA has been described as an irritation response, followed by inflammation and production of reactive oxygen species, which leads to secondary genotoxicity and ultimately an increased risk of cancer. When the MoA is well-supported, it may make sense to conduct risk assessment on early biomarkers or molecular changes. Ideally, the causal and quantitative relationship between the occurrence of the biomarker or molecular changes and the outcome of interest is understood. When the relationship is correlative or the quantitative aspects are poorly understood, the relevance to human experience becomes more tenuous. Validation of the causal pathways and description of the quantitative relationship and attendant uncertainties between the outcome of interest and the precursor events or biomarkers are important steps to consider in conducting this type of risk assessment.

Similarly, tests using structurally related compounds or any active metabolite of the compound of interest could also be considered for a comparison of results. However, toxicity studies of structural analogs and metabolites should be carefully considered in light of the MoA, metabolic issues, and other factors that may influence differences in response between the alternate chemical and the chemical of interest. Demonstrated relevance of the findings for analogs or metabolites to the chemical of interest is necessary. In addition, the limitations and uncertainties associated with using toxicity data from alternate chemicals should be thoroughly and explicitly discussed when reaching any risk assessment conclusions. When multiple toxicity studies are available, the studies should be reviewed with reference to the types of effects observed in different test species and strains. Consistency of response across species, sex, and/or route of exposure increases the WoE that the effect might occur in humans. In contrast, an effect observed in only one species or sex may need further evaluation. Results replicated by independent researchers would have increased credibility.

Once the evidence is evaluated, NIOSH assesses the toxicological database for completeness. A complete toxicological database includes studies that evaluate carcinogenic, genotoxic, reproductive, developmental, and other organ effects (e.g., immunotoxic, neurotoxic, nephrotoxic, irritation, and sensitization). Ideally, the literature describes the dose-response relationship; concordance across species, strain, sex, exposure routes, or in multiple experiments with respect to adverse effects; effects that are biologically plausible and of human relevance; and similar effects with structurally related compounds. However, a complete toxicological database is not essential for hazard identification if the observed adverse effects are relevant to occupational exposures. If there are only limited data on a specific chemical, then all available studies with limited information should be critically evaluated to determine the usefulness of the information for risk assessment. If concordance across species/strain/sex is not observed, then additional evaluation is needed; in the absence of information to the contrary, the more sensitive species/strain/sex is often used.

5 Dose-Response Assessment

5.1 Introduction

The dose-response assessment is the second step of NIOSH risk assessment. The aim of the dose-response assessment is to obtain reliable and valid estimates of the point of departure (PoD) in a cause and effect relationship between the exposure and outcome of interest or the risk at prescribed dose levels (e.g., risk per unit dose) that can be used in risk characterization.

The dose represents a quantitative metric d, usually derived from some external exposure, and believed predictive of an adverse effect. Whenever the relationship between the biologically effective dose and another dose metric (e.g., absorbed dose, inhaled dose, or exposure concentration) is well described by a constant ratio (i.e., a directly proportional relationship over the range of doses under consideration), then these doses are interchangeable and their dose-responses are equivalent. For example, if the inhalation rate during exposure is constant over the range of concentrations, then the inhaled dose rate is proportional to the concentration; but if the inhalation rate is not constant, then the dose-response based on inhaled dose requires adjustment to obtain the corresponding dose-response based on exposure concentration.

As another common example, consider a nonlinear rate of metabolic activation. The rate of metabolic activation of a toxicant may be best approximated as linear at low exposure concentrations, but it may become nonlinear at high concentrations. If the biologically effective dose is the amount that is metabolically activated, then the dose-response analysis is usually based on the amount activated rather than the exposure concentration, if that has been quantitatively described and validated.

In general, quantitative risk analysis relies on mathematical models of association used to describe the conditional probability of the adverse effect at different levels of exposure to the agent, given levels for other direct causes of the adverse effect. Statistical methods used in dose-response modeling are numerous and diverse. The onset of personal computing has led to advancements in this area that continue today. For example, at the time of this writing, considerable advancements in the EPA Benchmark Dose Software suite were ongoing. Thus, a detailed description of modeling methods preferred for all situations faced in risk assessment is beyond the scope of this Bulletin. However, simple modeling practices that may be encountered are described in the following sections to broadly illustrate dose-response modeling concepts. In specific situations, NIOSH encourages risk assessors to take advantage of the substantial technical progress that has been made in dose-response modeling techniques by referencing recent literature.

5.2 Dose-Response Modeling

Dose-response regression modeling provides a basis to estimate the expected response as a function of dose d and possibly other risk factors, $X_1, X_2, \ldots, X_c$, together with assumptions about the variability of responses. In animal toxicology studies, the dose-response is often simplified to expected response = $f(d)$ since the other risk factors are controlled by design or by the random assignment to dose levels. As an illustration, consider the outline of animal study data in Table 5-1. At each dose level d, there are n animals exposed, and the corresponding response, Y, is number of animals presenting with the adverse effect of interest. The expected proportion of animals with the adverse effect is related to each dose d and is equivalent to the probability of the adverse effect $f(d)$. The function $f(d)$ is evaluated at any dose between the background response (when $d = 0$) and the maximum observed dose.

Table 5-1. Illustration of data from an animal bioassay for a dichotomous response.[*]

Dose (d_i)	Number of exposed animals (n_i)	Number observed with the response (Y_i)	Observed proportion (Y_i / n_i)
d_0[†]	n_0	Y_0	Y_0 / n_0
d_1	n_1	Y_1	Y_1 / n_1
…	…	…	…
d_D	n_D	Y_D	Y_D / n_D

[*]For example, cancer incidence of a target organ or tissue.
[†]Typically, an unexposed group of controls is used and $d_0 = 0$.

It is preferable to base model selection on biologic plausibility. In practice, however, model specification with a clear advantage based on biology is seldom observed. Instead, a suite of plausible models is usually fit to the data. When multiple models of a response adequately describe the data, the model selected for a risk assessment is generally chosen by using criteria that are defined beforehand. For example, the Akaike information criterion (AIC) is a measure of model fit that is often used to select a model from among a group of models [Akaike 1974]. The selection process should be clearly described in the risk assessment. Because different model-selection criteria can lead to different model choices, model selection is often an area explored in sensitivity analysis. Multiple (alternative) estimates are then reported with a description of how each estimate was derived.

5.2.1 Parametric Dose-Response Modeling

The function $f(d_i; \boldsymbol{\theta})$, which describes the relationship between dose and the expected response for observation i, is often assumed to have a known form that depends on a vector of parameters $\boldsymbol{\theta}$ whose unknown values are estimated. This assumption places strong constraints on the shape of the dose-response curve, and the data are used to estimate $\boldsymbol{\theta}$. Unknown quantities of critical interest such as risk associated with a given dose or the dose associated with a given risk are estimated based on

the fitted dose-response $f(d_i; \hat{\boldsymbol{\theta}})$. Within the form adopted for $f(\cdot)$ multiple ways to describe the effect of dose may be available, e.g., $\theta_1 B_1(d) + \theta_2 B_2(d) + \ldots + \theta_K B_K(d)$, where the $B_k(d)$ are known functions of dose d, and K = dimension of the vector of parameters $\boldsymbol{\theta} = [\theta_1, \ldots, \theta_K]$ and $k \in \{1, \ldots, K\}$ identifies a component of $\boldsymbol{\theta}$. As an illustration, if the effect of dose is to be described by $\theta_1 d + \theta_2 d^2$ then $B_k(d) = d^k$ and $\theta_3 = \theta_4 = \ldots = \theta_K = 0$. This suggests that a hierarchy of increasing flexibility may be examined, e.g., $\theta_1 d$ followed by $\theta_1 d + \theta_2 d^2$, etc., but this should be done carefully since the inclusion of unnecessary terms decreases the degrees of freedom and therefore reduces statistical precision. The omission of a necessary term is likely to introduce a statistical bias into the estimation. Thus, there is trade-off between a potential for bias associated with an overly constrained model of the dose-response versus a degradation of precision, i.e., increased variance, from an unnecessarily flexible model. This relationship between potential bias and increased variance holds in general and is referred to as a bias-vs-variance trade-off. Ideally, a model is selected that is at the level of complexity at which an increase in bias is equivalent to the reduction in variance. In practice, there may not be an analytical solution for selecting the "best" model; therefore, resampling-based measures such as cross-validation and theoretical measures such as AIC and Bayesian information criteria (BIC) may be used to support model selection.

5.2.1.1 Dichotomous Response Data Modeling

Many different parametric models have been proposed for data from animal toxicology or human epidemiologic studies. For example, in the animal toxicology setting, the following model specifications are commonly used in dichotomous dose-response modeling [EPA 2012b]:

Equation 5-1. Logistic

$$f(d) = \frac{1}{1 + \exp[-(\alpha + \beta d)]}$$

Equation 5-2. Log-logistic

$$f(d) = \gamma + \frac{(1 - \gamma)}{1 + \exp[-(\alpha + \beta \ln(d))]}, \, 0 \le \gamma < 1, \beta \ge 1$$

Equation 5-3. Gamma

$$f(d) = \gamma + (1 - \gamma)\frac{1}{\Gamma(\alpha)} \int_0^{\beta d} t^{\alpha - 1} exp(-t) dt, \, 0 \le \gamma < 1, \alpha \ge 1, \beta \ge 0$$

Equation 5-4. Multistage (degree=2)

$$f(d) = \gamma + (1 - \gamma)\left[1 - \exp(-\theta_1 d - \theta_2 d^2)\right], \, 0 \le \gamma < 1, \theta_1 \ge 0, \theta_2 \ge 0$$

Equation 5-5. Probit

$$f(d) = \Phi(a + \beta d)$$

Equation 5-6. Log-probit

$$f(d) = \gamma + (1 - \gamma)\Phi[a + \beta \ln(d)], \, 0 \le \gamma < 1, \beta \ge 0.5$$

Equation 5-7. Quantal-linear

$$f(d) = \gamma + (1 - \gamma)\left[1 - \exp(-\beta d)\right], \, 0 \le \gamma < 1, \beta \ge 0$$

Equation 5-8. Quantal-quadratic

$$f(d) = \gamma + (1 - \gamma)\left[1 - \exp(-\beta d^2)\right], \, 0 \le \gamma < 1, \beta \ge 0$$

Equation 5-9. Weibull

$$f(d) = \gamma + (1 - \gamma)\left[1 - \exp(-\beta d^\alpha)\right], \, 0 \le \gamma < 1, \alpha \ge 1, \beta \ge 0$$

Equation 5-10. Dichotomous Hill

$$f(d) = \gamma + \frac{\eta(1 - \gamma)}{1 + \exp[-\alpha - \beta \ln(d)]}, \, 0 \le \gamma < 1, 0 \le \eta < 1, \beta \ge 1$$

where $f(d)$ is the probability of adverse response at d,

$$\Gamma(x) = \int_0^\infty e^{-u} u^{x-1} du$$

is the (complete) Gamma function evaluated at x, $\Phi(x)$ is the cumulative distribution function of a standard normal random variable at x (i.e., the integral of a N(0,1) density from $-\infty$ to x), and $f(0)$ = γ when $d = 0$ for models 5-2 to 5-4 and 5-6 to 5-9. The parameter η of Equation 5-10 represents an upper limit on $f(d)$, i.e., $f(d) < \eta$ for every dose; Equation 5-10 may be useful when an upper limit on $f(d) < \eta$ where $\eta < 1$ is plausible and it may necessitate that η be estimated from the dose-response data. Some bounds in the above models are arbitrarily set to prevent extreme properties and attendant computational problems, although nonlinear dose-response patterns remain available. Hence, modification of these constraints may be necessary when consideration of either pattern is unwarranted. Furthermore, although the models 5-1 through 5-10 encompass a wide variety of curves to represent the dose-response and have readily available software for their implementation, other parametric forms could be considered if necessary.

Dichotomous outcomes from animal bioassays are often modeled under an assumption that the sampling variation of the underlying experimental process is well represented by a binomial distribution. In some cases, especially where the data are pooled from multiple studies or substantial genetic variations of the animals are present, this assumption may not be appropriate and extra-binomial variability, or over-dispersion, may be observed. In these instances, beta-binomial, quasi-likelihood methods, or more fully defined models incorporating random effects are preferred.

5.2.1.2 Continuous Response Data Modeling

Continuous data arise when response values come from a continuous distribution, for example, precisely measured liver weights or pulmonary function tests. In these situations, a variety of parametric models can predict the mean response. For example, the following five parametric models are often considered when modeling continuous data [EPA 2012b]:

Equation 5-11. Linear

$$f(d) = \beta_0 + \beta_1 d$$

Equation 5-12. Linear-Quadratic

$$f(d) = \beta_0 + \beta_1 d + \beta_2 d^2$$

Equation 5-13. Power

$$f(d) = \beta_0 + \beta_1 d^{\beta_2}$$

Equation 5-14. Hill

$$f(d) = \beta_0 + \beta_1 \frac{d^{\beta_3}}{\beta_2^{\beta_3} + d^{\beta_3}}$$

Equation 5-15. Exponential

$$f(d) = \beta_0 \left\{ \beta_2 - (\beta_2 - 1) \exp\left[(-\beta_1 d)^{\beta_3} \right] \right\}$$

The parameters β_0, β_1, β_2, and β_3 are specific to the given model. It may be necessary to specify bounds on these parameters when fitting models. For example, the parameter appearing as the exponent of dose d of the Power model must be restricted to be greater than zero.

For continuous data, the choice of the response data distribution is important. Some response data distributions are right-skewed and are best approximated by a lognormal distribution. In others, the distribution of the data is symmetric around the mean and a normal distribution is preferred. To choose between multiple distributions, the AIC can be used to discriminate between different possible distributions. In such cases, it is necessary to compute the log-likelihood based on fully specifying the probability density functions.

The above models describe the mean response; however, additional modeling assumptions on the variance of the response data are generally needed. For example, in many situations, the variance may be a function of the mean, e.g., it may be a positive constant, or it may be proportional to the mean or power of the mean such as its square. Model fit is examined to assess whether the response mean and variance structures are supported.

5.2.1.3 *Parametric Dose-Response Modeling including Other Predictors*

The extension to include other predictors into the function $f(d_i, X_{1i}, X_{2i}, \cdots, X_{ci}; \boldsymbol{\theta})$ to describe the expected response shares much with the dose-only modeling described above in that the data are used to estimate $\boldsymbol{\theta}$ to obtain $f(d_i, X_{1i}, X_{2i}, \cdots, X_{ci}; \hat{\boldsymbol{\theta}})$. However, the models of the data are more complex and the vector of parameters $\boldsymbol{\theta}$ contains coefficients that govern the effect of dose and coefficients for the effects of the other variables. In epidemiological studies, d_i, is an exposure metric constructed from possibly complex employment histories, and identifying the optimum construct for d_i may, itself, be an important component of the modeling procedure. For human observational studies, predictors in the function $f(d_i, X_{1i}, X_{2i}, \cdots, X_{ci}; \boldsymbol{\theta})$ usually include age, sex, and other demographic variables and may

include interactions or effect modifiers, e.g., dose-rate effects or other effect modifiers that allow for the effect of dose to depend on the other predictors. These additional factors can make model selection using human data more complex, because confounders, effect modifiers, and complex selection processes can be present and often can enter the model in many ways. In addition, the differences between the study population and the target population should be considered for the risk estimation. If interactions are present, then the estimates of interest may be made conditional on fixed values of X_{1i}, X_{2i}, $\cdots$, X_{ci} or averaged over the appropriate marginal distribution of $X_{1i}, X_{2i}, \cdots, X_{ci}$, or a combination can be used, i.e., fixing some values and averaging the others.

5.2.2 Model Uncertainty and Model Averaging

Model averaging takes into account model uncertainty by incorporating results from all models into the estimation process through a weighted average of the model-specific excess risk estimates. This technique has been applied in a general modeling context by Raftery [1995], who suggested the use of the posterior model probabilities as weights derived from a Bayesian analysis of all models considered. Because a full Bayesian analysis is frequently computationally burdensome, Buckland et al. [1997] proposed simpler methods, where weights are based upon the penalized likelihood functions formed from the AIC and BIC [Schwarz 1978]. The AIC and the BIC are defined on likelihood functions where the AIC$= -2\ ln(\hat{L}) + 2p$ and the BIC$= -2\ ln(\hat{L}) + ln(n)p$, where p is the number of parameters in the model, $\hat{L}$ is the maximized value of the likelihood function of the model, and n is the sample size (i.e., the number of observations).

The NIOSH approach to model averaging is to use a model-averaged fit to synthesize risk estimates across multiple fitted parametric models. An estimate of the dose-response function $\hat{f}_{MA}(d)$ is calculated as a weighted average of K model-specific dose-response estimates $f_k(\hat{\boldsymbol{\theta}}_k, d)$ for $k = 1, \cdots, K$. Formally this is represented as

$$\hat{f}_{MA}(d) = \sum_{k=1}^{K} f_k(\hat{\boldsymbol{\theta}}_k, d) \cdot w_k, \text{ where } f_k(\hat{\boldsymbol{\theta}}_k, d)$$
is the adverse effect, given the dose d using the kth model, $\hat{\boldsymbol{\theta}}_k$ is the estimated parameter vector for the kth model, and wk represents the corresponding weight for the kth model. Given the model M_k in the model space that includes K models, the weight w_k is:

$$w_k = \frac{exp(-I_k/2)}{\sum_{i=1}^{K} exp(-I_i/2)}$$

where I_i represents the penalized information criterion described above (e.g., AIC or BIC). Other weighting mechanisms exist; for more information on these different strategies, see Morales et al. [2006] and Moon et al. [2005].

Recently, NIOSH collaborated with the EPA to develop extensions of the EPA's Benchmark Dose Software (BMDS) Version 3.0 that includes model averaging [EPA 2018b]. This method is a Bayesian approach, which computes the model weights through the Laplace approximation [Raftery et al. [1997]. In almost all circumstances, results using this approach are qualitatively identical to (i.e., lead to the same risk estimates as) the approaches mentioned above. Given the ease of use of this software and methodological advances of this approach, NIOSH prefers its use; however, given the similarities of previous methods, other model averaging approaches might be used on a case basis. More information on EPA benchmark dose tools, including BMDS Version 3.0 and later versions, is available at https://www.epa.gov/bmds.

5.2.3 Nonparametric Modeling

The use of parametric models to describe the dose-response relationship may not be necessary. Instead, a semiparametric or nonparametric curve can be used that allows for a more flexible approach of fitting data to a dose-response curve. The methodologies available to achieve this vary and often make the mild assumption of monotonicity with a possible smoothness constraint.

Wheeler and Bailer [2012] describe a Bayesian semi-parametric method that uses a flexible spline construction for dose-response analyses. This method was shown to be superior to the model averaging method of Wheeler and Bailer [2007] in terms of its statistical properties. The method is fully Bayesian, which requires attention to the specification of prior distributions, but it allows one to include prior information on such things as the incidence of the response in historical animal controls or in human reference populations. Even though this method is free of the model selection issues encountered in benchmark dose modeling, informed choices must still be addressed with this method. Its use requires the choice of spline basis functions located at specific knot locations, which should be selected before modeling begins. Ultimately, flexibility in the choice of these models comes at the expense of statistical and computational challenges in fitting such models.

Other fully semiparametric/nonparametric modeling methodologies have been developed for dichotomous and continuous data [Guha et al. 2013; Lin et al. 2015; Piegorsch et al. 2012; Piegorsch et al. 2013; Wheeler et al. 2015], some of which overcome the known selection problems of Wheeler and Bailer [2007]. These methods are fully nonparametric in that they assume no prior form of the dose-response curve except monotonicity. Lin et al. [2015] showed that their continuous method would converge to the true underlying dose-response curve for large samples. The method of Wheeler et al. [2015] accounts for uncertainty in the specified response distribution for continuous outcomes and the dose-response. This method was shown through simulation to produce accurate estimates of excess risk, provided studies had adequate numbers of observations. Like model averaging, these methods allow for a flexible representation of the dose-response curve and are often preferable to a single parametric model fit.

5.3 Point of Departure

The PoD is the point on the dose-response curve that is established from experimental or observational data generally corresponding to an estimated

level of no effect or a low effect level that is without significant extrapolation to lower doses. The PoD can be used in conjunction with uncertainty factors to derive a reference level of exposure or to mark the beginning of low-dose extrapolation to dose points associated with a target risk level. Extrapolation or the use of uncertainty factors is typically necessary when there is instability in model-based estimation at very low doses. These PoD concepts have their origins and continue to be widely used in animal toxicologic studies; therefore, much of the discussion on PoD metrics is in the context of methods using animal bioassay data. Nevertheless, these methods are adaptable to epidemiologic data [Bailer et al. 1997; Budtz-Jørgensen et al. 2001; Noble et al. 2009].

Three definitions of the PoD are commonly used in NIOSH risk assessments: (1) the No Observed Adverse Effect Level (NOAEL), (2) the Lowest Observed Adverse Effect Level (LOAEL), and (3) the Benchmark Dose (BMD), which are described in the following sections. Of these prospective PoDs, only the BMD approach requires fitting mathematical models to data, as described in the previous section. Thus, issues regarding model selection are restricted to the BMD approach. It is also noteworthy that the description herein is in the context of a single endpoint. Risk characterization may require consideration of multiple endpoints; therefore, additional methods may be necessary for comparing, contrasting, or combining information from dose-response analyses to describe the occupational risk. Figure 5-1 shows the relationship between the various PoD definitions, using a hypothetical dose-response curve.

5.3.1 NOAEL/ LOAEL-Based Assessments

The NOAEL is defined as the highest dose level at which there are no significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control; some effects may be produced at this dose level, but they are not considered adverse or precursors of adverse effects observed [EPA 2012b]. For example, given

a rank order series of exposure groups in an experimental study, the NOAEL is the administered dose level in the exposure group that immediately precedes the first exposure group in which the frequency of the observed adverse effect significantly differs from that in the control (no exposure) group. Similarly, the LOAEL is the lowest dose level or concentration at which there are significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group [EPA 2012b].

Usually, statistical hypothesis tests with a significance level of 5% (one-sided) are used to identify NOAELs or LOAELs. As such, problems arise in studies with few subjects observed at low exposure levels, resulting in insufficient signal-to-noise ratios and statistical power. It has been shown in most animal studies that the highest exposure group qualifying as a NOAEL is, on average, equivalent to a model-based BMD using a BMR of 10%, which is empirical evidence that many NOAELs were associated with an increased response that did not meet the standard significance level of 0.05 [Wignall et al. 2014]. Other limitations in using a NOAEL/LOAEL approach are that it does not allow for consideration of the shape of the dose-response curve, which would inform estimation at lower levels, and that it is constrained to be one of the levels of exposure selected in the experiment. In addition, the spacing of exposures in an experiment can result in only high doses having sufficient power to detect statistically significant differences from the background condition [Crump 1984], even though biologically significant effects at lower doses may have been missed due to limited statistical power or sampling error. Hence, basing an interpretation of a NOAEL as representing a threshold below which effects are null is generally unfounded. Despite these limitations, the NOAEL/LOAEL approach may be the only alternative for determining a PoD for application of uncertainty factors when data are insufficient to model the dose-response adequately. NIOSH has used a NOAEL/LOAEL approach in assessing risks of occupational exposures to ethylene glycol ethyl ethers and associated chemicals [NIOSH 1991].
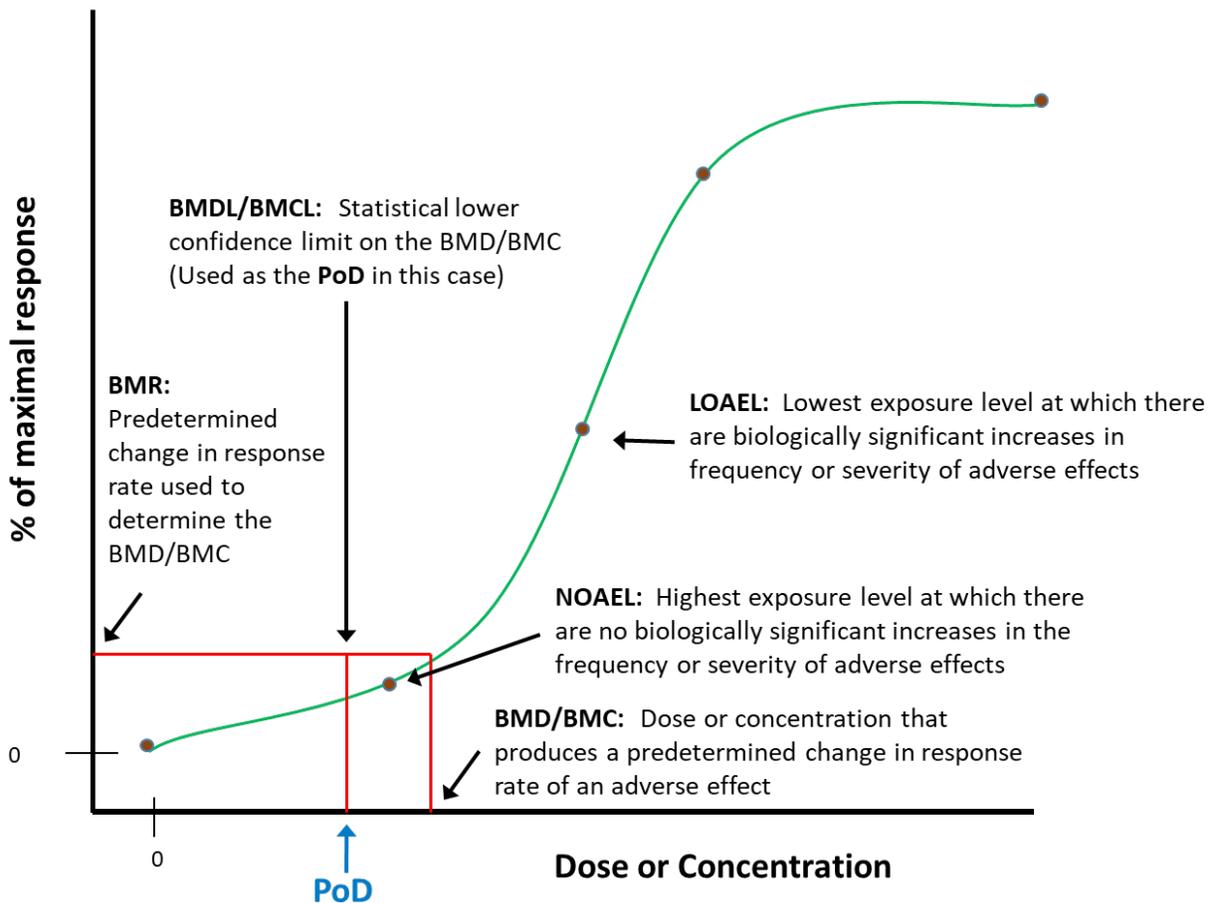
Figure 5-1. A hypothetical dose-response association from an animal study with five dose groups. The lower limit on the benchmark dose or concentration (BMDL/BMCL) is selected as the point of departure (PoD). Other potential PoDs are the No Observed Adverse Effect Level (NOAEL) and the Lowest Observed Adverse Effect Level (LOAEL). The figure is adapted from EPA [2010].

5.3.2 The Benchmark Dose Approach

Given the limitations of the NOAEL/LOAEL approach, the risk assessment community has widely adopted the BMD approach originally proposed by Crump [1984] for determining the PoD when observed data are adequate to model the dose-response (see Section 5.5). The BMD is defined as the dose or concentration on the dose-response curve that produces a predetermined change in the response rate of an adverse effect relative to the background response rate of this effect. This predetermined change is called a benchmark response, or BMR. A default level is not specified, because the

choice of the BMR should be based on biological and statistical considerations that are specific to each risk assessment. In general, the BMR should be biologically reasonable and should be supported by the observed data (i.e., the PoD does not require significant extrapolation). For quantal data, the BMR is usually in the range of 5%–10% extra risk (see Section 6.1) for animal toxicologic data, which is the limit of responses typically observed in well-conducted animal experiments [EPA 2012b]. Much smaller values (e.g., ≤ 1%) are typically supported by quantal human data. Ideally, the BMR for continuous data represents the smallest change in
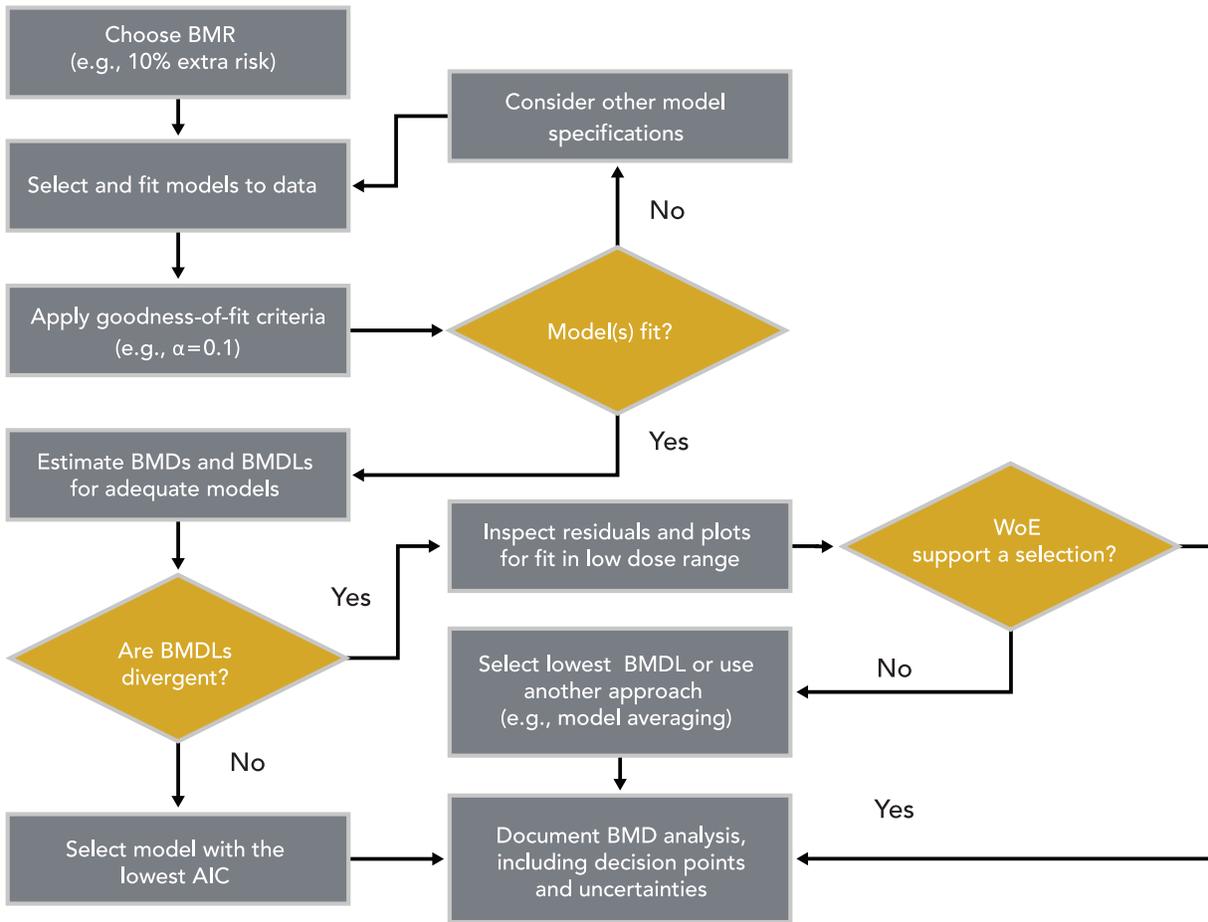
Figure 5-2. The Benchmark Dose (BMD) method, selecting a single parametric model. Adapted from Davis et al. [2011].

Abbreviations: AIC, Akaike information criterion; BMR, benchmark response; WoE, weight of evidence on toxicity.

response that is considered biologically significant; however, change points greater than this level may be necessary because of statistical limitations. Conversely, a statistically significant change may not indicate an adverse effect when low variability in the data is observed [Haber et al. 2018].

Given a BMR value that is selected *a priori*, the risk assessor fits various dose-response models to the observed data. This approach is applicable to dichotomous, ordinal, or continuous response data and categorical or continuous exposure data [Chen and Chen 2014; Crump 1984; Crump 1995]. For continuous response data, the BMR is usually based

on a central measure of the biological effect (e.g., mean organ weight), a measure of its variability (e.g., standard error), and the number of observations at each dose level [Davis et al. 2011]. Regression models are fit to data that should include at least two dose groups above the control and in the low-dose range of interest (e.g., in the range of the BMR). The resulting curve(s) are used to calculate the BMD and its one-sided lower 95% confidence limit (BMDL). The BMDL is typically used to define the PoD. This process accounts for the variability and uncertainty in the experimental results, but not uncertainty in model selection [Davis et al. 2011]. The general BMD approach is illustrated in Figure 5-2.

This BMD approach is preferred by the EPA [2012b] and NIOSH, who have collaborated to develop BMDS Version 3.0, which is readily accessible to risk assessors worldwide [EPA 2018b]. Specifically, the EPA software allows for the examination of a suite of dose-response functions for selection of the best single dose-response model using both frequentist and Bayesian methods. Additionally, BMDS Version 3.0 included Bayesian model averaging techniques to account for model uncertainty. Currently, model averaging is available only for dichotomous response models. The remainder of this section refers to single models. Model averaging was described previously in Section 5.2.2.

Model fitting is achieved by maximum likelihood (traditional frequentist modeling approach) or using a Bayesian approach. The adequacy of models is judged by goodness of fit (i.e., testing for lack of fit), typically using a critical value of 0.1 as a threshold for acceptance. Selecting the best-fit model from a set of adequately fitting nested models can be accomplished, in part, by likelihood ratio tests. Similarly, selecting a model from a set of models that are not hierarchically nested can be achieved by comparing AIC or BIC values. NIOSH risk assessors examine the variability in BMD or BMDL estimates across adequately fitting models. Reasonable agreement in estimates among a set of models suggests little model dependence; therefore, selection based on the lowest AIC value is well supported. Conversely, divergence in model estimates is indicative of model dependence. The EPA guidance does not explicitly define "divergence"; however, it has been suggested by others that BMDL values within a factor of 3 are sufficiently close [Haber et al. 2018].

It is important to note that model dependence results from extrapolation; therefore, it is more likely to occur when the BMR value is below the observable range. It is prudent to examine adequately fitted models closely to determine if the variability is attributable to anomalies in the data. Risk assessors may reject models that do not adequately describe the low-dose portion of the dose-response relationship, as determined by examining residuals and model plots. When the group of adequately fitted models is divergent and in lieu of other evidence supporting model rejection, a health-protective approach is to select the model that provides the lowest BMDL estimate [EPA 2012b]. In practice, however, selecting the lowest BMDL can be suboptimal in some cases, such as when the BMD confidence intervals are inordinately wide, suggesting that the true BMD might be much greater than the BMDL. Ultimately, the decision on model selection lies solely with the risk assessor, who must consider all available information and document the decision. Options for single-model selection include summary estimates from multiple models, such as in model averaging analyses (Section 5.2.2) or the use of semiparametric or nonparametric models (Section 5.2.3).

Ideally, risk assessors directly estimate the dose-response and its associated uncertainty within the range of the observed data. Still, frequently the PoD is determined at a higher response rate than a response of interest; therefore, extrapolation toward the origin of the dose-response curve may be required. For example, a PoD based on a BMR of 10% excess risk of cancer is likely to require extrapolation to a much lower dose-risk region of interest to support a suitable estimate of lifetime risk. In animal toxicology, the common practice of (1) setting the BMR at 10% extra risk, (2) using the BMDL as the PoD, and (3) linearly extrapolating to the risk level of interest is well supported by studies showing that the BMD is often in the range of the NOAEL [Sand et al. 2011; Wignall et al. 2014]. For example, NIOSH typically uses linear extrapolation for cancer risk assessments unless mechanistic or mode of action (MoA) data support a different approach (Section 6.2.1). In cases in which data support a nonlinear dose-response, then low-dose extrapolation is accomplished via the selected parametric dose-response curve or by model averaging, semiparametric, or nonparametric methods. When extrapolation below the range of the data is necessary, risk estimates are of unknown validity. Model goodness-of-fit does not address this problem. Mechanistic data or information from biologic models (e.g., PBPK models) with well-understood

low-dose behaviors may be necessary to support low-dose risk estimates.

NIOSH used the BMD approach in its risk assessment of occupational exposures to carbon nanotubes and nanofibers [NIOSH 2013b]. The dataset was abstracted from short-term and subchronic studies of nonmalignant pulmonary responses in exposed rats and mice. Both quantal and continuous response data were examined. The BMR was set at 10% added risk of early stage adverse lung effects. The one-sided 95% BMDL was selected as the PoD. Modeling was conducted with the EPA benchmark modeling software. Although several models were specified, only a multistage (polynomial degree 2) model adequately fit quantal response data used in this risk assessment. The continuous dose-response data were fit with a second order polynomial model for all data with three or more dose groups, and a linear model for data with two groups. As a departure from traditional methods, model goodness-of-fit was considered adequate at $P > 0.05$. The authors explained the choice as "… a trade-off in the type I or type II error." Nevertheless, all selected models (i.e., NIOSH 2013b, Tables A-3 to A-5) met $P \geq 0.10$. NIOSH also applied BMD concepts to epidemiologic data in its assessment of the risk associated with occupational diacetyl exposure [NIOSH 2016]. Multiple BMRs describing pulmonary impairment were derived from continuous data on pulmonary function.

5.3.2.1 Determining the PoD with Model Averaging and Semiparametric Methods

Linear extrapolation below the PoD is unnecessary when using model averaging, semiparametric, or nonparametric approaches [Wheeler and Bailer 2012; Wheeler and Bailer 2007] because the estimation of exposures corresponding to small excess risks is model-based. The model-based extrapolation may result in a value similar to a linear extrapolation from a PoD unless substantial evidence against the latter is present in the data. For example, when applied to actual data and investigated in simulation studies, model-averaging and semiparametric approaches have adequately described both the model and statistical uncertainties at excess risk levels well below the 5% or 10% level. Wheeler and Bailer [2013] found that for dose-responses that were low-dose linear, these approaches yielded estimates that differed negligibly from a linear extrapolation from the 10% level for target risks as low as 0.001%. For nonlinear dose-response relationships, these methodologies were observed to provide superior estimates (i.e., BMDLs that maintained nominal coverage but were closer to the point estimate) than the PoD linear extrapolation while still accurately describing the risk. These two methodologies were also observed to be internally consistent in producing similar estimates, usually within a factor of three, across all excess risk levels examined.

Given limited information on the validity of extrapolations below 1% risk using model averaging in BMDS Version 3.0 [EPA 2018b], NIOSH recommends comparing the extrapolation to the semiparametric and previous model average approaches. If the results are similar, then it is reasonable to use the extrapolation using BMDS Version 3.0. If they are different by a factor greater than 3, then NIOSH computes the BMD at a BMR of 1% or above and linearly extrapolates below-risk levels less than 1%.

In addition to examining single parametric models, NIOSH used a model-averaging method to summarize risk estimates from linear-quadratic, Weibull, and log-probit models in its risk assessment of lung cancer and titanium dioxide (TiO_2) exposure [NIOSH 2011]. This approach was chosen because the dose-response relationship appeared nonlinear, and the specific models used in the three-model-average procedure did not impose low-dose linearity for risk extrapolation. In this model, Weibull and log-probit models were weighted more heavily than the linear-quadratic, which supported a dose-response that was sublinear at low doses (Figure 5-3).
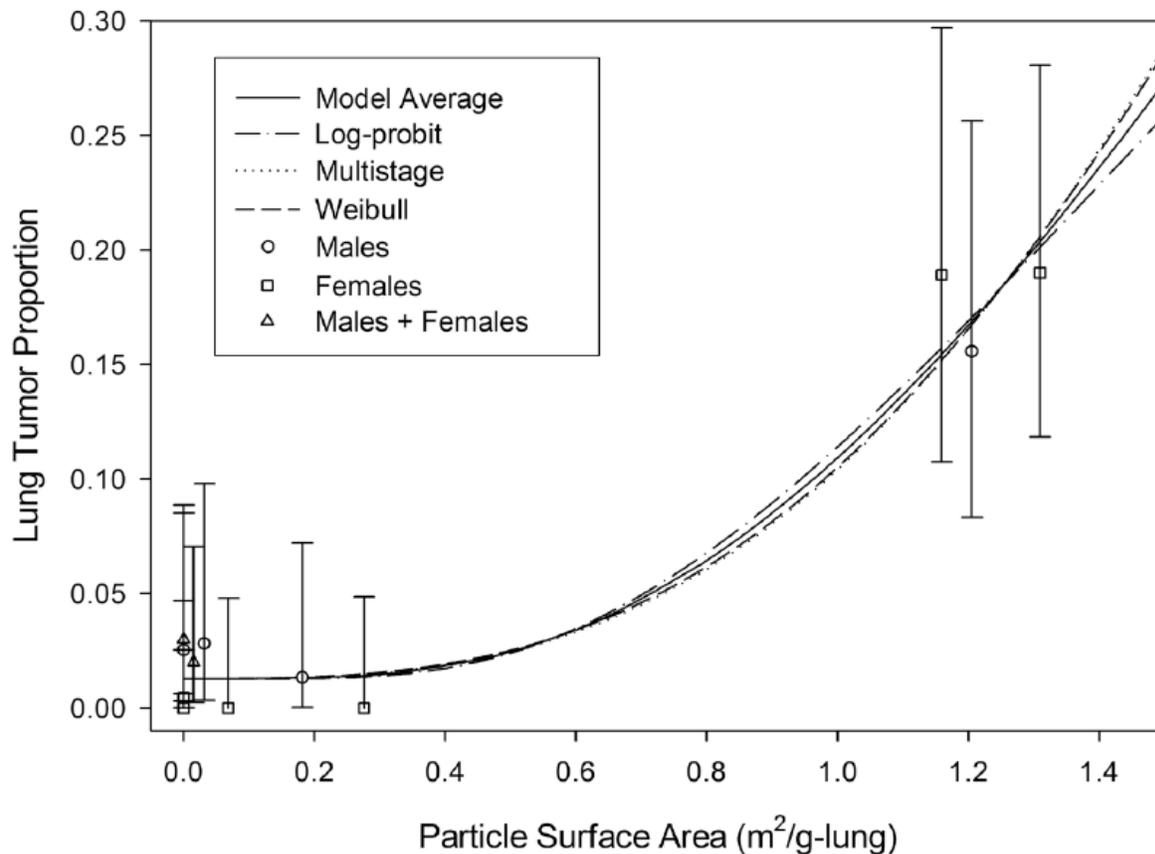
Figure 5-3. BMD models and three-model-average fit to the lung tumor data (without squamous cell keratinizing cysts) in male and female rats chronically exposed to fine or ultrafine TiO$_2$ [NIOSH 2011].

5.4 Selecting a Dose-Response Modeling Method

The estimated dose-response curves from multiple biologically plausible models can differ substantially over a range of doses that can include the low dose region. Thus, in addition to biologic plausibility, the strength of the data and the statistical methodologies must be assessed to inform the choice on approaches to estimating risks and quantify relevant uncertainties. Misspecification of the model-form can lead to spurious dose-response estimates (see Appendix B). Moreover, although widely recognized as a fundamental component of statistical inference, the model selection process

itself is seldom integrated into inference [Buckland et al. 1997]. Therefore, even if estimates are unbiased, precision (e.g., as indicated by the width of confidence intervals) is likely overestimated (e.g., confidence intervals are too narrow). In response, there are several statistical procedures available to assist in model specification and to account for model uncertainty (Appendix B).

One strategy for accounting for model uncertainty is to use model averaging methods. These methods have been shown to be both robust and flexible. As stated previously, NIOSH generally prefers to use a Bayesian model averaging approach to address model-form misspecification and to account for model uncertainty in assessing dose-response (see

Section 5.2.2). Still, every dose-response analysis is unique and requires careful consideration of the approach used. For example, possible exceptions to using nonparametric, semiparametric, and model averaging techniques are when (1) compelling mechanistic or statistical evidence supports a specific dose-response function and (2) data limitations require a simpler approach or a more parsimonious model.

5.5 Laboratory Animal Data

The adequacy of the database to support dose-response analysis based on animal studies is an important consideration in occupational risk assessment. Risk assessors evaluate animal studies in the context of the risk assessment questions under investigation. Studies are identified that may shed light on the research question. For example, a single-dose acute toxicity study may not have much relevance for assessing chronic exposures to a chemical, but it may be useful for setting an immediately dangerous to life and health (IDLH) value or a short-term exposure limit (STEL), depending on the specifics of the study. Ideally, risk assessors evaluate all studies that may contain relevant information on the dose-response relationship. Each study is evaluated for adequacy of study design and conduct (duration of exposure, dosing regimen, species, numbers and sexes of animals, description of experimental conditions), health endpoints observed, statistical analyses conducted, and how the data support the conclusions of the study. Risk assessors give greater weight to studies reporting statistically and/or biologically significant dose-response associations. Alternatively, risk assessors may apply statistical methods to make joint inferences from multiple heterogeneous datasets [Triantafillou and Tsamardinos 2015; Vesterinen et al. 2014]. Relevance of the endpoint to human health, severity of the health endpoint, and the sensitivity of the health endpoint should be considered. Preferably, risk assessors clearly document the rationale for including/excluding or grouping studies, dose groups, or health endpoints from analysis in the risk assessment.

For dose-response modeling of dichotomous response data, both the number of animals showing the effect in the group and the total number of subjects in the group are necessary, at a minimum. For modeling of continuous response data, individual animal data are strongly recommended, although information on central tendency and variability may be sufficient; typically, data on the number of subjects, mean of the response, and variability measure (e.g., standard deviation, standard error, or variance) for each group are adequate to perform the analysis. For dose-response modeling of categorical responses, the number of animals examined and the counts for each response category of each dose group are generally sufficient [EPA 2012b; Hertzberg 1989].

When the dose-response analysis is conducted with benchmark dose analysis and/or model averaging, there are specific requirements for the datasets. In general, toxicologic animal studies with more than one dose group are required for dose-response analysis. Ideally, there are responses in more than one dose group that are different from background and different from the maximal response. Multiple intermediate responses of this type increase confidence that the study contains adequate information on the dose-response curve and does not represent only background or only maximal responses. It may be possible to calculate a BMD and BMDL with only a single dose showing a response near the BMR [Kavlock et al. 1996]. However, if the studies show responses in more than one dose group but all the responses are at the background level, are near the maximal response level, or appear as a very steep rise of the dose-response curve over a small range of doses, then the data may not be adequate for regression modeling. Thus, it is preferable to have studies with observed responses sufficient to provide a unique solution to the optimizing procedure. For the dichotomous data models, this usually requires at least two dose groups with responses intermediate between background and maximal. An additional advantage accrues from having at least one dose group near the BMR, to yield a better estimate of the BMD [EPA 2012b].

Overall, the specific type of toxicity information required is dependent upon the question to be addressed and the interplay with human data. For occupational risk assessment, data from well-conducted chronic bioassays, preferably in more than one species (typically one in rats and one in mice), a two-generation reproductive study, and a developmental study in mammalian species would provide a reasonable database to reduce the uncertainty and increase the confidence in the risk estimates. A well-conducted subchronic study that evaluated a comprehensive array of endpoints could also be useful, especially in the absence of chronic bioassays, if significant differences in adverse effects are not expected from longer exposures. In most cases, NIOSH is concerned about chronic exposures to hazards, but in some cases, acute or intermediate-duration hazards may be of concern. In other cases, data needs are endpoint-specific. For example, if acute or subchronic data demonstrate neurotoxic, immunotoxic, or cardiotoxic effects, then a neuro-toxicity, immunotoxicity, or cardiotoxicity battery of tests could satisfy the data requirements [EPA 1994; EPA 2002]. When the typical animal bioassays are not available, data from alternative testing systems such as high-throughput molecular toxicity assays and quantitative structure-activity relationship (QSAR) models could be used to inform the risk assessment and to fill the data gaps. NIOSH has not had extensive experience in using these types of data, so each use would be on a case-by-case basis.

5.5.1 Parallelogram Approach

First introduced by Sobels [1977], the "parallelogram approach" (Figure 5-4) is an argument by analogy for inferring missing data when you have closely related data that is especially useful for cross-species extrapolation. It has been used in genotoxicity studies to predict human germ cell mutations from measured mouse germ cell mutations, mouse somatic cell mutations, and human somatic cell mutations [Anderson et al. 1994]. It has been used in PBPK studies to predict human *in vivo* metabolic parameters from measured mouse

in vitro parameters, mouse in vivo parameters, and human *in vitro* parameters [Kienhuis et al. 2009]. NIOSH, in part, used this technique to assess comparative potency of the closely related chemicals diacetyl and 2,3-pentanedione, when both human toxicity and animal toxicity data were available for diacetyl but only animal toxicity data were available for 2,3-pentanedione [NIOSH 2016].
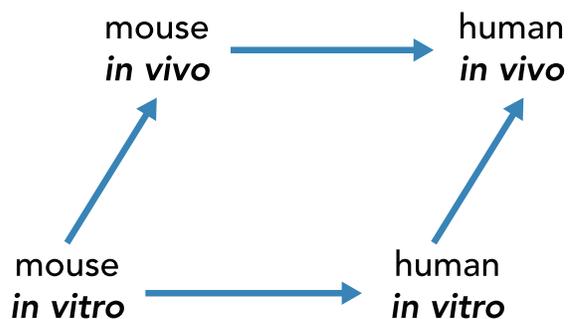
Figure 5-4. An example of the parallelogram approach.

The parallelogram approach is conceptually very simple but requires explicit assumptions. For example, to estimate the metabolic constants for a substance to use in a PBPK model, one must assume the following:

- There is a constant and knowable relationship between metabolic constants measured *in vitro* and metabolic constants measured *in vivo* within a species.

- The relationship between *in vivo* and *in vitro* metabolic constants is the same, regardless of species.

Therefore, once the ratio between mouse *in vitro* and *in vivo* metabolic constants has been measured and the human *in vitro* metabolic constant is known, the mouse ratio can be applied to the human *in vitro* constant to estimate the human *in vivo* metabolic constant.

Similarly, for genotoxicity studies, one must assume the following:

- There is a constant and knowable ratio between somatic mutations and germ cell mutations within a species.

- The relationship between somatic mutations and germ cell mutations is the same, regardless of species.

Therefore, once the ratio between mouse somatic mutations and mouse germ cell mutations has been measured and the human somatic mutations have been measured, the mouse ratio can be applied to the human somatic mutations to estimate the human germ cell mutations.

For the comparative potency example, NIOSH had mouse toxicity data and human epidemiology data on diacetyl. NIOSH was also interested in a closely related (1-carbon different) flavoring chemical, 2,3-pentanedione. However, there were no human data on 2,3-pentanedione toxicity. In this case, NIOSH assumed the following:

- There is a constant and knowable relationship between the lung toxicity in mice and the lung toxicity in humans for a chemical.

- Di-alpha-ketones such as diacetyl and 2,3-pentanedione are related closely enough that they share toxic modes of action.

- The relationship between lung toxicity and hazardous exposure in mice and humans is constant for these closely related chemicals.

Although NIOSH did not follow this logic through to predict human risk estimates for 2,3-pentanedione, the same logical structure applies. NIOSH stopped with an assessment that 2,3-pentanedione was in a similar range of toxicity as diacetyl and used the diacetyl risk assessment to set a recommended exposure limit for 2,3-pentanedione. In this case, the uncertainties in the method and the sparseness of the data argued for cautious application [NIOSH 2016].

Applying a parallelogram approach requires that the measured values used to construct the ratios reflect the same or very closely allied methods and data sources. This will not work if the technique or type of tissue used for mouse *in vitro* assays is substantially different from the human assays. The assumptions regarding which values in the

parallelogram are similar should be carefully examined. The uncertainty in the parallelogram approach is lessened with cross-species validation. For example, similar measured ratios of *in vitro* to *in vivo* metabolic parameters in mice, rats, and hamsters strengthens the argument that it is reasonable to extrapolate to humans. Depending on the data available, this step is not always possible. Finally, the parallelogram approach is a useful tool to consider when key data are unavailable, but it requires strong assumptions that must be closely examined and carefully justified.

5.6 Dosimetry Adjustments for Human Equivalent Concentrations

Ideally, occupational risk assessment is based on the biologically effective dose (e.g., tissue dose) that mediates the adverse response observed in workers. In practice, enough information to directly estimate the dose from exposures in humans is seldom available. Instead, dosimetry methods are commonly employed to estimate the dose delivered to target sites in laboratory animals, which are then adjusted for relevance in humans by accounting for the physiological differences between species [EPA 1994]. Herein, dosimetry refers broadly to methods relating exposure metrics to a biologically effective dose from the agent(s) of interest. Dosimetry models are the foundation of animal-to-human extrapolation.

In general, a critical dose observed in an animal study (i.e., an estimate of the biologically effective dose in the animal) is extrapolated to humans by using dosimetry modeling. This extrapolation is referred to as the human-equivalent concentration (HEC) for inhalation exposure or dose (HED) for other routes of exposure [EPA 1994; FDA 2005]. The HEC is an amount of the agent in humans that is believed to induce the same magnitude of toxic effect as the experimental animal species' concentration or dose. Describing all aspects of dosimetry methods that may be used in NIOSH risk assessment is beyond the scope of this report.

However, basic dosimetry modeling for estimating human risks from exposures to particulates, gases, and vapors is described in the following sections. The regions of the respiratory tract are also briefly described.

5.6.1 Respiratory Tract Regions

The respiratory tract in both humans and laboratory experimental animals is divided into three regions based on structure, size, and function: the extrathoracic (ET) region extends from nose to larynx, the tracheobronchial (TB) region extends from trachea to the terminal bronchioles, and the pulmonary (PU) region includes the respiratory bronchioles, alveolar sacs, alveolar ducts, and alveoli (Figure 5-5). The pulmonary region is where gas exchange occurs (i.e., uptake of oxygen and release of carbon dioxide). Diseases of the respiratory tract have been associated with exposure to substances that deposit in each of these regions. These regions also correspond to the inhalable, thoracic, and respirable particle size fractions for airborne sampling [ACGIH 2015].

5.6.2 Particle Exposure

5.6.2.1 Overview

In quantitative risk assessment of inhaled particles, the dose from particles deposited or retained in the respiratory tract region is estimated by dosimetry modeling methods. Models for particulate exposures must account for interspecies differences in the factors that determine the deposition, clearance, and retention of particles (spherical or nonspherical) from the respiratory tract [EPA 1994; Kuempel et al. 2015]. Dose estimation is one of the major sources of uncertainty in a risk assessment (e.g., as discussed for carbon nanotubes in NIOSH [2013b], Section A.6.3). Use of validated dosimetry models reduces the uncertainty in extrapolating animal data to humans.
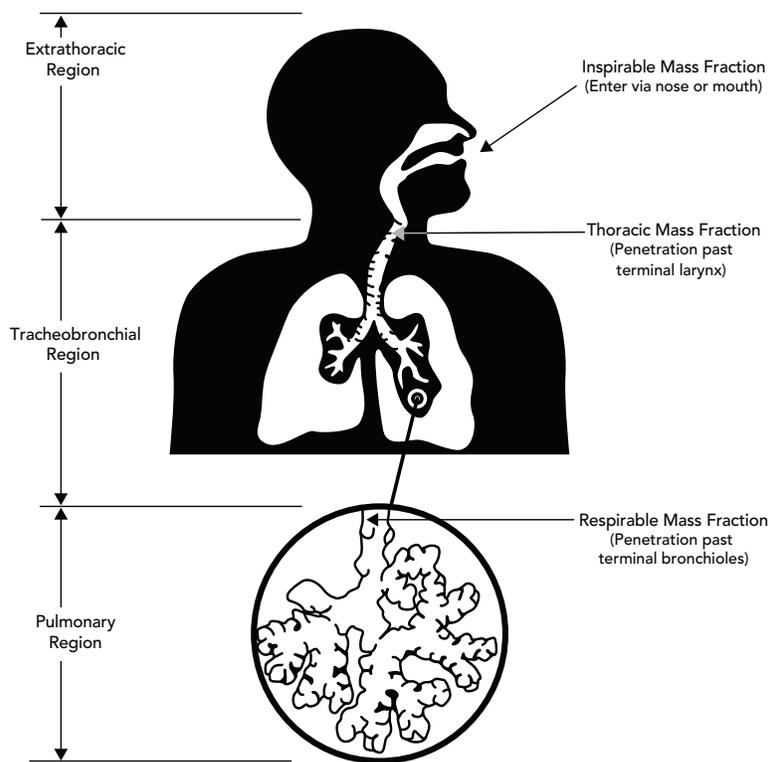

Figure 5-5. Human respiratory tract regions [EPA 1994].

To estimate a human-equivalent internal dose or exposure concentration of particles by using animal data, the main dosimetry method options are (1) application of uncertainty factors (see Section 6.3.4), (2) general/categorical adjustments (e.g., EPA "Regional Deposited Dose Ratio" in respiratory tract), and (3) substance-specific PBPK models (e.g., to account for particle dissolution and translocation beyond the respiratory tract). Application of uncertainty factors (UFs) is simpler and requires less information but is also associated with greater uncertainty. Other methods generally require additional information and involve complex analysis but may provide more accurate dose estimates for the risk assessment.

5.6.2.2 Deposition Mechanisms

Particle size is a key factor in estimating the deposited doses in the respiratory tract region. Standard definitions of airborne particle size fractions include inhalable, thoracic, and respirable [ACGIH 2015]. Inhalable particles are those capable of entering the nose or mouth and depositing anywhere in the respiratory tract. For example, particles with an aerodynamic diameter of 100 μm have an approximately 50% probability of being inhaled and deposited in the respiratory tract. The extrathoracic fraction is the mass fraction of inhaled particles with low probability of penetrating beyond the larynx. The thoracic fraction refers to the mass fraction of inhaled particles capable of reaching beyond the larynx into the thoracic region and depositing in the conducting airways. The respirable fraction is the mass fraction of inhaled particles that is capable of reaching and depositing in the gas-exchange region of the lungs [Brown et al. 2013].

Aerodynamic equivalent diameter is defined as the diameter of a sphere of standard density of one gram per cubic centimeter (1.0 g/cm³), having the same terminal velocity when settling under gravity as the particle under consideration [Hinds 1999]. Diffusion equivalent diameter is defined as the diameter of a sphere with the same thermal or Brownian diffusivity as the particle under consideration [Hinds 1999]. For nonspherical particles

such as fibers, shape and orientation are additional factors that can influence deposition [Sturm and Hofmann 2009]. Dosimetry models can provide dose estimates based on different metrics (e.g., the total particle mass, volume, or surface area in specific respiratory tract regions), which can be used in extrapolating dose-response relationships across species [Asgharian et al. 2018].

Respiratory tract deposition models can take into account these particle properties to predict the deposited dose in each region. In addition to the particle properties, lung morphology can influence particle deposition. Differences in airway structure, lung volume, and breathing patterns (e.g., nasal only or oronasal) have been observed among individuals and are also related to age, gender, and race [Schulz et al. 2000]. Some deposition models account for interindividual variability in lung morphology [ARA 2009; ICRP 1994]. Activity level (e.g., resting or exercising) influences the ventilation rate and breathing pattern, thereby affecting particle deposition in the respiratory tract.

At a minimum, data are generally available to estimate the deposited dose of particles in a respiratory tract region of humans or animals, given the exposure concentration, duration, and airborne particle size estimates. Examples of these basic methods and information sources are discussed next.

5.6.2.3 Ventilation Rates and Activity Levels

5.6.2.3.1 Humans

NIOSH generally uses the International Commission of Radiological Protection (ICRP) standard reference value for workers for the total air intake (volume inhaled), which is 9.6 m³ in an 8-hour workday [ICRP 1994]. This total air intake is equivalent to an average minute ventilation rate of 20 liters of air per minute (L/min) (i.e., 9.6 m³ = 20 L/min × 480 min × 0.001 m³/L). These reference values are based on adult males, assuming 5.5 hours of light exercise and 2.5 hours of rest/sitting. The adult male minute ventilation rates are 25 L/min for light exercise and 9 L/min for resting (sitting).

Thus, the total air intake in an 8-hour workday in men is calculated as follows:

Equation 5-16.

$$9.6 \text{ m}^3 = [(5.5 \text{ hours} \times 60 \text{ minutes per hour}) \\ \times 25 \text{ L/min}] + [(2.5 \text{ hours} \times 60 \text{ minutes} \\ \text{per hour}) \times 9 \text{ L/min}] \div [1{,}000 \text{ L/m}^3]$$

Minute ventilation (V_E, in L/min) is calculated as the product of the tidal volume (V_T, in L) and the breathing (respiratory) frequency (f, in min^{-1}):

Equation 5-17.

$$V_E = V_T \times f$$

Tidal volume is the volume of air inspired or expired in each respiratory cycle, and the respiratory frequency is usually described in breaths per minute [EPA 1994]. These respiratory values (tidal volume and breathing frequency) vary by age, gender, and activity level [ICRP 1994]. For example, V_E of 25 L/min (as used in Equation 5-16) is calculated from V_T of 1.25 L and f of 20 min^{-1} (as shown in Table 8 of ICRP [1994]). For adult female workers, the average air intake is 8.2 m^3 in an 8-hour workday, assuming the same activity levels and using the gender-specific values for V_T and f in ICRP [1994].

For dosimetry modeling, these respiratory values are used to estimate deposited dose, given the exposure scenario. In the Multiple-Path Particle Dosimetry (MPPD) model, v.3.04 [ARA 2015], the breathing frequency and tidal volume are required input values. For example, for a resting adult male human, values of V_T and f have been reported as 625 milliliters (ml) and 12 min^{-1} ICRP [ICRP 1994]. For workers, NIOSH [2011] used the values of 1,143 ml for V_T and 17.5 min^{-1} for f, which are weighted averages of the respiratory values that correspond to the average male worker reference values of 20 L/min (V_E) and 9.6 m^3 (total volume inhaled) in an 8-hour workday, as described above.

5.6.2.3.2   Animals

Species-specific ventilation rates are required for estimating the deposited dose of airborne particles in the respiratory tract of animals. When experimental ventilation rates are not available, species-specific average ventilation rates can be calculated with the following allometric scaling equation:

Equation 5-18.

$$\ln(V_E) = b_0 + b_1 \times \ln (BW)$$

where V_E is the minute ventilation (L/min) as described previously; BW is body weight in kilograms (kg), and b_0 and b_1 are the species-specific parameters (e.g., as reported in EPA [1994]). For example, estimates of $b_0 + b_1$ are -0.578 and 0.821, respectively, in rats (in Table 4-6 of EPA [1994]).

For a 300-g rat, V_E is calculated from equation 5-19 as follows:

Equation 5-19.

$$0.21 \text{ L/min} = \exp[-0.578 + 0.821 \times \ln (0.3)]$$

This V_E corresponds to the value estimated from the breathing parameters for tidal volume of 0.21 ml and breathing frequency of 102 breaths/min, which have been used in estimating lung dose in rats with body weight of 300 g [NIOSH 2013b] as shown in equation 5-20:

Equation 5-20.

$$0.21 (\text{L/(min)}) = 2.1 (\text{ml}) \times 102 (\text{min}^{-1}) \times \\ 0.001 (\text{L/ml})$$

5.6.2.4 Deposited Dose Calculation

The deposited dose of inhaled particles in the respiratory tract region is a biologically relevant estimate of equivalent dose in humans or animals. Equivalent dose metrics are needed to extrapolate dose-response relationships and risk estimates from animals to assess human risk.

The deposited lung dose can be estimated as follows:

Equation 5-21.

Deposited lung dose (mg)

= exposure concentration (mg/m^3) × duration in hours (hours per day × days per week × weeks exposed) × ventilation (L/min) × 0.001 m^3 /L × 60 minutes per hour × regional deposition fraction

Exposure concentration and duration would be as reported in the animal or human study, or for the exposure scenario of interest. Minute ventilation is calculated as shown in Section 5.6.2.3. The regional deposition fraction of interest is estimated for the respiratory tract region associated with the adverse effect in the risk assessment. The regional deposition fraction is estimated from the airborne particle diameter, and these values have been measured in various particle sizes, including in a study of several small laboratory animals [Raabe et al. 1988]. The deposition fraction can also be estimated in MPPD [ARA 2015] for several species and strains (human, rat [Sprague-Dawley and Long-Evans], mouse [BALB/c and B6C3F$_1$], rhesus monkey, pig, or rabbit). Airborne particle size (mean ± SD) and density are required input values in MPPD.

For example, to estimate the deposited lung dose in a rat subchronic (13-week) inhalation study at a pulmonary effect level of 5 mg/m³, the exposure concentration and duration (in Equation 5-21) are as reported. The minute ventilation is calculated as shown in equation 5-19, and the pulmonary deposition fraction is estimated in MPPD. Typically, the particle size data are also reported. For simplicity, assuming particle mass median aerodynamic diameter (MMAD) of 1 μm, monodisperse (geometric standard deviation of 1), and unit density (1g/cm³), a rat pulmonary deposition fraction of approximately 0.06 is estimated in MPPD [ARA 2015]. The deposited lung dose (Equation 5-21) in this example in rats is calculated as follows:

Equation 5-22.

$$1.5 \text{ mg} = 5 \text{ mg/m}^3 \times (6 \text{ hours per day} \times 5 \text{ days per week} \times 13 \text{ weeks}) \times (0.21 \text{ L/min} \times 0.001 \text{ m}^3/\text{L} \times 60 \text{ minutes per hour}) \times 0.06$$

If lung doses are not reported in a rodent study, then the deposited dose can be estimated by this method. The worker-equivalent airborne concentration can then be estimated by back-calculating to determine the airborne concentration that would result in the equivalent pulmonary-deposited dose in humans

(Figure 5-6). More biologically relevant dose estimates may also take into account the clearance of particles by respiratory tract region to estimate the retained dose over time, as discussed below.

5.6.2.5 Biokinetic Mechanisms and Models of Inhaled Particles

5.6.2.5.1 Clearance, Retention, and Translocation

The biological mechanisms of particle clearance depend on the respiratory tract region in which the particles deposit and on the physicochemical properties of the particles. Particles that deposit in the TB region are cleared mainly by mucociliary transport, in which particles or other exogenous materials are transported toward the mouth, where they are swallowed or expectorated. Mucociliary transport occurs from the terminal bronchioles to the larynx. Insoluble particles that deposit in the TB region are generally cleared relatively rapidly, with biological half-times on the order of hours. Soluble particles may dissolve in the mucus [EPA 1994]. Particles that deposit in the pulmonary region are cleared primarily by alveolar macrophages that phagocytose (engulf) particles, where they are dissolved or transported to the TB region for mucociliary clearance [Schlesinger 1985]. Clearance of poorly soluble particles can differ across species because of differences in the rates of mucociliary transport in the conducting airways and macrophage-mediated clearance from the alveolar region [Miller 2000; Snipes 1989]. Pulmonary clearance is approximately 10 times slower in humans than in rats, based on first-order clearance assumptions [Snipes 1989].

Retention is described as the temporal distribution of uncleared particles in the respiratory tract [Lioy et al. 1984]. In humans, two distinct phases of particle retention occur. The first phase is thought to represent mucociliary clearance of particles depositing in the TB region and is complete within approximately 24 hours, although a particle size–dependent slow clearance fraction has also been demonstrated [ICRP 1994; Stahlhofen et al. 1989]. The second phase, which involves retention half-times from approximately 30 to several hundred

Rodent

Exposure-response data

Dose-response modeling

Calculate benchmark dose*

Dosimetry model

Estimate lung dose

Extrapolate

Adjust for species differences influencing dose

Human

Occupational exposure limit

Technical feasibility (e.g., limit of detection)

Daily exposure concentration

Estimate exposures leading to lung dose

Equivalent lung dose
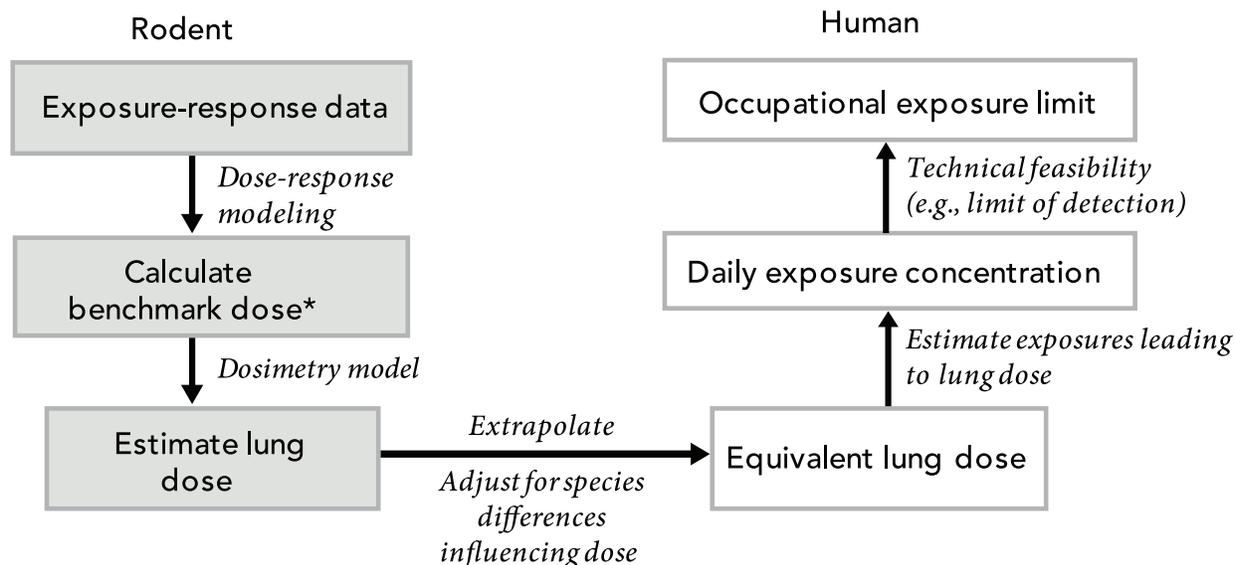
Figure 5-6. Dosimetry and risk assessment steps used by NIOSH to develop occupational exposure limits for airborne particles extrapolated from animal data (adapted from Kuempel [2011] and Oberdörster [1989]).

days or longer, may represent particle clearance within the alveoli (air sacs) and interstitium (connective tissue separating the alveoli) of the pulmonary region.

Particles or fibers retained in the lungs can move into the lung interstitial tissue (either alone or inside macrophages). Particle retention in the interstitium increases the risk of fibrosis for poorly soluble particles. Translocation of particles from the lungs to the lung-associated tissues and systemic organs has also been reported, for particles from coal dust to carbon nanotubes [LeFevre et al. 1982; Mercer et al. 2013]. The physicochemical properties that influence the clearance or retention of particles from the respiratory tract include the chemical composition, size, surface properties, solubility, and shape [Kreyling et al. 2013].

5.6.2.5.2 Models of Long-term Particle Retention in Humans

Studies in workers have shown that the long-term retention of respirable particles involves the sequestration of some portion of the dust in the lungs, even at low exposures that would be below overloading

in rats [Gregoratto et al. 2010; Kuempel et al. 2001]. These independent studies include workers exposed to particles from relatively low (radioactive cobalt) to high (coal dust) mass concentrations. The human pulmonary clearance and retention models that include an interstitial sequestration compartment have been shown to provide better prediction of long-term retained lung burdens in humans with either low or high dust exposures compared to models with either simple first-order clearance or dose-dependent overloading (first-order clearance until reaching a critical dose associated with decreasing clearance rate) [Gregoratto et al. 2010; Kuempel and Tran 2002; Kuempel 2000; Kuempel et al. 2001; Tran and Buchanan 2000]. Consistent with these findings, a study comparing rat and human particle retention patterns in the lungs showed that coal miners retained a greater proportion of particles in the alveolar interstitial tissue, whereas rats retained a greater proportion of particles in the alveolar spaces [Nikula et al. 2001].

In a dosimetry model of the respiratory tract, the ICRP [1994] included three first-order pulmonary (alveolar-interstitial, or AI) clearance compartments.

A fixed proportion of respirable particle deposition in the alveolar region is assigned to each compartment (i.e., 30%, 60%, and 10% for AI_1, AI_2, and AI_3, respectively). The first-order clearance rate coefficients are 0.02, 0.001, and 0.0001 day^{-1}, corresponding to retention half-times of 34, 693, and 6,930 days, respectively. More recently, the ICRP published an updated model [Paquet et al. 2015]. Regarding long-term particle clearance, the main difference between models is a much higher particle retention fraction in the pulmonary region in the updated model.

In the studies reported in ICRP [1994], the particle lung clearance in humans was quantified for up to approximately one year after inhalation. Based on those studies, ICRP [1994] estimated that 50% of the alveolar deposited particle dose remains at 300 days following inhalation. Studies published since that report show much higher long-term particle retention in the lungs of humans. For example, in workers accidentally exposed to radioactive particles, "a significant fraction (>10%)" of particles was retained in the thorax at 10 years after the acute exposure (Paquet et al. [2015], Section A.2.3). An interstitial sequestration compartment was found to be necessary to adequately fit the particle retention data in coal miners [Kuempel et al. 2001]. This model structure is more biologically reasonable, including an alveolar compartment with clearance to the bronchial region, and an interstitial compartment that clears slowly to the lymph nodes. The kinetics of particle clearance in human lungs differs from that in rodents. In rodents, first-order clearance is faster and the translocation of particles to the interstitium occurs primarily after overloading of alveolar clearance. In humans, a fraction of the respirable particles that deposit in the alveolar region may not be cleared but may enter the interstitium and be retained for a longer duration. These findings were confirmed in additional studies in humans, including at much lower particle exposures [Gregoratto et al. 2010; Paquet et al. 2015]. Gregoratto et al. [2010] applied the Kuempel et al. [2001] model to the more recent data in humans, as well as to the original data that had been used

in ICRP [1994]. The parameter values fitted to the pooled data resulted in an alveolar clearance half-time estimate of approximately 250 days, with approximately 33% of the initial alveolar deposited mass dose of insoluble particles being sequestered in the interstitium [Paquet et al. 2015].

The MPPD human clearance and retention model (including v. 1.0 to current v. 3.04) [ARA 2015; Price et al. 2002] uses the ICRP [1994] model to predict clearance and retention in humans. Consistent with the updated ICRP model, higher worker lung burdens were estimated in the interstitial sequestration model [Kuempel et al. 2001] than in the MPPD, v. 1.0 [Price et al. 2002], as reported in Dankovic et al. [2007]. Thus, the earlier ICRP model (or models using it as their basis) may underpredict the average long-term particle retention in humans and therefore may underestimate the risk of adverse effects associated with retained particle dose in the lungs.

5.6.2.6 PBPK Models to Estimate Dose

Physiologically-based pharmacokinetic (PBPK) models provide mathematical estimates used to simulate the distribution of chemicals and metabolites in the body after exposure to a substance over time. These models incorporate the use of a series of differential equations to account for physiological parameters such as blood flow and volume, and metabolic capacity of discrete tissue types (e.g., lung, richly perfused tissues, poorly perfused tissues, and liver). Many of these parameters were compiled for several animal species by Brown et al. [1997]. Other factors such as dosing route are also considered for the physiological differences in uptake rate, metabolism, and distribution of chemicals that occur when exposures are by differing routes.

Some examples of PBPK models that have been used in NIOSH risk assessments include respiratory tract models to estimate the particle deposition and clearance kinetics for inhaled particles, such as titanium dioxide and carbon nanotubes [NIOSH 2011; NIOSH 2013b]. PBPK or dosimetry models are used to estimate more biologically relevant doses

for use in dose-response modeling in quantitative risk assessment. These models can be useful for temporal extrapolation of dose when the relationship between the external exposure and internal dose is nonlinear. This is because PBPK models can account for capacity-limited processes in the absorption/uptake, distribution, metabolism, and/or excretion of a toxicant. Capacity limitation may be due to saturation of a key process, e.g., involving a receptor or enzyme. An example of an important capacity-limited process that influences the clearance kinetics and dose of inhaled particles in rodents is the overloading of pulmonary (alveolar macrophage-mediated) clearance of particles, which results in a dose-dependent increase in the retained particle dose [Bellmann et al. 1991; Bolton et al. 1983; Morrow 1988; Stöber et al. 1990]. As a result, the biological mechanisms and pathways operating at lower, non-overloading doses can differ from those operating at higher doses, when defenses of cells or organisms are overwhelmed [McClellan 1997; Oberdörster et al. 2005b]. In this case, a dosimetry model that does not account for changes in clearance kinetics may provide a poor estimate of dose and underestimate the retained lung dose at higher airborne exposures [Kuempel et al. 2015].

Additionally, PBPK models provide mathematical modeling estimates of aggregate exposure dosing (oral, inhalation, dermal) and target tissue dose estimates of both parent chemical exposure and metabolites. This information may reduce uncertainty in risk assessment calculations compared to those using dose estimates based on absorption only.

In addition to the use of PBPK models for particle dose estimation, these models are also applicable to dose estimation for other chemical forms, including gases and vapors (see Section 5.6.3.6). In an example involving a liquid, a PBPK model for dichloromethane was used to illustrate the steps to estimate tissue dose in chemical risk assessments [Andersen et al. 2005]: 1) identify toxic and critical effects in animals and humans; 2) catalogue MoAs, metabolism, parent compound/metabolite data; 3) identify potential MoA for the

critical effect; 4) develop potential relationship between tissue dose (associated with toxicity) and the response; 5) develop the PBPK model based on relevant routes of exposures, exposure concentrations, and species; 6) provide estimates of dose metrics during exposures that produce toxicity; and 7) use outputs to estimate risk for human exposures of interest with the assumption of a similar dose-response relationship between PBPK test species and humans.

Although risk assessment methods may be advanced using PBPK models, there are important limitations to consider. PBPK models often require data intensive inputs on physiological and biochemical/metabolic processes that often come from separate sources or may be missing or poorly characterized [Khalil and Laer 2011]. In addition, validation of PBPK model outputs using empirical data can be difficult or impractical given data limitations. Lastly, PBPK modeling efforts typically require specialized software and expertise that may have limited availability in some situations.

Detailed guidance on developing PBPK and/or computational fluid-dynamics models is beyond the scope of this report. Additional information on these topics is available in Andersen et al. [2005] and in guidance provided by the U.S. EPA: "Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment" [EPA 2006a].

5.6.2.7 Overloading Considerations in Rodent Model and Dose Estimation

The effects of particle overloading of lung clearance in rats and mice involve a sequence of events including persistent pulmonary inflammation in both species, fibrosis primarily in rats, and cancer in rats [Baan 2007; Elder et al. 2005; Oberdörster 1995]. Rats have been shown to be better predictors of lung cancer from inhaled particles that are carcinogenic to humans (i.e., classified by IARC as having limited or sufficient evidence), in comparison with mice or hamsters, which yield false-negative results more often [Mauderly 1997].

This well-studied rodent phenomenon of particle overloading of pulmonary clearance is the basis for the risk assessment approach of identifying the non-overloading dose in rats as the NOAEL to extrapolate to humans [Morrow et al. 1991; Pauluhn 2010]. Although this concept seems reasonable on the basis of the rat data, it may not be adequate to estimate chronic responses in humans because of differences in the clearance and retention kinetics (as discussed in Section 5.6.2.8).

The dose metrics associated with overloading of lung clearance include particle mass (unit density particles), particle volume (particles with density other than 1.0 g/cm^3), and particle surface area (nanoparticles) [Bellmann et al. 1991; Morrow 1988; Tran et al. 2000]. In contrast to microscale particles, nanoscale particles or highly toxic particles have been shown to cause impaired pulmonary clearance at a lower mass or volumetric particle dose than for microscale poorly soluble low toxicity (PSLT) particles [Bellmann et al. 1991; Oberdörster et al. 1994]. Particle surface area has been shown to better describe the decreased clearance and pulmonary responses to nanoscale compared to microscale particles [Tran et al. 2000]. Since particle dosimetry models are generally based on the particle mass, dose conversion may be necessary between the estimation of effect level in the rodent study (e.g., surface area dose associated with adverse effect) and the estimation of the equivalent dose in humans.

5.6.2.8 Interspecies Dose Estimation in Risk Assessment

Scientific models are generally available to estimate the human-equivalent lung doses of inhaled particles from those in rodents [ARA 2015; Paquet et al. 2015]. Less well understood are the human and rat biological responses to equivalent mass, surface area, or volumetric particle lung doses. For example, the biological MoA for the development of lung tumors in rats exposed to PSLTs by chronic inhalation appears to involve secondary genotoxicity resulting from chronic inflammation and cell proliferation [IARC 2010; NIOSH 2011; Olin

2000]. Thus, at low lung doses in rats (i.e., below lung overload), where inflammation and cell proliferation are not present, lung cancer would not be anticipated [Greim et al. 2001]. Mice also showed overloading of lung clearance but had lower inflammatory response than rats in a subchronic inhalation study of a PSLT (carbon black); hamsters did not show overloading or lung inflammation in that study [Elder et al. 2005].

The interpretation and use of rat dose-response data of inhaled particles in human hazard and risk assessment and OEL development has been discussed and debated for many years [Cherrie et al. 2013; IARC 2010; Kuempel et al. 2014; Morfeld et al. 2015; Oberdörster 1995; Olin 2000; Pauluhn 2014; Warheit et al. 2016; Yu 1996]. Yet, the rat chronic bioassay data have been shown to give fewer false negatives for inhaled particles classified by IARC as human carcinogens than have the mouse and hamster data [Mauderly 1997]. Moreover, human particle lung doses in workers in dusty jobs such as coal mining have been shown to be equivalent to the mass-overloading doses in rats exposed chronically to particles [IARC 2010; Kuempel et al. 2014; NIOSH 2011].

In general, the rat is considered a useful model for human non-neoplastic lung responses to PSLT, and in the absence of mechanistic data to the contrary, the rat model is relevant to identifying potential carcinogenic hazards in humans [Olin 2000]. Rat chronic inhalation data of PSLT were used by IARC [2010] in its evaluation of the carcinogenicity of inhaled PSLT (titanium dioxide and carbon black) and by NIOSH [2011] in its hazard classification and REL for nanoscale and microscale titanium dioxide.

Scientific questions on rat lung overload that still need to be resolved were discussed by Borm et al. [2015], who cite two publications that contribute to the debate [Morfeld et al. 2015; Pauluhn 2014]. To date there is no clear resolution of this issue in the scientific community. Therefore, interpretations of the rat dose-response data for risk assessment have differed widely for inhaled PSLT, including those for nanoscale titanium dioxide, using the

same basic data [NIOSH 2011; Relier et al. 2017; Warheit et al. 2016]. Although the scientific debate may continue, dosimetric adjustments to account for differences in PSLT aerosol particle size and respiratory tract disposition and/or clearance between rodents and workers have been used to account for toxicokinetic differences, and uncertainty factors can be applied to account for toxicodynamic differences [EPA 1994; ICRP 1994; Jarabek et al. 2005; Kuempel et al. 2015; Oller and Oberdörster 2016]. Animal inhalation studies used in risk assessment should include sufficient doses to characterize the dose-response relationship, including low doses to overloading doses [Kuempel et al. 2014; Oberdörster 1997; Olin 2000; Pauluhn 2011].

Despite the differences in particle clearance and retention kinetics, the overloaded rat model may be relevant to predicting risk to workers exposed to inhaled particles. Overloading doses of microscale PSLT in rats have been observed as low as 0.5 mg/g lungs, with complete cessation of clearance at doses >10 mg/g lungs [Muhle et al. 1990; Oberdörster 1995]. By comparison, workers in dusty jobs historically have had average retained particle mass doses >10 mg/g lungs [Douglas et al. 1986; Freedman and Robinson 1988; Stöber et al. 1965]. Thus, only at overloading doses does the particle lung burden in rats reach the higher levels that have been reported in coal miners. These findings suggest that the rat is an appropriate model for human health risk assessment of respirable particles.

Studies in mice and hamsters are not as predictive of the human particle-associated lung responses, and results were negative for some particles that have been classified as known human carcinogens [Mauderly 1997]. In a quantitative comparison of lung cancer risk estimates in rats and humans associated with chronic exposure to various types of respirable PSLT (coal mine dust, carbon black, titanium dioxide, or crystalline silica), the rat- and human-based estimates were statistically consistent, given the level of imprecision in the animal and human data [Kuempel et al. 2009; NIOSH 2011]. These studies suggest that the rat may be the most reasonable and sensitive rodent model to estimate

the risk of chronic exposure to respirable particles, despite the species differences in the clearance and retention kinetics, which can be adjusted for by using dosimetry modeling.

5.6.2.9 Tools/Models (deposition and/or clearance)

The most widely used dosimetry models for inhaled particles and fibers are found in the MPPD suite of models [ARA 2015; Price et al. 2002]. These models have largely replaced the U.S. EPA Regional Deposited Dose Ratio (RDDR) model, which allowed estimation of the equivalent deposited dose in the respiratory tract across species but did not include clearance [EPA 1994]. However, the MPPD does not include models for all test species. For example, the RDDR model is still needed for studies using hamsters, because this species is not included in the MPPD.

Several deposition and clearance models are included in MPPD, as described in the model overview and details in the software (MPPD v. 3.04). The MPPD has been developed over a decade or more with funding by various U.S. governmental sources (including EPA, Navy, and NIOSH) and nongovernmental sources. It is publicly available to download at https://www.ara.com/products/multiple-path-particle-dosimetry-model-mppd-v-211.

NIOSH-funded revisions to earlier versions include batch capability in running the deposition and clearance models in humans and rats (in MPPD v. 2.1 [ARA 2009]); addition of oronasal deposition in animals and humans, including olfactory deposition of nanoscale particles [Garcia and Kimbell 2009; Garcia et al. 2015]; and extension of the spherical particle model to include nonspherical and fibrous particles based on aerosol characterization and measurement of deposition efficiency in human respiratory tract replicas [Su and Cheng 2015; Su and Cheng 2014].

The MPPD is for poorly soluble particles (spherical or nonspherical) but does not account for particle dissolution. It is also limited to the respiratory tract and does not include translocation to other organs.

Other dosimetry/PBPK models are needed to estimate internal dose of soluble particles in the lungs or other organs.

In general, data available for PBPK modeling are limited. When validated models are available, they are preferred to application of uncertainty factors to estimate human-equivalent dose because they account for material- and species-specific factors influencing the dose-to-target tissues. Many individual PBPK (dosimetry) models have been developed for inhaled particles and fibers; their use would need to be evaluated on a case-by-case basis. Some useful tools and references associated with dosimetry modeling are listed in Table 5-2.

When searching the literature for information on lung dosimetry models of aerosols, note that multiple databases might need to be used, such as PubMed, Web of Science or Scopus, Toxline, and/or Embase. Although PubMed is a major research database and perhaps the most widely used, it does not provide citations for some of the journals in which aerosol research is published (e.g., the *Journal of Aerosol Science*). Past practices have demonstrated that broader search strategies may be needed to identify relevant articles in this area.

5.6.3 Gas and Vapor Exposures

In general, the major factors influencing the internal dose from gas or vapor inhalation are anatomy (ventilation rate), physiology (diffusion, dissolution, blood flow, metabolism, and elimination rates), and physicochemical properties (e.g., gas or vapor solubility, reactivity) of the chemical [Bogdanffy and Jarabek 1995; Hanna et al. 2001; Jarabek 1995; Kuempel et al. 2015]. The components of the inhalation dosimetry adjustment for gases are the following.

1. Conversion of units from ppm to mg/m³: The concentration in the inhalation toxicity studies on gases are usually reported in units of ppm or mg/m³. For exposure levels reported as ppm, this should be converted to the standard units of mg/m³ by using the following formula:

$$\text{mg/m}^3 = \frac{\text{ppm} \times \text{MW}}{24.45}$$

where MW is the molecular weight in grams and 22.45 is the volume occupied by 1 g-mol of any compound in the gaseous state at 25°C and 760 mm Hg.

2. Duration adjustment: Many inhalation toxicity studies in laboratory animals are conducted with discontinuous exposure, often with exposure frequencies of 6 to 8 hours per day and 5 days per week. Occupational risk estimates are derived with the intention to protect workers against the exposure of 8 hours per day for 5 days per week, totaling 40 hours per workweek. Therefore, duration-adjusted exposure level is

$$\text{Adjusted concentration (mg/m}^3) = \\ E(\text{mg/m}^3) \times D/8 \times W/5$$

where E is the experimental exposure concentration, D is the work day adjustment of the number of hours exposed in 8-hour daily increments, and W is the workweek adjustment of the number of days of exposure in 5-day workweek increments.

3. Human Inhalation Rate: The human inhalation rate for light exertion while doing work of 9.6 m³/8 hours should be included in the risk estimate.

4. Human Equivalent Concentration (HEC): The HEC is the concentration of a substance in humans that is believed to produce an effect equal to a dose in experimental animals, adjusted for exposure duration and physiological parameters such as breathing rate.

5.6.3.1 NIOSH Practice

The current NIOSH practice for calculating HEC is as follows:

1. Experimental animal dose in ppm is converted to daily mg/kg inhaled dose.

2. In the absence of chemical-specific information on metabolism or dosimetry, this dose is extrapolated to humans, assuming dose equivalence in units of mg/kg·day, scaled according to body weight to the 0.75 power [Kleiber 1932; Sidhu 1992].

3. The human mg/kg·day dose is then converted to ppm for an 8-hour workday.

Table 5-2. Examples of available tools and resources for dosimetry modeling (adapted from Kuempel et al. [2015]).

Name of Tool or Resource	Description	Source and Availability
Multiple-path particle dosimetry model (MPPD)	Deposition, clearance, and retention estimation of inhaled particles in the respiratory tract of the human, rat, and mouse	ARA [2015], http://www.ara.com/products/mppd.htm Based on several models including Anjilvel and Asgharian [1995], Asgharian et al. [2001; 2014], and ICRP models [ICRP 1994; Paquet et al. 2015]
Respiratory tract region deposited dose equations	Deposited-dose estimation of inhaled particles or vapors Interspecies dosimetric adjustments Derivation of reference concentrations	U.S. EPA [1994; 2012a], https://www.epa.gov/risk/methods-derivation-inhalation-reference-concentrations-and-application-inhalation-dosimetry http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=244650
Human respiratory tract model	Deposition, clearance, and retention estimation of inhaled particles (including non-radioactive) in the human respiratory tract	ICRP Publication 66 [ICRP 1994], http://www.icrp.org/ http://www.sciencedirect.com/science/journal/01466453/24/1-3
Physiologically Based Pharmacokinetic (PBPK) modeling guidance	Guidance on principles of characterizing and applying PBPK models in risk assessment	U.S. EPA [2006a], https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=157668 IPCS [2010], http://www.who.int/ipcs/en/ http://www.inchem.org/documents/harmproj/harmproj/harmproj9.pdf Loizou et al. [2008] and McLanahan et al. [2012]
Human reference values	Anatomical and physiological parameters (reference values) in humans Inter-individual variability by age and gender Parameters for PBPK models	ICRP Publication 89 [Valentin 2002], http://www.icrp.org/ http://www.sciencedirect.com/science/journal/01466453/32/3-4
Interspecies reference values	Physiological parameters for dose normalization or PBPK modeling Application to Biological Exposure Indices	Brown et al. [1997], Davies and Morris [1993], Mercer et al. [1994], Stone et al. [1992], Boxenbaum [1982], and Fiserova-Bergerova [1990]
Particle size definitions	Criteria for airborne sampling of particle size fractions by probability of deposition in human respiratory tract regions	ACGIH [2015], ACGIH [1985], and Lioy et al. [1984]

The following example is taken from a hypothetical study of the effects from 1-bromopropane inhalation using a 2-year bioassay of B6C3F$_1$ mice dosed 6 hours per day. The PoD for lung tumors in female mice (the outcome of interest) in this study was 0.64 ppm. The experimental animal dose in ppm is converted to a daily mg/kg inhaled dose:

$$\text{Mouse BMDL} = 0.64 \text{ ppm} \times 5.031 \frac{\text{mg/m}^3}{\text{ppm}} \times$$
$$\frac{0.060 \text{ m}^3/\text{day} \times 6 \text{ hour}/24 \text{ hour}}{0.0353 \text{ kg}}$$
$$= 1.37 \text{ mg/kg·day}$$

where 0.64 ppm is the dose; 5.031 mg/m^3 per ppm is the molecular weight (122.99 g/mol) divided by 24.45; 0.060 m^3/day is the reference inhalation rate for female B6C3F$_1$ mouse; and 0.0353 kg is the reference body weight for female B6C3F$_1$ mouse in a chronic study.

This dose is extrapolated to humans, assuming dose equivalence in units of mg/kg·day scaled according to body weight to the 0.75 power:

$$\text{Human BMDL} = \text{Mouse BMDL} (1.37$$
$$\text{mg/kg·day}) \times (0.0353 \text{ kg}/70 \text{ kg})^{0.25} =$$
$$0.205 \text{ mg/kg·day}$$

where 70 kg is the reference human body weight. Here the exponent value of 0.25 reflects body weight (BW) scaling to the ¾ power (i.e., BW$^{3/4}$) in units of mg/kg-day (rather than mg/day), such that BW$^{1/1}$/BW$^{3/4}$ = BW$^{1/4}$.

The human mg/kg·day dose is then converted to ppm for an 8-hour workday:

$$\text{Human BMDL} = 0.205 \text{ mg/kg·day} \times$$
$$\frac{70\text{kg}}{9.6 \text{ m}^3/8 - \text{hour workday}} \times \frac{1\text{ppm}}{5.031\text{mg/m}^3}$$
$$= 0.297 \text{ ppm, or about } 0.3 \text{ ppm}$$

where 9.6 m^3 per 8-hour workday is the reference inhalation rate for humans.

5.6.3.2 U.S. EPA Practice

The HEC is calculated from a PoD (e.g., NOAEL, LOAEL, or BMDL) by using the following formula:

$$\text{PoD}_{[\text{HEC}]}(\text{mg/m}^3) = \text{PoD}_{[\text{ADJ}]}(\text{mg/m}^3) \times \text{RGDR}$$

where RGDR is the regional gas deposited ratio, which is the ratio of regional gas dose in laboratory animal species to that of humans for the target region.

The EPA categorized the gas, on the basis of the physicochemical properties and the regions of the effect in the respiratory tract, into categories 1, 2, and 3. Category selection for a given chemical should be based on the properties of the chemical and its target effects in the body, as described in Table 5-3.

5.6.3.3 Category 1 Gases

Category 1 gases are highly water soluble or reactive and thus produce an effect mostly in the respiratory tract itself. Because of the high-level deposition along with high reactivity, local tissue damage is expected from these gas exposures. Only a small fraction of these gases could penetrate deeper than the ET region under normal circumstances. However, during heavy exercise, fires, explosions, etc., these gases could penetrate deeper, leading to tissue damage in the distal respiratory tract. The following equations are used to calculate RGDR for different regions of Category 1 gas. If the calculated value is greater than 1, then RGDR$_{ET}$ is set to 1.

1. RGDR$_{ET}$ for Category 1 gas:
$$\text{RGDR}_{ET} = \frac{(V_E/SA_{ET})_A}{(V_E/SA_{ET})_H}$$

where V$_E$ is the minute volume (cm^3/min), SA$_{ET}$ is the surface area of the extrathoracic region (cm^2), and terms A, H represent laboratory animal and human, respectively. Later EPA guidance suggested that there is internal dose equivalency in the ET region for rats and humans. This guidance suggests that in lieu of specific modeling data, the default RGDR$_{ET}$ is 1, rather than 0.2–0.3 as predicted by the equation above [EPA 2012a].

Table 5-3. Gas categories and characteristics.

Category	Water Solubility	Reactivity	Accumulation in blood	Site of toxicity	Examples
1	High	Rapidly irreversibly reactive	Not significant	Portal of entry	Hydrogen fluoride, chlorine, formaldehyde, volatile organic acids and esters
2	Moderate	Rapidly reversibly reactive, or moderately to slowly irreversibly metabolized in respiratory tract tissue	Potential	Portal of entry, maybe systemic	Ozone, sulfur dioxide, xylene, propanol, isoamyl alcohol
3	Low	Unreactive in surface liquid and tissue	Yes	Systemic toxicity	Styrene

Adapted from EPA [2012a].

2. $RGDR_{TB}$ for Category 1 gas:

$$RGDR_{TB} = \frac{(V_E / SA_{TB})_A}{(V_E / SA_{TB})_H}$$

where V_E is the minute volume (cm³/min), SA_{TB} is the surface area of the TB region (cm²), and terms A, H represent laboratory animal and human, respectively.

3. $RGDR_{PU}$ for Category 1 gas:

$$RGDR_{PU} = \frac{(Qalv / SA_{PU})_A}{(Qalv / SA_{PU})_H}$$

where Qalv is the alveolar ventilation rate (mL/min) and is equal to $0.6 \times V_E$.

5.6.3.4 Category 2 Gases

Category 2 gases are moderately water-soluble and have the potential to penetrate bronchi and thereby the blood. Therefore, both local and systemic effects could be observed following exposure to these gases. HECs for respiratory tract effects are calculated by the equations for a Category 1 gas, whereas HECs for extra-respiratory effects are calculated by the Category 3 equations. In cases where respiratory tract effects are caused by systemic distribution of the chemical, such as chloroform and naphthalene, the HEC should be calculated as a Category 3 gas.

5.6.3.5 Category 3 Gases

Category 3 gases have very low water solubility and limited reactivity with respiratory epithelium. These gases readily penetrate to the pulmonary region and are absorbed into the systemic circulation. Most of the effects are observed distal to the respiratory system except in cases where metabolism in the upper-respiratory tract leads to local effects. The following equation is used to calculate the RGDR for Category 3 gases:

$$RGDR = \frac{(H_{b/g})_A}{(H_{b/g})_H}$$

where the value $\frac{(H_{b/g})_A}{(H_{b/g})_H}$ is the ratio of the blood:gas (air) partition coefficient of the chemical for the laboratory animal species to the human value. A value of 1.0 is used for the ratio of $(Hb/g)_A > (Hb/g)_H$. A value of 1.0 is used as the default when one or both of the partition coefficients are not available. Blood:air partition coefficients for some chemicals are available from Gargas et al. [1989].

5.6.3.6 PBPK and Computational Fluid Dynamics Approaches

PBPK modeling (see Section 5.6.2.6) also applies to gas and vapor exposures to derive target tissue

dose estimates in various species. As stated previously, the construction and development of a PBPK model for an individual chemical involves a large amount of data and understanding of the absorption, metabolism, distribution, and elimination of the chemical in the test species and in humans. One of the examples of PBPK modeling used in occupational risk assessment is use of the methylene chloride PBPK model to derive target tissue dose estimates for lung tumors in mice [OSHA 1997].

Computational fluid dynamics–PBPK (CFD/PBPK) models are designed to model the fluxes of vapor between tissue phases (e.g., between epithelial and submucosal tissues) and allow for a differential blood flow and coupling the respiratory tract to the whole body. This type of model has been used to evaluate the dosimetry of many compounds, including diacetyl and styrene [Gloede et al. 2011; Sarangapani et al. 2002]. NIOSH used CFD/PBPK modeling in its risk assessment of occupational diacetyl exposure [NIOSH 2016].

5.7 Dose-Response Modeling with Epidemiologic Data

NIOSH prefers the direct estimation of occupational risks in working populations because: (1) data reflecting actual exposures and responses within the population of interest are inherently superior for risk assessment, and (2) the uncertainty in extrapolating data from animal toxicologic studies can be much larger than that in well-designed epidemiologic studies [Hertz-Picciotto et al. 1995; Smith 1988; Stayner et al. 1999]. Of the NIOSH risk assessments listed in Table 1-1, nine (70%) quantitatively examined the dose-response relationship by statistical models using epidemiologic data. In contrast, epidemiologic data have been used in less than 10% of Integrated Risk Information System (IRIS) assessments conducted by the EPA [Persad and Cooper 2008].

Many of the concepts discussed previously concerning animal data are also applicable to human data, especially for experimental designs or when modeling binary outcome data from observational studies without time-dependent variables (e.g., using logistic regression). Although methods of analyses may be identical, the majority of human data for risk assessment stems from observational studies, which have less control of extraneous factors and are more prone to bias than studies of experimental data (see Section 4.3.4). The design of epidemiologic studies contributing to risk assessment can vary, as can study aims, which also may not fully align with risk assessment goals.

NIOSH risk assessors first decide, in a systematic way, if human data are suitable for quantitative dose-response analyses, and if so, whether the data will serve as (1) the primary basis for risk extrapolation or (2) supporting information for a risk assessment primarily based on animal toxicologic data. The evaluation may be made concurrently with the WoE assessment in hazard identification, although data supporting hazard identification may lack the rigor necessary for dose-response analyses. In any event, all decisions on data suitability should be fully described in the risk assessment documentation. As a starting point, risk assessors have applied the framework first described by Hertz-Picciotto [1995], who suggested judging the suitability of epidemiologic data for quantifying dose-response by using five criteria. These criteria, slightly modified for NIOSH risk assessment purposes, are as follows:

1. The data consistently indicate a stable positive statistical association between the agent and adverse effect.

2. The data are abstracted from studies that are of high overall quality.

3. There is no substantial potential for confounding or other source of major bias.

4. There is a quantitative assessment of exposure that is deemed appropriate for dose-response analyses.

5. There is evidence of a monotonic dose-response.

Hertz-Picciotto [1995] suggested that compliance with criteria 1 through 4 provides a minimum basis

for risk extrapolation using human data; compliance with 2 of the first 3 criteria is considered suitable for quantifying risks as a plausibility check with animal-based assessments. Thus, it is clear that more weight is to be placed on criteria 1, 2, and 3. Criterion 1 is directly related to Hill's guidelines on strength of association and consistency (see Section 4.1). This criterion differs from that originally specified, which included only moderate to strong positive associations [Hertz-Picciotto et al. 1995]. This modification was made in recognition that excellent studies reporting weakly positive but consistent associations can inform the dose-response relationship. For example, Park et al. [2004] conducted a quantitative risk assessment of lung cancer from exposure to hexavalent chromium that used data from Gibbs et al. [2000], who reported modestly elevated lung cancer risk (e.g., SMR <2) in chromium production workers compared to the general population (SMR = 1.80; 95% CI: 1.49–2.14). This risk assessment helped form the basis for the NIOSH REL on hexavalent chromium exposure [NIOSH 2013a]. Criteria 2 and 3 are related; both prefer study designs that reduce the potential for an inaccurate estimated effect. Criterion 4 was modified to recognize that quantitative exposure data at the individual level, as originally recommended [Hertz-Picciotto et al. 1995], is sparse in epidemiologic studies. The lack of individual-level measurements should not disqualify study data from quantitative risk assessment; however, their presence is preferred to aggregate exposure measures that are more vulnerable to bias from shared error or exposure misclassification (see Appendix B). Criterion 5 coincides with Hill's guideline on a biologic gradient, which is not necessary in either case but certainly supports data use. Note that there are many explanations for a lack of observed monotonicity in dose-response data, such as measurement error, biologic saturation, and depletion of a susceptible population [Stayner et al. 2003]. Last, there may be exceptional circumstances in which other criteria may better apply or in which modification to existing criteria is prudent. Risk assessors should describe these exceptions in the risk assessment document. For example, a potential for

substantive confounding may exist (criterion 3); however, data may allow for an examination and/or adjustment of its effect on dose-response estimates. In this example, the risk assessment document should fully describe the potential for bias, the alternative analyses for examining the effects on dose-response estimates, and any consequent actions.

NIOSH risk assessors strive to make the best use of epidemiologic data that are available in dose-response modeling strategies, given that these data provide the important advantage of directly addressing human risk. When epidemiologic data are available and appear suitable for quantifying exposure-related effects, the risk assessor generally adopts a statistical modeling approach that includes an evaluation of potential sources of biases. NIOSH risk assessors endeavor to select statistical methods that best account for identified sources of uncertainty and therefore improve the reliability and validity of dose-response estimates.

As discussed previously, exposure estimation in human studies is often fraught with limitations. Risk assessors consider ways to account for exposure uncertainty in developing a risk modeling approach. Given the relative uniqueness of most epidemiologic datasets, it is not feasible to describe all possible modeling strategies in this report. However, this section discusses some overall modeling approaches using human data methods that are unique to aggregate data from published reports and time-to-event data from longitudinal studies.

5.7.1 Limited Data

Although dose-response analyses using individual exposure and outcome data are preferred, the lack of these data does not preclude examining statistical associations and regression relationships between aggregate measures of exposure and measures of population risk using summary estimates from human data. In fact, risk assessments have used limited data comprising only an aggregate exposure measure (e.g., average cumulative exposure) and a measure of relative risk (e.g., SMR, SIR, and OR).

For example, a simple dose-response model can be specified with data from a study reporting only a cohort SMR and average exposure by assuming a linear relationship exists between the SMR (or any measure of relative risk) and exposure (x): SMR = 1 + $x\beta$, where the dose-response slope, β, represents the change in relative risk (e.g., the SMR) per unit dose [Smith 1988; Stayner et al. 1995]. Figure 5-7 shows a plot of this relationship for a hypothetical cohort.

An SMR from an occupational study may be negatively biased from a healthy worker hire effect (see Appendix B for more information). This effect can be countered by using an adjusted SMR, derived on the basis of the study type and outcome [Park et al. 1991] or by fitting another parameter to the model to adjust for the background hazard rate [Stayner et al. 1995]. Similarly, information on other potential sources of bias can be included as model covariates. As another example, if SMRs are reported at different levels of exposure, then weighted least-squares regression or maximum likelihood estimation methods can be used. Examples of these techniques have been described in several reports [Breslow and Day 1987; Crump and Allen 1985; Hanley and Liddell 1985; Rothman et al. 2008; Smith 1988; Smith et al. 1994; Steenland and Savitz 1997].

There are some important limitations in the methods described above. First, we assume the true dose-response is linear, given that it is biologically plausible, generally appears conservative in the low-dose range compared to alternative models, and tends to fit epidemiologic data. Alternatively, a nonlinear dose-response function could be fitted, which may result in marked differences in estimates in the range of interest. In practice, however, adequate data preferring a nonlinear model are unlikely in most situations. Second, pooling SMRs in dose-response analysis is less than ideal, given that multiple SMRs (stratum-specific) may not be comparable because of indirect standardization. Pooling SMRs could bias estimates from differences in age, race, sex, or some other confounder across exposure groups. Fortunately, strong statistical confounding from stratum heterogeneity is not

typically observed in most cases [Breslow and Day 1987]. Nonetheless, risk assessors must address the potential for bias from heterogeneous comparison groups. Third, using weighted least squares to regress multiple responses at different exposure levels (e.g., SMRs or log-SMRs) does not account for correlations between response measures induced by sharing a common reference group. Methods have been developed to account for these correlations in trend estimation in both single study and meta-analytic (meta-regression) designs [Greenland and Longnecker 1992; Hamling et al. 2008; Orsini et al. 2012]. Of course, these methods are crude and generally inadequate to serve as the sole basis for NIOSH recommendations on OELs. Instead, they may be informative in risk characterization when used in conjunction with other supporting data.

A NIOSH example of a limited data approach is not available; however, examples are available in the literature [Chovil et al. 1981; Crump and Allen 1985; Hanley and Liddell 1985; Smith 1988; Steenland and Savitz 1997]. For example, Steenland and Savitz [1997] used a simple linear model to examine the dose-response between airborne nickel levels and lung cancer mortality. The dataset was abstracted from a previous epidemiologic study of Ontario nickel refinery workers (n = 495) followed from 1963 to 1978 [Chovil et al. 1981]. The relative risk per unit exposure was estimated by the slope parameter from a weighted least-squares linear regression of the SMRs at specified cumulative dose levels. The expected numbers of lung cancer deaths were used as weights and the model forced the intercept at unity. A simple estimate of lifetime excess cancer was estimated by $R_{AR} = R_0(x\beta)$, where R_{AR} is the added lifetime risk from exposure x, R_0 is the background lifetime risk of lung cancer death, and β is the upper 95% confidence limit on the slope parameter.

5.7.2 Longitudinal Data

In longitudinal studies, data on observation time, demographics (e.g., age, race, and gender), and time-varying predictors (e.g., exposures) are available.
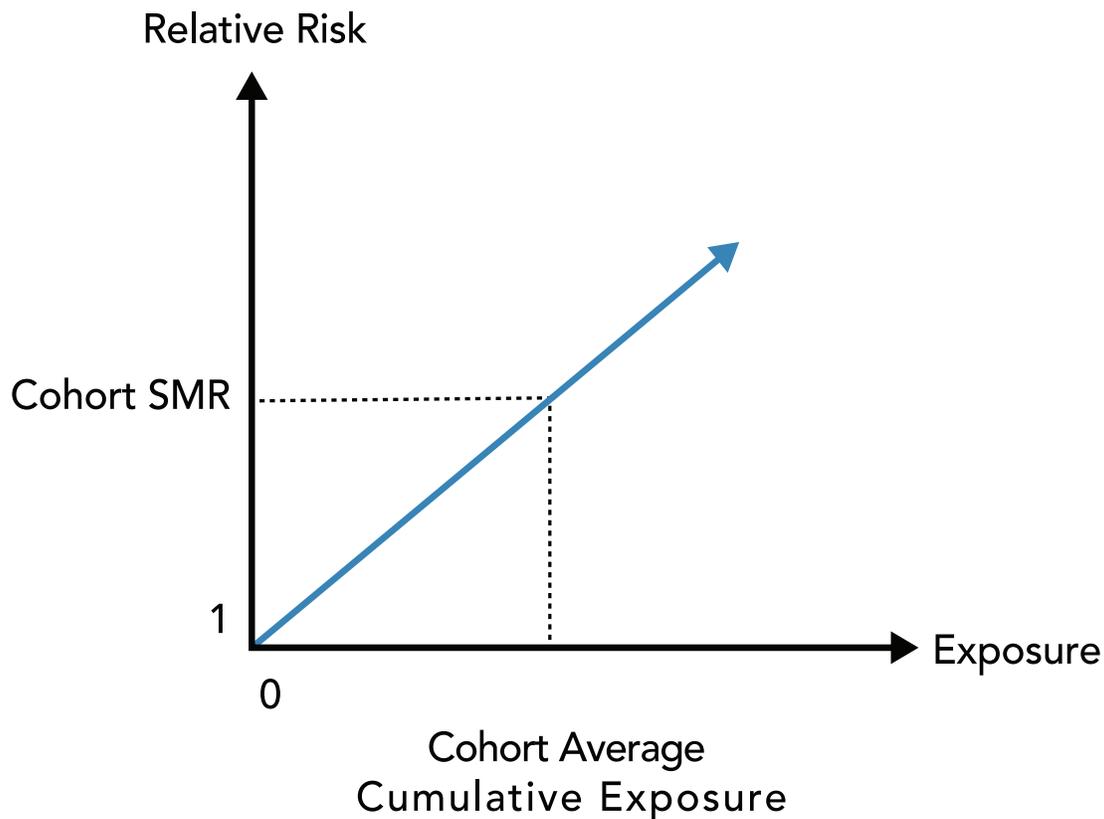
Figure 5-7. Linear dose-response slope estimates using average cumulative exposure and reported standardized mortality ratio (SMR) from an epidemiologic study (adapted from Smith et al. [1988]).

Approaches to modeling must be consistent with the data, although more than one approach may be available. For example, data from a cohort study of cause-specific mortality can be expressed as the amount of observation time and an observed count of adverse responses cross-classified on the basis of other predictors in order to estimate the incidence rate.

In general, previous risk assessments have applied a tiered approach, whereby categorical analyses and splines are first used to evaluate the shape of the dose-response curve, which aids in defining a set of parametric models that are most appropriate for risk assessment [Steenland and Deddens 2004]. The risk assessor may then select a preferred model from the set of models on the basis of prior knowledge of the expected response (biologic plausibility) and model fit. In any event, the choice of

the best model should not rest solely on statistical grounds [Breslow 1990]. This is because competing statistical models can often yield roughly equivalent fits to the data in the observable-effect dose range, yet extrapolation below the observable range (i.e., in the range of interest) can result in estimates that are orders of magnitude apart [Brown and Koziol 1983; Stayner et al. 1995]. Methods within the framework of this approach can vary, and an exhaustive discussion of all modeling possibilities is beyond the scope of this report. More information is available in many important epidemiologic texts [Breslow and Day 1987; Rothman et al. 2008; Woodward 2013].

Dose-response modeling of longitudinal data has been approached with use of a wide array of methods but is generally conducted by regression of survival data (i.e., failure-time data) or person-years

data. Survival regression models can be fully parametric models of the distribution of failure times (e.g., Weibull models) or semi-parametric (i.e., Cox proportional hazards model). Poisson regression modeling is an example of a modeling approach for data on response counts and person-years of observation. Most epidemiologic studies have examined dose-response relationships from longitudinal study data by using general relative risk models with maximum likelihood estimates obtained from Cox proportional hazards or Poisson regression techniques for cohort data and conditional logistic regression for nested case-control designs.

5.7.2.1 Poisson Regression

Follow-up data can be recorded as counts of responses, i.e., the number of events (e.g., deaths) and the number of person-years in strata of other variables (e.g., age, sex, exposure, etc.). Furthermore, dose-response curves can be fitted to the count data Y_i and person-years based on Poisson regression modeling, i.e., $Y_i \sim Poisson[f(d_i, X_{1i}, X_{2i}, \cdots, X_{ci}; \boldsymbol{\theta}) \cdot \tau_i]$ where Y_i represents the count observed during an accumulation of person-time τ_i; if each record of the data is constructed from one person, then $Y_i \sim Binomial[f(d_i, X_{1i}, X_{2i}, \cdots, X_{ci}; \boldsymbol{\theta}) \cdot \tau_i \mid \eta_1 = 1$ may be substituted. If a reference population is available that provides information on the rate associated with age, sex, and other demographic variables, then it can be incorporated to improve estimate precision. However, the assumption of Poisson or binomial variations is a strong one, and it may be necessary to accommodate response variation exceeding that predicted by the model (i.e., over-dispersion), such as using quasi-likelihood methods or models that incorporate random effects.

Examples of Poisson regression modeling in NIOSH risk assessment include dose-response models of the relationships between lung cancer and hexavalent chromium [NIOSH 2013a; Park et al. 2004] and asbestos [Stayner et al. 1997].

5.7.2.2 Cox Proportional Hazards Regression

In survival analyses, the hazard function (or hazard) is the rate of failure at an instant in time, t,

given that the individual survives up to t. In other words, it is the instantaneous risk that the event (e.g., death, cancer diagnoses) will occur at t. In most longitudinal studies, the time scale of interest is age. The hazard ratio (HR) is the hazard of one individual (e.g., the exposed) divided by another individual (e.g., the unexposed), typically holding all other predictors constant; therefore, it is a measure of the relative risk. Since its introduction in 1972, the Cox proportional hazards (CPH) regression model has become the most widely used approach to quantifying conditional hazards [Cox 1972]. A general form of the CPH model for the hazard, h, cumulative dose, D, and attained age, t, is

$$h(t|D(t),Z(t)) = h_0(t) \, f(D(t); \beta) \, exp[\boldsymbol{\gamma}^T \boldsymbol{z}],$$

where h_0 is the baseline hazard, $\boldsymbol{Z}$ represents a vector of model covariates, model parameters β and $\boldsymbol{\gamma}$ are to be estimated, and $f(D(t); \beta)$ is the relative rate as a function of cumulative dose at attained age. This model is semi-parametric because the baseline hazard is an unspecified function, but a parametric form is assumed for the effect of predictors on the hazard. Several options for specifying a dose rate function are available; the most common is an exponential form, i.e., $(D(t); \beta) = exp(\beta D(t))$, which is sometimes referred to as a log-linear dose-response model. In this form, the CPH model is a simple additive model of the log of the hazard. Another common form is a linear response function, $f(D(t); \beta) = 1 + \beta D(t)$, where β is the excess relative rate per unit dose in the exposed individual relative to the unexposed. Validity of this model relies on a rather strong assumption that the hazards in the group of interest are proportional to the hazards in the referent group, and this proportionality is constant over time when $D(t)$ is constant. A significant interaction between $D(t)$ and t would be evidence against such proportional hazards. Additional statistical methods (e.g., stratification, fully parametric, or piecewise proportional models) may be necessary in the event of strong modification of the dose effect on the hazard over time [Allison 2010].

Examples of CPH regression methods in NIOSH risk assessment include dose-response modeling of

the relationships between lung cancer and exposures to radon [Hornung and Meinhardt 1987] and cadmium [Stayner et al. 1992a; Stayner et al. 1992b].

5.7.2.3 Conditional Logistic Regression

Case-control designs are typically analyzed with logistic regression, as previously described. The fitting of matched or stratified logistic regression models is sometimes referred to as conditional logistic regression [Breslow and Day 1980; Rothman et al. 2008]. When time-dependent predictors are present, nested case-control studies often rely on conditional logistic regression. For nested case-control studies with one case per matched set (i.e., 1:n matching), the form of the likelihood function for conditional logistic regression reduces to that of the CPH model for the continuous time scale. In both cases, the data are organized into risk sets (sometimes referred to as a matched set in conditional logistic regression), whereby a risk set is the collection of individuals at risk for the event at each time point in which a failure is observed. For example, a nested case-control study may specify a conditional logistic regression model that uses controls drawn from risk sets of individuals matched to cases on attained age. In this instance, the controls are selected by using incidence-density sampling methods [Beaumont et al. 1989; Richardson 2004]. Computational limitations may restrict full risk-set analyses (i.e., CPH model); therefore, a nested case-control study using conditional logistic regression is an appealing alternative to full cohort modeling.

5.7.2.4 Additional Considerations

In epidemiological studies, d_i is an exposure metric constructed from possibly complex employment histories, and identifying the optimum construct for d_i may itself be an important component of the modeling procedure (see Section 4.3.3.1). Moreover, predictors in the function $f(d_i, X_{1i}, X_{2i}, \cdots, X_{ci}; \boldsymbol{\theta})$ usually include age, gender, and other demographic variables and may confound or modify the effect of dose. Thus, the risk assessor must consider effects on estimates from the selected model or set of models

that are due to the exposure metric construct and other predictors (see Appendix B for discussion on possible study biases).

Attenuation of the dose-risk relationship at higher doses is a common observation in occupational epidemiologic studies [Stayner et al. 2003; Steenland et al. 2015]. This effect typically presents as a monotonically increasing slope at low exposure levels that diminishes or becomes negative at high exposure levels. Among possible explanations are a depletion of the susceptible population; healthy worker survivorship; a natural limit on the relative risk for diseases with a high background rate; measurement error; influence of unknown risk factors that may vary by the level of exposure adaptive responses; and biologic saturation. Regardless of cause, the risk assessor must consider the possible effects of high-dose attenuation when estimating responses at low doses, given that a "best fit" model may be a poorer choice for risk assessment. For example, a linear excess relative risk model that is best fit to the full range of exposures may underestimate the low-dose response as a result of risk attenuation (artifactual or otherwise) at high doses. Conversely, using a logarithmic transformation of exposure (i.e., a power model) may improve the model fit; however, this model is prone to overestimation of the response at low doses [Ginevan and Watkins 2010; Steenland and Deddens 2004; Steenland et al. 2011]. The potential for high-dose attenuation can be explored with categorical models, transformations of the exposure metric such as square-root or logarithmic, and the use of splines. However, the response in the low-dose region of the dose-response curve can widely vary between these approaches [Steenland and Deddens 2004; Steenland et al. 2011]. When selecting preferred models for risk assessment, the risk assessor must evaluate the low-dose behavior of the models with respect to the potential effects of attenuation. Modification or replacement of the best-fit model may be required in order to avoid unrealistic estimates of effects in the range of dose that is most meaningful to the protection of workers. For example, simple piecewise linear models that allow for different slopes

between high- and low-dose regions (e.g., a two-piece linear spline) may be appealing, given they account for high-dose attenuation but allow for interpretation of risk at low dose that is suitable for risk assessment purposes [Steenland and Deddens 2004; Steenland et al. 2011].

Dose-rate effects are of interest because they can have a substantial impact on low-dose extrapolation common in risk assessment. A dose-rate effect occurs when, for a given dose (e.g., the product of the chemical concentration and exposure duration), the dose-response relationship depends on the exposure intensity (e.g., the magnitude of the airborne chemical concentration). A positive dose-rate effect (i.e., higher exposure intensities having a greater effect) suggests that transient or peak exposures may have an important role in disease induction [Checkoway and Rice 1992; Esmen 1984; Rappaport 1991]. For example, peak exposure is obviously most important for evaluating acute toxicity. Peak exposure can also be the primary index when the agent is rapidly eliminated from the body or when nonlinear rates of biologic damage occur during periods of intense exposure [Esmen 1984; Rappaport 1991]. Nonlinearity may result from exposure-related responses that are reversible and/or have a threshold for the onset of biologic damage.

Dose-rate effects that act to attenuate the response at higher exposure intensities are sometimes referred to as protraction enhancement or inverse dose-rate effects. These effects were evident in studies of the dose-response association between lung cancer and radon exposures in underground uranium miners [Lubin et al. 1995b]. The actual mechanisms involved in the radon inverse dose-rate effects are unknown; however, some suggested plausible explanations are nonlinear cellular responses, such as a bystander effect (i.e., a dose effect observed in non-irradiated cells) at very low dose rates [Brenner et al. 2001], or physical differences in the particle size distribution of radon progeny at different airborne concentrations [Leonard 2007]. Addressing dose-rate effects is challenging in dose-response modeling. Interpretation will be largely dependent on the dose index used; however, given

the complex and largely unknown biology associated with these nonlinear effects, mechanistic data are likely insufficient to inform a modeling strategy. Nevertheless, complete understanding of the underlying cause-and-effect relationship may not be necessary if a dose-response relationship between the chosen exposure metric and the adverse effect can be quantified.

Finally, there has been considerable advancement in statistical methods used in dose-response modeling of epidemiologic data since the onset of personal computing. New techniques are emerging to model nonlinear dose-response functions and to address data and modeling uncertainty. Modeling strategies might draw on newly developed statistical methods to account for modeling uncertainty and data incompleteness or imperfection, such as the following:

- Unobserved variables that affect observed exposure-response associations (e.g., using latent-variables methods and finite mixture-distribution models) [Leisch 2004; Rosseel 2012]

- Missing data values (e.g., using multiple imputation and conditional expectation methods, data augmentation, and the expectation-maximization [EM] algorithm) [Schafer and Olsen 1998; Wei and Tanner 1990]

- Measurement errors and estimation errors in exposure and other explanatory variables (e.g., using regression calibration or Monte Carlo simulation techniques; see Appendix B) [Carroll et al. 2006]

- Model specification errors and model uncertainties (e.g., using model average methods; see Appendix B) [Buckland et al. 1997; Raftery et al. 1997]

- Inter-individual heterogeneity and variability (e.g., using mixed models accounting for random effects)

- Correlated or interdependent explanatory variables.

5.8 Alternative Analysis

The choice of modeling approach can markedly influence risk estimates. Moreover, limitations in available data often make the correct model specifications impossible to determine with confidence. When this occurs, risk assessors should candidly acknowledge the uncertainty in risk characterization. Limitations in available data often require scientific judgment in order to fill gaps in model specifications. Risk assessors identify and characterize these judgements by conducting additional analyses to test plausible alternative assumptions, examine the robustness of main analyses, and improve transparency in the risk assessment process. These alternative analyses comprise sensitivity and modeling uncertainty analyses. NIOSH defines sensitivity analysis as a study of the uncertainty in estimates from the mathematical model that can be apportioned to uncertainties in its inputs. In other words, it is a study of the robustness of the modeling outputs to uncertainty in model inputs. Model uncertainty addresses the possibility that the model itself—that is, the formula or algorithms for calculating outputs from inputs—is incorrect (see Appendix B). In alternative analyses, plausible alternative risk assessment strategies, defaults, and assumptions are quantitatively evaluated for their impact on risk estimates. As stated in *Science and Decisions* [NRC 2009],

> *"… analysis could be performed when risk estimates for alternative hypotheses that are sufficiently supported by evidence are reported. This approach would require development of a framework with criteria for judging when such an analysis should be performed. The goal is not to present the multitude of possible risk estimates exhaustively but to present a small number of plausible cases to provide the risk manager a context for understanding additional uncertainty contributed by considering assumptions other than the default."*

This means a targeted, hypothesis-driven strategy for conducting alternative analyses is preferred.

In large part, alternative analyses are examinations of risk estimates over a range of plausible values for uncertain data that are used in the risk assessment. Largely divergent estimates (or large uncertainties) suggest a high degree of model dependence, whereas reasonable agreement in findings suggests estimate robustness. Sensitivity analysis of a model that is known to correctly describe the causal relationship between inputs (including exposure histories) and outputs (including worker risks) is also useful for identifying how changes in factors change worker risks, which could then be targeted as priorities in risk management. Finally, alternative analyses can be a useful tool for model development and refinement [Frey and Patil 2002].

Alternative analysis should be part of the initial risk assessment plan. Analysis planning generally includes a description of any iterative methods intended for model development and refinement. Alternative analysis can be structured into the main analysis so that a variety of risk estimates is produced and the decision path to the final risk estimate is well supported and transparent. Risk assessors are cautioned against *post hoc* analyses as a substitution for planned alternative analyses. Nevertheless, there are instances when these analyses are appropriate or even expected. For example, subsequent analyses may occur in response to review comments.

It is not practical to list all alternative analyses possible in risk assessment; however, Table 5-4 lists some examples of analyses that appear most often in the literature. Some areas of typical analyses are discussed in subsequent sections.

5.8.1 Choice of Adverse Effect

There may be more than one adverse effect available for dose-response analysis. Decisions about which adverse effect to analyze rely on consideration of the site of the effect and its relevance to the human toxicity of concern, severity of effect, reversibility of effect, MoA, sensitivity of the test species (or human subpopulation), and consistency of

Table 5-4. Example scenarios for alternative analyses.

Source of Uncertainty	Research Question	Possible Sensitivity Analysis
Response variable	Are there alternative definitions of the adverse effect? If so, how do these definitions affect dose-response estimates?	Alternative models using different specifications of the response variable
	Is more than one adverse effect (not on the same causal pathway) associated with the hazardous exposure? If so, how do risks differ?	Alternative models using array of plausible responses
Explanatory variables	How does measurement error in the primary exposure affect risk estimates?	Alternative models using array of plausible estimates of exposure based on uncertainty
	Are there alternative exposure metrics? If so, how do risk estimates differ across metrics?	Alternative multiple models using array of exposure definitions
	If exposure is categorical, how does the choice of category cutpoints affect risk estimates?	Alternative models with varying exposure cutpoints
	Is there a potential for unmeasured confounding (e.g., smoking data unavailable in analysis of cancer) by one or more sources? Can these effects be estimated?	Alternative models using array of plausible estimates of the confounder
Model specification	How does model choice of dose-response function affect risk estimates?	Alternative models using array of plausible dose-response functions
	How does the choice of confounding control (e.g., stratification versus covariate control) affect risk estimates?	Alternative models using array of methods for confounding control
Animal to human risk extrapolation	How do assumptions on the animal-human relationship for metabolism, distribution, and toxicity affect risk estimates?	Alternative models using array of plausible assumptions

effects across sex/species (or population groups). When multiple adverse effects are possible, and there is no clear choice for a single health effect of interest, it is a general course to examine multiple endpoints and choose the most limiting as the critical effect. Sensitivity analyses should include plausible alternative adverse effects and/or multiple indicators of a common effect. For example, different respiratory endpoints could include different measures of lung function (e.g., forced expiratory volume in 1 second [FEV1], forced vital capacity [FVC], and the ratio of FEV1 to FVC), self-report of symptoms, and/or diagnosed respiratory effects. For cancer studies, a variety of tumor sites could be analyzed. In animal toxicology studies, adverse effects could include analysis of both cancer and non-cancer effects, a selection of tumor sites, and more. The rationale for selecting the adverse effects in the main analysis and the sensitivity analysis should be explained.

5.8.2 Model Uncertainty Analyses

When practical, it is generally preferable to use non-parametric causal graph modeling techniques or model averaging methods to address model uncertainty (see Appendix B). That said, a standard practice in NIOSH dose-response modeling involving model selection is to specify models of interest beforehand and then test the specification by examining alternative specifications. When different plausible assumptions lead to very different estimates, then multiple ranges of plausible estimates, with the key assumptions leading to each, can be more informative and useful than a single range. Alternative models should be plausible and parsimonious. It is preferred that the model uncertainty analysis approach used, including the suite of alternative models to be examined, be specified *a priori*; however, model output information has been used in *post hoc* specification of alternative models in some analyses. This is likely to occur when results from main models point to the need for further development or if new information is found during analysis or in review afterward.

The validity of modeling defaults should be examined in a sensitivity analysis when additional chemical-specific information is available that challenges those values. In addition, when there are alternative plausible assumptions on explanatory variables used in an analysis, it is reasonable to explore the impact of these assumptions in sensitivity analysis. Typical examples of key assumptions in epidemiologic studies include exposure lag times, homogenous dose-response among grouped outcomes (e.g., all cancers) and irreversible effects of chronic exposure, especially for non-cancer adverse effects. When examining alternative assumptions or default vales, it is important to use credible values that reflect the available data.

In some cases, the potential effects of measurement error or unmeasured confounding can be examined by sensitivity analysis [Chu et al. 2006; Greenland 1996; Groenwold et al. 2010]. For example, consider a study reporting a positive dose-response association between lung cancer and exposure to chemical X. Smoking data are unavailable. One could assume a range of plausible smoking behaviors (and their effects) that vary by degree of correlation with chemical X to examine the potential for residual confounding by smoking in main analyses. If a significant effect is not observed under plausible scenarios, then it is unlikely that smoking patterns explain the dose-response observed.

The complexity of these sensitivity analyses can vary widely, from a simple examination of a single binary variable to complex computer simulations for examining joint effects of multiple factors. Some examples of sensitivity analyses over this range are readily available in several highly cited articles [Frey and Patil 2002; Greenland 1996; Greenland et al. 2005; Lash and Fink 2003; Lin et al. 1998]. Regardless of analysis design, it should be evident that reasonableness hinges on the range and values examined; therefore, risk assessors must carefully consider the choice of plausible values.

In all modeling efforts, including sensitivity analyses of alternative models, NIOSH risk assessors must clearly describe the approach used in sufficient detail such that results can be replicated. Special attention should be given to providing a sound basis for any *post hoc* analyses conducted. Risk assessors should be aware that model specifications made using *post hoc* information, say, from a stepwise regression approach, can introduce bias from a lack of accounting for the informed choices made [Harrell 2015].

For example, consider a dose-response model that includes an exposure lag period accounting for disease latency. Risk estimates from models using a lag that is fixed *a priori* lack consideration of the uncertainty attributable to the lag choice. This uncertainty could be examined in a sensitivity analysis of models fit using alternative lags, although the main analysis still assumes a fixed lag. Alternatively, the lag could be estimated from the data (e.g., the lag that maximizes the likelihood) using methods fully accounting for the uncertainty in the lag [Richardson et al. 2011].

5.8.3 Extrapolation Methods

Model extrapolation occurs when inferences are made beyond the calibration or validation of the model [Frey and Patil 2002]. This can occur when model inputs used to predict risk are beyond the dataset used to develop the model. For example, the application of animal toxicologic data to assess human risk is a common extrapolation. When extrapolating risk from animals to humans, depending on the metabolism, distribution, and toxicity of the chemical, assessors may have a choice of extrapolation methods. In this case, it is reasonable to explore the impact of plausible extrapolation methods in the sensitivity analysis. An example of this can be found in the diacetyl risk assessment, in which the BW3/4 extrapolation method was compared to the EPA RGDR method for reactive gases/vapors [NIOSH 2016].

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6 Risk Characterization

Risk characterization is the third and final step in the NIOSH risk assessment process. It is the qualitative and, wherever possible, quantitative determination, including attendant uncertainties, of the probability of occurrence of known and potential adverse effects of an agent in a given organism, system, or population, under defined exposure conditions [IPCS 2004]. In environmental risk assessment, risk characterization describes the likelihood and severity of exposure-related adverse effects using information on the degree of potential exposure to the hazard within a population and its dose-response relationship with the adverse effect. Risk characterization in NIOSH risk assessments is restricted to health risks and focuses on the translation of information on the risk of workplace exposures into a basis for recommendations on limiting exposure. The process of extrapolating risks observed in animals in an experimental study to workers exposed over the course of their employment is an example of NIOSH risk characterization. In particular, NIOSH used the dose-response relationship observed in chronic inhalation studies in rats to predict lung cancer risks in humans from exposure to titanium dioxide to form the basis of recommended airborne exposure limits corresponding to increased risk in humans of about 10^{-3} over a working lifetime [NIOSH 2011]. That said, an underlying principle in NIOSH risk characterization is the preference for direct estimation of the risk in the affected working population, data permitting.

Risk characterization is the culmination of information gathered for the risk assessment in order to meet its intended purpose of informing risk management decisions. Risk characterization synthesizes and communicates the risk assessment science to a broad audience, primarily in NIOSH Criteria documents or Current Intelligence Bulletins

containing RELs, RML-CAs, and alternative authoritative recommendations, such as the NIOSH occupational exposure banding process (see Appendix C). Thus, to the maximum extent practicable, NIOSH risk assessors follow the guiding principles of transparency, clarity, consistency, and reasonableness in risk characterization as first described by the EPA [Fowle and Dearfield 2000] (see Table 6-1). Above all, NIOSH risk characterization serves to (1) characterize and communicate the risk basis for NIOSH recommendations, (2) describe the overall confidence in this basis, and (3) provide other information that may assist in decision-making on mitigating risk.

6.1 Risk Definitions Common to NIOSH Risk Assessment

As described in Section 1.0, occupational risk (in the context of this document) is simply the potential (probability) and severity of adverse health effects in workers from their exposure to workplace hazards. This definition is consistent with that offered by the WHO for risk assessment: risk is the probability of an adverse effect in an organism, system, or (sub)population caused under specified circumstances by exposure to an agent [IPCS 2004]. In most NIOSH assessments risk is portrayed as the incidence of the adverse effect (e.g., disease onset) occurring in subject(s) over a specified period, given that the subject(s) were disease free at the beginning of that period. Under this definition, it is a measure corresponding to an average individual-specific risk (i.e., cumulative incidence).

Quantitative risk assessment relies on estimates of excess risk per unit dose obtained from the dose-response assessment. In most settings, NIOSH broadly defines excess risk as the increased incidence or prevalence of the adverse effect above a

Table 6-1. Guiding principles of NIOSH risk characterization.[*]

Principle	Definition	Criteria for Risk Characterization
Transparency	Explicitness is key in the risk assessment process.	Use a risk analysis plan
		Describe assessment approach, assumptions, extrapolations, and use of models
		Describe plausible alternative assumptions
		Identify data gaps
		Distinguish science from policy
		Describe uncertainty
		Describe relative strength of assessment
		To the extent practical, use published information and make data available to other researchers
Clarity	The assessment itself is free from obscure language and is easy to understand.	Be brief and concise[†]
		Use plain English (avoid jargon)[†]
		Avoid technical terms
		Use simple tables, graphics, and equations
Consistency	The risk assessment conclusions harmonize with those in other risk assessments and with other NIOSH actions.	Follow NIOSH policies on technical writing and peer review
		Place assessment in context with similar risk assessments
Reasonableness	The risk assessment uses sound science and sensible judgment.	Use review by peers
		Use best available scientific information
		Use good judgment

[*]Adopted from the *EPA Risk Characterization Handbook* [Fowle and Dearfield 2000].

[†]Because complex analyses may require detailed explanations for understandability, brevity may be at odds with clarity.

control level or background that is attributable to the exposure. However, one can express excess risk in multiple ways, such as the following.

- **Added Risk:** The difference in risk (or in the probability of a response) between subjects exposed and those not exposed to a hazard. For example, it is the increment by which the probability of adverse effect exceeds background probability, calculated as $P(d)-P(0)$, where $P(d)$ is the probability of response at dose d and $P(0)$ is the probability of response at zero dose (i.e., background risk). By this definition, added risk is also attributable risk.

- **Extra Risk:** The measure of the proportional increase in risk of an adverse effect adjusted for the background incidence of the same effect. In other words, extra risk is the added risk relative to the proportion of the population not responding to the background risk, calculated as $[P(d)-P(0)]/[1-P(0)]$. For example, dose-response analyses of quantal toxicologic data often use a BMR of 10% extra risk, which generally coincides with the sensitivity of animal bioassays. Extra risk approaches added risk with decreasing

contributions from background. This value is most commonly used in risk assessment [Haber et al. 2018].

- **Relative Risk:** Typically reserved for human studies, the relative risk is the ratio of the risk in the exposed population to that observed in those unexposed (or exposed to a lesser degree). Relative risk is synonymous with risk ratio. One typically expresses or approximates relative risk as rate ratios, hazard ratios, odds ratios, SIRs, and SMRs. Some studies report excess relative risk (ERR), which is relative risk (or rate) - 1.

6.2 Risk Characterization Framework

The direct measurement of exposure-related risk in the region of interest is not practical in most cases, given that acceptable risks dwell below the observational level in most toxicologic and epidemiologic research. Instead, risk characterization relies on the extension of dose-response information by means of one of two general approaches to using dose-response data:

- **Extrapolation Approach (Risk-based):** Obtain quantitative estimates of low-dose risk by model-based extrapolation of the risk at doses below the observable data. For example, a linear non-threshold (LNT) model would support extrapolation by extending a line from the origin of the dose-response curve (i.e., the point of no exposure and no excess risk) to the human equivalent point of departure (PoD) in the observable range. This approach generally assumes an absence of a response threshold; therefore, one estimates the residual risk under one or more exposure scenarios using probabilistic means and target risk levels (e.g., the dose estimated to cause a lifetime excess risk of 1 in 10,000). Most NIOSH risk assessments have used this approach (Table 1-1).

- **Point of Departure/Uncertainty Factor (PoD/UF) Approach (Health-based):** Divide the estimated PoD by factors (see Section 6.3.4) that account for identified sources of uncertainty to arrive at an estimate of safe dose. Here the term *safe* implies an exposure level in which the associated risk is absent or negligible. The PoD/UF approach is appropriate for systemic toxicity, in which hemostasis and adaptive mechanisms must be overcome before an adverse effect can manifest (i.e., a threshold response). In this approach, risk is not explicitly quantified (i.e., the dose is implicitly risk-free); however, probabilistic means may be used to quantify risk from exposure above the safe level.

The concept that toxic effects have exposure-response thresholds is fundamental to toxicology [Aldridge 1986; Klaassen et al. 2013; Rhomberg et al. 2011; Rodricks et al. 2007]. As such, chemical risk assessments related to occupational diseases, excluding cancer, have mostly used a PoD/UF approach. In contrast, early risk assessments of cancer from ionizing radiation exposure recognized that induced mutagenesis exhibited effects that were proportional to dose and absent of a dose-response threshold [NRC 1956; Sievert and Failla 1959]. Continued research into low-dose radiation effects led to the now widely accepted notion of the LNT dose-response for radiocarcinogenesis [NRC 2006; UNSCEAR 2015]. Assuming the LNT dose-response was also applicable to chemical carcinogenesis, the EPA adopted LNT extrapolation in its risk assessments of carcinogens beginning in the late 1970s [Albert et al. 1977].

Refinements in risk assessment methods since the 1970s have placed more emphasis on MoA evaluations, given that some carcinogens exhibit nonlinearity at low doses. In fact, many of the factors contributing to nonlinearity in the dose-response curve at low doses for noncarcinogenic agents (e.g., clearance pathways, cellular defenses, and repair processes) may also support nonlinearity at low doses for some carcinogens. Conversely, some non-cancer endpoints may be better suited to risk extrapolation, with an allowance for a dose-response that appears LNT at low doses. In fact, reference points (e.g., occupational exposure limits, known as OELs) derived in PoD/UF assessments often reside at levels well below observation. Thus, quantitative

substantiation of the absence of harm is not possible. Large interindividual variability in the low-dose threshold of a noncancer endpoint (i.e., widely varying susceptibility) can result in a dose-response that approaches linearity at low dose.

Exceptions to the existing cancer/noncancer dichotomy have prompted calls for the harmonization of risk characterization methods [Barton et al. 1998; Crump 2011; Crump et al. 1997; NRC 2009; Rhomberg et al. 2011; White et al. 2009]. In response, some researchers have suggested a unified approach to risk characterization that is either extrapolation [NRC 2009; White et al. 2009] or PoD/UF-based [Crump 2011; Crump et al. 1997; Gaylor et al. 1999] or some combination of the two [Baird et al. 1996; Chen et al. 2007; Chiu and Slob 2015]. Still others have suggested a framework continuing to allow both approaches [Barton et al. 1998; Rhomberg et al. 2011]. For example, Rhomberg et al. [2011] suggested that the cancer/noncancer paradigm is valid in most cases, yet acknowledged that exceptions may occur; therefore, the choice between approaches should be based on the degree of compatibility of the methods on a case-by-case basis.

The approach used for risk characterization can have major impact on its findings; therefore, its selection is a critical decision point in NIOSH quantitative risk assessment. Unfortunately, risk assessors often face a difficult choice given sparse MoA data, uncertainty in the dose-response at very low doses, and other limitations (such as measurement error and interindividual variability in the dose-risk relationship). For example, uncertainty in the presence of a toxicity threshold is unavoidable; therefore, risk-extrapolation may predict residual risk when the true (but unknown) risk is zero, and the POD/UF approach may underestimate risk in the absence of a response threshold. Therefore, methods can appear interchangeable and a preference for one over the other can appear less than objective.

To avoid inconsistency among risk assessments and to ease transparency, NIOSH has developed a risk characterization framework that incorporates decision logic for systematically selecting a strategy for using extrapolation and PoD/UF approaches in conjunction with current science and NIOSH policy (Figure 6-1). NIOSH risk assessors are encouraged to follow this logic for planning and conducting risk characterization. NIOSH realizes that exceptions to the framework are possible, given nuances in every risk assessment; therefore, risk assessors are discouraged from forcing a fit. Above all, a WoE approach for evaluating and applying MoA must be the foundation of any method selected for risk characterization.

For example, linear extrapolation is the default approach for characterizing the general class of chemical carcinogens. However, it is plausible that a non-genotoxic or non-DNA-reactive carcinogen may have sufficient MoA information to support nonlinearity or even a practical response threshold at low doses. In this instance, it may be more appropriate to use nonlinear extrapolation (or even a PoD/UF approach) rather than LNT. In addition, data availability is an important factor for deciding on a risk characterization approach. For example, a PoD can be determined from a NOAEL or LOAEL even if data are insufficient to quantify the dose-response relationship. Furthermore, this framework is applicable only to NIOSH risk assessments; factors used in its development may be unrelated to, or may weigh differently on, risk characterization conducted elsewhere.

6.2.1 Carcinogens

NIOSH has separately published its policy on the classification and risk characterization of chemical carcinogens [NIOSH 2017]. The policy establishes the process for determining a Risk Management Limit for Carcinogens (RML-CA), which is an exposure limit for chemical carcinogens, preferably based on a target risk; this represents a starting place for controlling exposures.[§] In forming the policy, NIOSH surmised that for most chemical carcinogens there is no *known* safe level of exposure;

[§]Prior to the policy [NIOSH 2017], NIOSH expressed limits on carcinogens as RELs.
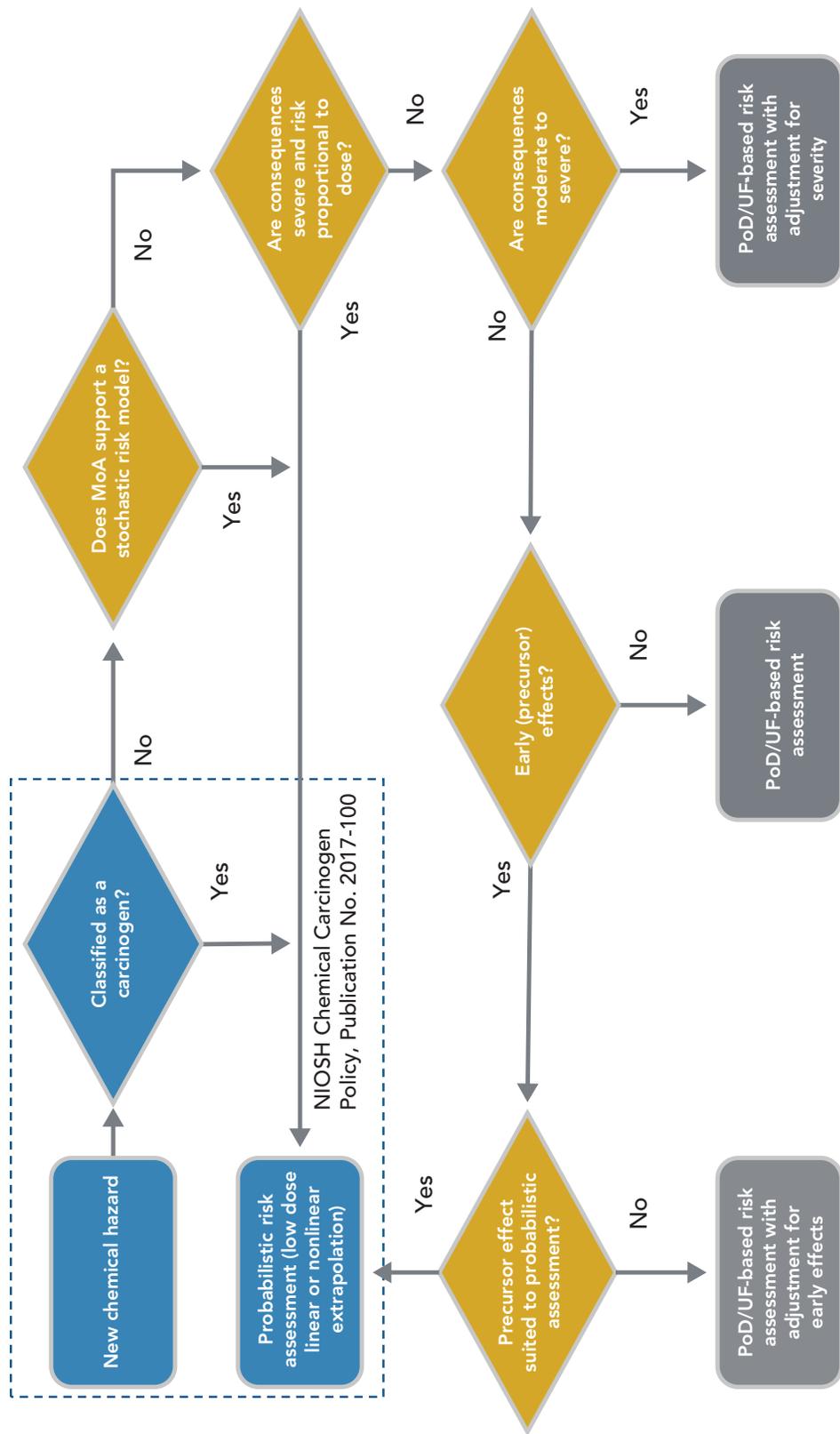
Figure 6-1. Framework for risk characterization of a potential chemical hazard. The steps enclosed by the dashed line are explicitly addressed in the NIOSH Chemical Carcinogen Policy [NIOSH 2017].

therefore, an extrapolation approach is generally required for characterizing carcinogenic risk at low doses. However, there is emerging scientific evidence that some carcinogens may have enough MoA information to allow conclusion that the dose-response is nonlinear at low doses. In these situations, simple linear extrapolation may substantially overestimate cancer risk. Thus, the policy allows for nonlinear extrapolation for chemical carcinogens with enough MoA evidence supporting nonlinear dose-response relationships at low doses.

As shown in Figure 6-1, the NIOSH Chemical Carcinogen Policy does not explicitly address using a PoD/UF approach for carcinogens with threshold responses [NIOSH 2017]. Instead, when data are adequate for modeling the dose-response, NIOSH prefers addressing potential threshold responses in carcinogens by using a sublinear, but non-threshold, mathematical model. Nevertheless, the policy does not expressly disallow other methods, including a PoD/UF approach, when data support an alternative approach.

NIOSH recognizes three general types of carcinogens, based on the weight of MoA evidence for carcinogenesis (adapted from Streffer et al. [2004]):

- **Genotoxic carcinogens consistent with LNT.** These include all mutagens and most direct-acting (DNA-reactive) genotoxic carcinogens, separated into two subgroups: (1) those in which the WoE supports LNT (e.g., ionizing radiation and vinyl chloride) and (2) those in which mechanisms are uncertain or generally unsupportive of a threshold at low doses (e.g., acrylamide, acrylonitrile). For the latter, LNT is used as a default health-protective measure. For example, acrylamide is clearly genotoxic at the chromosome level and is metabolized through the cytochrome P450 CYP2E1 pathway to a potentially reactive metabolite; therefore, it has generally been treated as a direct-acting mutagen [Streffer et al. 2004]. There is a growing body of evidence of nonlinearity in the slope of the response for acrylamide; however, underlying genotoxic mechanisms

are still poorly understood [Maier et al. 2012; Shipp et al. 2006]. Until the WoE is supportive of an alternative approach, risk characterization for acrylamide would likely utilize LNT extrapolation as a primary risk characterization approach.

- **Genotoxic carcinogens inconsistent with LNT.** These genotoxic carcinogens have adequate evidence of underlying mechanisms suggesting nonlinearity in the response at low doses. These carcinogens are primarily non-DNA-reactive substances in which the interaction is with proteins or protein systems at the chromosome level (e.g., aneugenicity or clastogenicity). These substances have a weak potency for direct mutagenicity relative to secondary mechanisms. This group also includes those substances in which carcinogenesis is associated with repetitive local tissue damage and cell proliferation (e.g., chloroform and vinyl acetate). For example, evidence suggests that chloroform is a substance in which carcinogenicity occurs through cytolethality and regenerative cell proliferation. As such, the EPA considers chloroform to be a probable human carcinogen that is not likely to cause cancer in humans without exposure conditions that cause cell death and regrowth (i.e., a practical threshold exists) [EPA 2001].

- **Non-genotoxic carcinogens that act solely through secondary mechanisms (e.g., endocrine modification, tumor promotion, immunosuppression, and inflammation).** These are non-genotoxic carcinogens that have widely varying MoA and tissue specificity but generally act through perturbation of cellular structures that can result in genomic instability. These processes tend to exhibit a threshold and be complex (i.e., requiring alteration of multiple pathways for cancer induction); therefore, non-genotoxic carcinogens are generally thought to be best described by sublinear or threshold responses at low doses [Hernández et al. 2009]. For example, TiO_2 is not directly genotoxic; however, a plausible mechanism for

carcinogenesis is a nonchemical interaction of inhaled particles with the cells in the lung, causing persistent inflammation and mediation by secondary genotoxic processes. This complex mechanism may explain the sublinear carcinogenic response observed at low doses, as described in the NIOSH risk assessment [NIOSH 2011].

Genotoxic carcinogens consistent with LNT extrapolation have been the most commonly observed in risk assessment. The other types of carcinogens form a much smaller subset that either are non-genotoxic or have genotoxicity that is limited compared to other mechanisms (e.g., cell proliferation); therefore, nonlinear extrapolation may be preferred in risk characterization. For example, Bevan and Harrison [2017] identified a small number of genotoxic substances that have recommended health-based OELs, founded on MoA evidence of practical thresholds (Table 6-2). Similarly, Hernández et al. [2009] estimated that non-genotoxic carcinogens comprise about 12% of substances listed in IARC Groups 1, 2A, and 2B.

Figure 6-2 shows a logic diagram for choosing an extrapolation approach. This diagram is a slight modification of concepts adopted by the Scientific Committee on Occupational Exposure Limits (SCOEL) [Bolt and Huici-Montagud 2008]. As in the risk characterization framework, this diagram is a generalization that may not accurately depict the specific situation encountered in an actual risk assessment. Mechanisms of carcinogenesis are highly complex and vary widely among chemicals; therefore, exceptions to this diagram are inevitable. Above all, the risk assessor must thoroughly evaluate the evidence of nonlinearity to determine the appropriate course. When the information is equivocal, it may be informative to characterize risks by using multiple approaches.

Methods for carcinogenic risk characterization have varied within the risk assessment community. In assessments supporting regulation in the United States, most have estimated the carcinogenic risk at low doses by using LNT, with the exception

of the EPA's assessment of chloroform [EPA 2001]. In contrast, others have used a PoD/UF approach to derive safe levels for non-genotoxic and some genotoxic carcinogens [Bevan and Harrison 2017; Kirman et al. 2016; Pecquet et al. 2018; Seeley et al. 2001; Thompson et al. 2016]. For example, Pecquet et al. [2018] determined a no-significant-risk level for tetrabromobisphenol A (TBBPA), using a PoD/UF approach, based in part on MoA data supportive of a threshold in carcinogenic response. NIOSH carcinogenic risk assessments have exclusively used extrapolation by mathematical models to quantify risks at low doses. Of agents assessed, only TiO_2 demonstrated a nonlinear response, which NIOSH accounted for in the dose-response modeling. The lack of evidence of a threshold at low doses for any carcinogen does not prove the absence of an exposure level at which effects are negligible or zero. Similarly, strong evidence of a threshold may still be insufficient to estimate a numerical value for exposure that is considered risk-free, given statistical limitations, interindividual variability, and analysis uncertainty [Crump 2011]. Thus, PoD/UF methods and threshold-based mathematical models are absent in previous NIOSH risk assessments of occupational carcinogens, but they may be viable alternatives to linear and nonlinear extrapolation in future assessments.

NIOSH generally assumes carcinogenic effects from exposures are cumulative and irreversible; therefore, NIOSH estimates lifetime carcinogenic risk. In most cases, nontrivial background cancer risk is expected in a population (i.e., due to factors other than the occupational exposure); therefore, a competing risk model is preferred. NIOSH typically estimates risks for an array of exposure scenarios and uses a target risk level to recommend a limit on exposure to carcinogens. The target risk level for cancer, as stated in the NIOSH Chemical Carcinogen Policy [NIOSH 2017], is one excess cancer case in 10,000 workers exposed in a 45-year working lifetime (i.e., 10^{-4} risk). In the absence of opposing evidence, NIOSH assumes that the attributable risk persists up to the age at death. The age at death used in NIOSH risk assessments has varied over
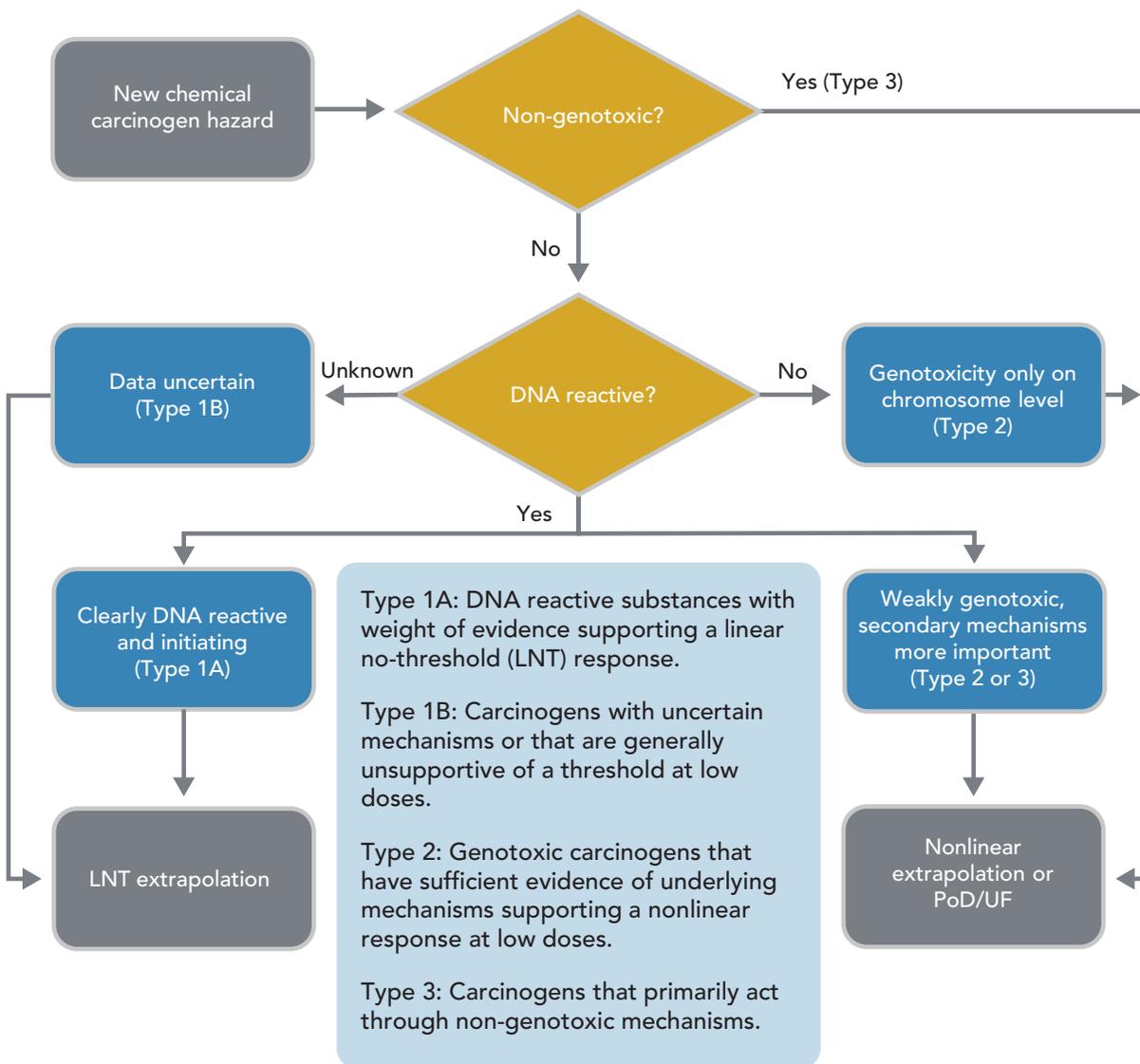
Figure 6-2. Risk characterization of chemical carcinogens using WoE (adapted from Bolt and Huici-Montagaud [2008]).

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Table 6-2. Examples of genotoxic carcinogens with evidence against LNT response (adapted from Bevan and Harrison [2017]).

Substance	Primary Cancers	Mechanism and OEL Supporting Document*
Cadmium (and cadmium compounds)	Lung, kidney, and prostate	Indirect genotoxic MoA characterized by different and non–mutually exclusive mechanisms, including oxidative DNA damage, induction of oxidative stress, inhibition of DNA repair, and deregulation of cell proliferation [SCOEL 2010]
Formaldehyde	Nasopharynx	Genotoxic amplification (at low exposures) by chronic proliferative processes caused by the cytotoxic effects [SCOEL 2008]
Nickel compounds (water soluble)	Lung, nasal cavity, and paranasal sinuses	Indirect genotoxic MoA characterized by interference with DNA repair systems and DNA methylation patterns, which lead to clastogenicity and an increased genomic instability [SCOEL 2011]

*All are OEL recommendations made by SCOEL, which advises the European Commission.

Abbreviations: DNA, deoxyribonucleic acid; MoA, mode of action; OEL, occupational exposure limit; SCOEL, Scientific Committee on Occupational Exposure Limits.

time; however, recent assessments have projected risks to age 85 years, based on the availability of stable population rates (see Section 6.3.2).

Recent examples of NIOSH risk assessments include occupational carcinogens such as hexavalent chromium [NIOSH 2013a] and titanium dioxide [NIOSH 2011]. The MoA evidence for these materials differs, supporting low-dose linear response modeling for hexavalent chromium and nonlinear dose-response modeling for titanium dioxide. Risk characterization for these carcinogens follows the framework discussed, except NIOSH used a target risk level of 10^{-3} as the risk basis for RELs of both materials, according to the policy in place at the time.

6.2.2 Non-Carcinogens

The NIOSH risk characterization framework generally considers a nonmalignant disease to have a toxicity threshold unless there is evidence to the contrary. Therefore, the PoD/UF approach is preferred

for many noncancer endpoints. However, there can be exceptions to this rule. For illustration, consider the case of a chemical in which endogenous levels are near threshold levels (e.g., endogenous estrogens and androgens); thus, very low exogenous exposure may appear to have a non-threshold effect for some endpoints. Similarly, several endocrine-disrupting chemicals have been determined to be hormonally active at extremely low doses, making an assumption of a threshold for these chemicals untenable [Futran Fuhrman et al. 2015]. Finally, the response may vary so widely within the exposed population that it is best modeled with the assumption that there is no practical threshold.

Ideally, adequate MoA information would be available to support the decision on risk characterization without equivocation; however, in practice this is rarely the case. Instead, a decision against PoD/UF usually follows careful consideration of the nature and severity of the adverse effect, its observed association with the agent of interest, and the

heterogeneity of the population at risk. For example, occupational pneumoconioses (e.g., silicosis, asbestosis, and coal worker's pneumoconiosis) are severe apical health effects in terms of disability, survivorship, and risk persistence. As such, lung diseases are among the most common noncancer endpoints investigated in NIOSH quantitative risk assessments, and most have invoked an extrapolation approach to risk characterization when quantitative dose-response data were available [NIOSH 2016; Park et al. 2002; Park and Gilbert 2018]. An illustration is NIOSH's recently completed assessment of the risks from diacetyl exposure in the workplace [NIOSH 2016]. Diacetyl, and some related chemicals such as 2,3-pentanedione, is used in the manufacture of food flavorings. Obliterative bronchiolitis is a rare, fibroproliferative, incurable, potentially fatal disease of the small airways of the lung linked to diacetyl exposure in some epidemiologic studies of flavoring workers. However, data from these studies were insufficient for direct quantification of the excess risk of obliterative bronchiolitis (i.e., the apical adverse effect) from diacetyl exposure. Instead, NIOSH assessed data on changes in lung function in exposed workers believed to precede obliterative bronchiolitis, given that respiratory obstruction is a common presentation of the disease. Pulmonary dysfunction observed among exposed diacetyl workers appeared irreversible. The natural history of obliterative bronchiolitis is highly variable, and there is little information on its pathology related to initiation by toxic exposure; therefore, a practical threshold for diacetyl toxicity is not known (although this is perhaps present on an individual basis). As with cancer risk assessments, NIOSH estimated airborne concentrations corresponding to a variety of target risk levels, while assuming a 45-year working lifetime. In this case, the risk-based REL was derived by using a target excess risk of one case in 1000 [NIOSH 2016].

6.3 Using Risk Assessment as a Basis for RELs or RML-CAs

NIOSH risk assessments provide the quantitative scientific basis for NIOSH recommendations,

including RELs for noncancer agents and RML-CAs for carcinogens. Although the ultimate decision on a REL or RML-CA is a risk management decision and outside the scope of this report, it is important for risk assessors to understand the issues that contribute to those decisions in order to provide well-supported advice for the risk manager.

Although NIOSH may develop RELs to protect against occupational exposures of any duration—and, in fact, the bases of many RELs are adverse effects due to acute exposures—RELs (and RML-CAs) based on quantitative risk assessment usually focus on the prevention of chronic illnesses from longer duration exposures to lower levels of hazardous agents. In other words, NIOSH has typically conducted quantitative risk assessments for serious, chronic adverse effects such as cancer, pneumoconioses, neurological disorders, reproductive outcomes, and other exposure-related cumulative health effects. In part, this is in response to the NIOSH mandate in the Occupational Safety and Health Act of 1970 [29 USC 15] (as amended through January 1, 2004) to

> *". . . develop criteria dealing with toxic materials and harmful physical agents and substances which will describe exposure levels that are safe for various periods of employment, including but not limited to the exposure levels at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience" [29 USC 669 (a) (3)].*

It also is in response to the codified directive to OSHA to ensure:

> *". . . on the basis of the best available evidence, that no employee will suffer material impairment of health or functional capacity even if such employee has regular exposure to the hazard . . . for the period of his working life" [29 USC 655 (b) (5)].*

Because data describing health effects to workers exposed over a working lifetime are rare, risks are
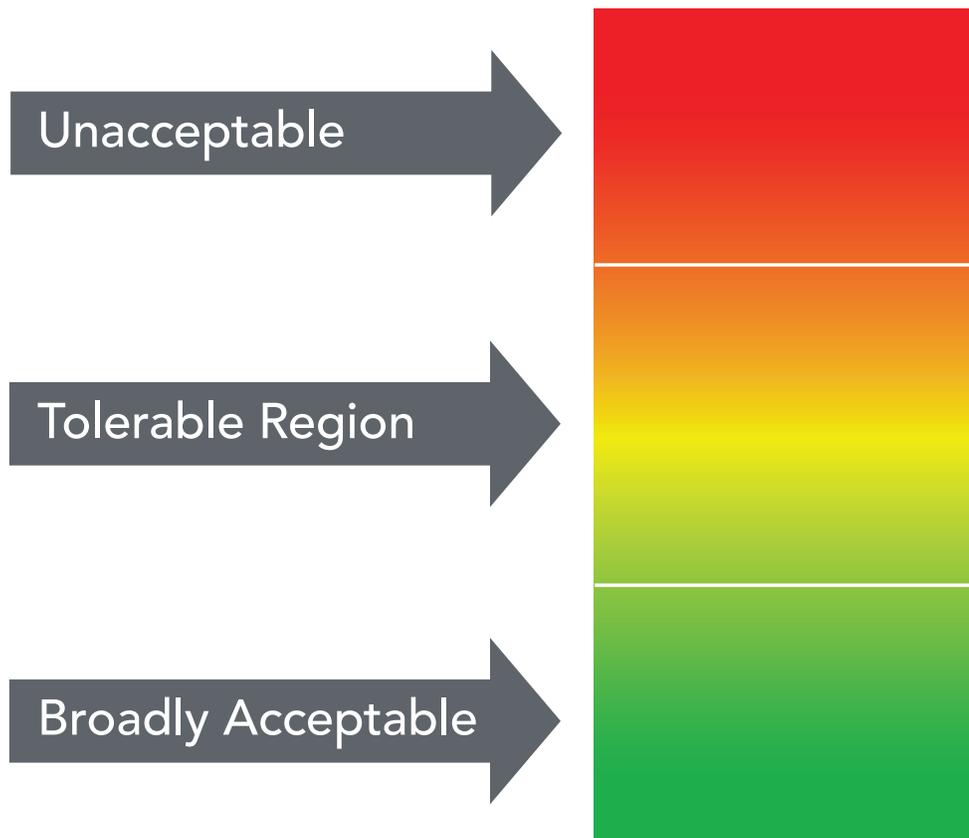
Figure 6-3. Framework for the tolerability of risk (adapted from HSE [2001]).

estimated according to the guidelines described in this document. This includes integration of hazard identification and dose-response analysis. In applying these procedures, some assumptions and defaults are generally necessary to synthesize the information into risk estimates. The following sections describe the targets, defaults, and assumptions typically used in the NIOSH risk assessment process to provide an integrated picture of risks to workers.

6.3.1 Target Risk Levels

As previously discussed, model-based extrapolation in quantitative risk assessment assumes that any level of exposure to the agent, no matter how

small, has an associated health risk (i.e., no response threshold). Complete removal of the agent, albeit ideally preferred, is not practical in many industrial settings; therefore, a continuum of exposure-related risk must be managed. This continuum represents a gradient of occupational health risks, ranging from high levels that are clearly unacceptable to extremely low levels in which efforts further reducing exposure result in a negligible reduction in risk [Hunter and Fewtrell 2001]¶. The upper and lower boundaries of this gradient define the *unacceptable*

¶The concept of *acceptable risk* implies a risk level that everyone will find acceptable. This notion is difficult to reconcile and rarely achievable given individual perceptions of risk. Nevertheless, many situations require a baseline for residual risk that is generally accepted [Hunter and Fewtrell 2001].

and *broadly acceptable* regions, respectively (Figure 6-3). Between these regions lies the *tolerable* region, which is characterized by a general willingness to tolerate risks in the region, given assurances that the risk is managed to an extent that is reasonable and practical [HSE 2001; Tchiehe and Gauthier 2017]. Here the terms *reasonable* and *practical* refer to using risk mitigation strategies that are proportionate to the magnitude of the risk involved [Jones-Lee and Aven 2011]. This is a commonly used risk-reduction principle sometimes referred to as the As Low as Reasonably Practicable (ALARP) principle. Historically, NIOSH used this principle in its recommendations for exposure to carcinogens. Instead of a numerical REL, the carcinogen was given a "Ca" designation, which indicated that employers should implement substitution, engineering, work practice, and personal protective equipment strategies to reduce exposures as low as feasible [NIOSH 2007; NIOSH 2017].

When there is residual risk, quantitative risk assessment will often estimate an array of risk levels for risk management purposes. For example, NIOSH uses quantitative risk assessment to estimate chemical exposures corresponding to risks ranging from one excess cancer case in 100 workers, or 10^{-2}, to 10^{-6}, assuming continuous workday exposure over a 45-year working lifetime [NIOSH 2017]. NIOSH typically estimates the airborne concentration corresponding to a hazard at a single level within the tolerable region, designated as a target risk level. Multiple methods and principles are available for establishing risk acceptance criteria, and the adopted methods and principles will undoubtedly influence the choice of criteria [Vanem 2012]. Moreover, risk acceptance is often founded more on sociopolitical significance rather than science. Thus, risk acceptance (or tolerance) criteria are more likely to be unique to the situation at hand rather than be pre-defined [Rodrigues et al. 2014; Vanem 2012]. Nevertheless, some examples of target risk levels are available for major hazards [HSE 2001; NIOSH 2017]. For example, the British Health and Safety Executive (HSE) established that the tolerable region for work-related fatality

lies between an individual risk of 10^{-3} and 10^{-6} per annum [HSE 2001]. The HSE recommends using ALARP to manage risks within the tolerable range but toward the lower bound.

As another example, NIOSH has established a target risk level for non-threshold carcinogens of one excess case per 10,000 workers continuously exposed over a 45-year working lifetime [NIOSH 2017].** Prior to this policy, assessments have used a target risk of 10^{-3} lifetime catastrophic disease risk of cancer and non-malignant outcomes from occupational exposures [NIOSH 2011; NIOSH 2013a; NIOSH 2016]. As in the HSE, NIOSH target risk values have established reasonable starting places for risk mitigation strategies for chemical carcinogen exposure where residual risk is assumed. Figure 6-4 depicts a simple framework for determining target risk levels based on the relationship between the severity of the adverse effect and its probability of occurrence. For example, given a relationship between a catastrophic adverse effect and some hazardous exposure (e.g., leukemia from benzene exposure), the chart reveals a target level for a remote excess working-lifetime risk that lies between 10^{-3} and 10^{-5}.

The setting of target risk levels is a fundamental component of risk management; therefore, actions are primarily the responsibility of the decision-makers and not the risk assessor. As such, a detailed discussion on the various principles in play for determining these levels is beyond the scope of this report, although discussion is available in several published reports [Aven 2016; HSE 2001; Rodrigues et al. 2014; Tchiehe and Gauthier 2017; Vanem 2012]. Finally, it should be clear that health risk is among many aspects considered to derive a target risk level, given that risk tolerance can depend on the combination of individual, societal, economic, and environmental impacts. Although these other factors may be considered by employers in managing risks, NIOSH quantitative risk

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**When practical, NIOSH bases its risk estimates on the 95% lower confidence limit of the central estimate [NIOSH 2017].

assessment focuses solely on characterizing health risks according to its mandate; therefore, criteria for establishing NIOSH target risk levels to date have not considered costs and benefits [NIOSH 2017].

6.3.2 Working Lifetime and Persistent Risk

NIOSH currently defines a working lifetime of exposure to a chemical as an 8-hour shift, 5 days a week, 50 weeks a year, for 45 years of exposure (i.e., from age 20 to age 65). This represents the maximum amount of exposure anticipated for a worker. However, because the adverse effects of interest are typically chronic effects, the distribution of exposure over a week (or a year) does not usually affect the risk estimate. Therefore, whether a worker is exposed 4 days a week for 10 hours a day or 5 days a week for 8 hours a day does not usually make a difference in the final working lifetime risk estimate or the resulting 8-hour time-weighted average (TWA) REL or RML-CA. For chronic, cumulative hazards, NIOSH typically assumes that if the exposure duration was less than working lifetime, then risks would be lower than estimated. For risks that do not accumulate across a lifetime (for example, short-duration hazards or adverse effects with an exposure threshold), the 45-year working lifetime is not a relevant measure.

The exposure-related biologic insult may be irreversible for some toxicants, and the initiated toxicity pathway may progress throughout life after exposure has ended. For example, significant excess solid-cancer risk persists in the Japanese atomic-bomb survivors 60 years after their acute exposure to ionizing radiation [Ozasa et al. 2012]. To account for risk persistence, NIOSH projects the added or extra risk used in developing the OEL to end of life. Recent NIOSH risk assessments assume a terminal age of 85 years. This value takes into account the limitations on data describing background rates of chronic illnesses at older ages. Examples of NIOSH risk assessments projecting persistent lifetime excess risk are available for diacetyl exposure and pulmonary impairment

[NIOSH 2016]; nonmalignant respiratory disease and silica exposure [Park et al. 2002]; as well as lung cancer and exposure to asbestos [Stayner et al. 1997], hexavalent chromium [NIOSH 2013a; Park et al. 2004], silica [Rice et al. 2001], and cadmium [Stayner et al. 1992a; Stayner et al. 1992b].

6.3.3 Competing Risks in Projecting Lifetime Risk

Many exposure-related chronic illnesses present very late in life and have multiple risk factors other than occupational exposure to the agent of interest. Therefore, risk assessments include an accounting of competing risks of mortality and background disease rates when projecting lifetime risks. Among many available approaches, competing risk models have most commonly been accomplished by using actuarial methods (life-table analysis) that account for age-specific death rates and background disease incidence, under the common assumption that the relative risk, conditional on exposure, is independent of age [Cornfield 1957; Goldberg et al. 1956; NRC 1988; Zdeb 1977]. A life table provides a systematic record of the rate at which members of a hypothetical cohort (say, 10,000 workers who are 'risk free' at beginning of working age) withdraw during follow-up by either death or the illness, based on reference mortality and incidence rates that vary by age.

The life table predicts risks within age intervals that are conditional on survival to each age interval for intervals specified over the working lifetime period. The summation of the conditional probabilities of diagnoses (or death) in each interval using baseline disease rates provides an estimate of the lifetime risk in the unexposed (R_0). Likewise, summing the conditional probabilities calculated from rates adjusted for exposure provides a corresponding risk measure, R_x, in the exposed. These measures can then be used to determine the excess lifetime risk [e.g., lifetime additive risk = $(R_x - R_0)$ or lifetime extra risk = $(R_x - R_0)/(1 - R_0)$]. NIOSH uses these excess lifetime risks to determine the health basis for the REL or RML-CA.
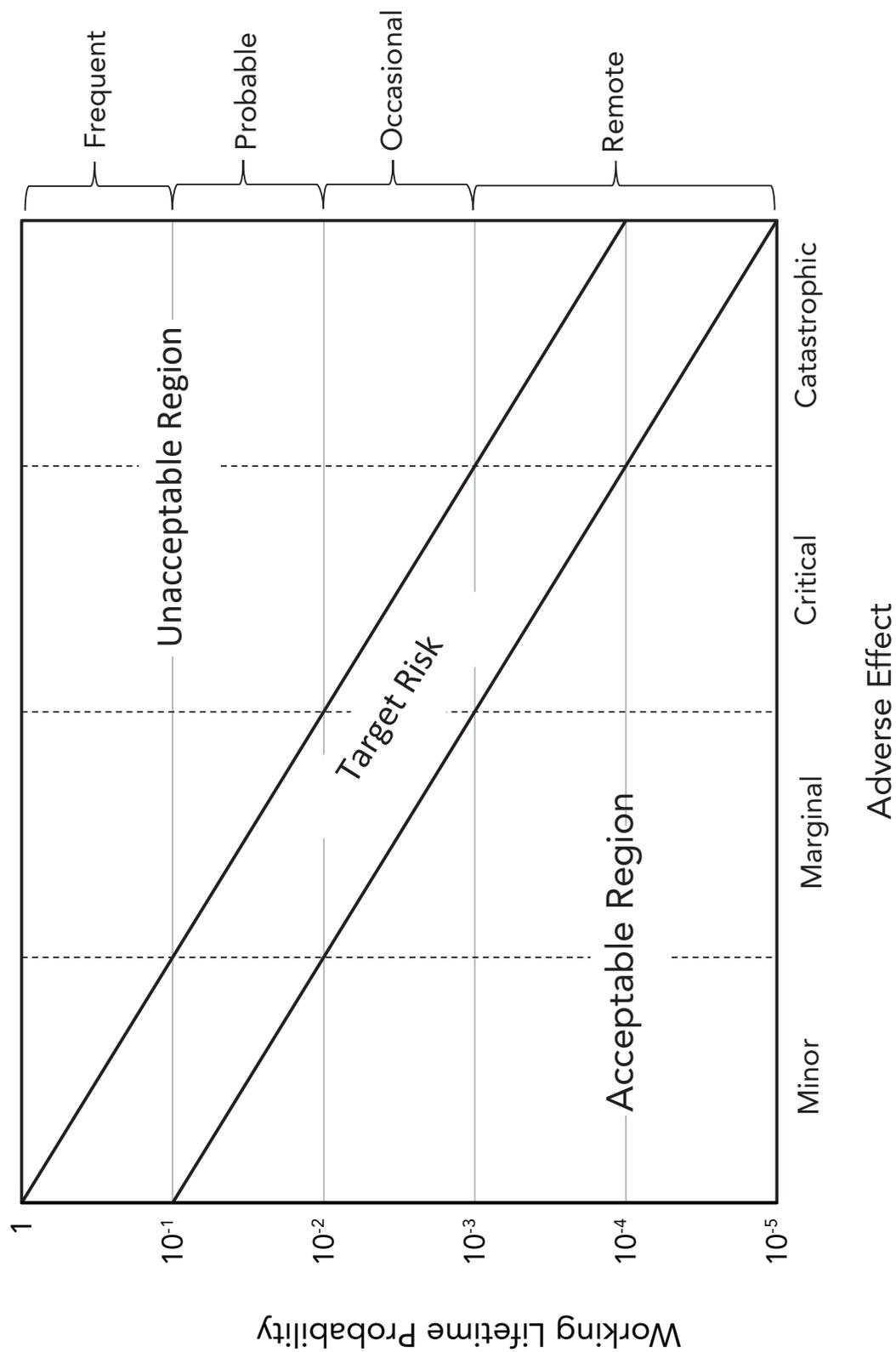
Figure 6-4. Example of target risk based on adverse-effect severity and probability of occurrence.

6.3.4 Application of Uncertainty Factors (UFs)

To address uncertainty in non-cancer adverse effects, NIOSH risk assessors have typically adjusted estimates by using UFs. The adjusted estimate represents a "safe" level of exposure, which is essentially the human equivalent PoD (e.g., NOAEL, LOAEL, or BMDL) for the critical effect, divided by a series of UFs. For example, NIOSH based its REL for occupational exposure to glycol ether on a PoD (i.e., NOAEL and LOAEL) and application of UFs [NIOSH 1991]. In this assessment, NIOSH determined a NOAEL from animal studies of reproductive and developmental toxicity (the most sensitive adverse effect), which was then adjusted to account for the animal inhalation rate, body weight, and fraction of the day exposed and converted to an equivalent exposure for humans. NIOSH applied two UFs: a factor of 10 for interspecies variability and another factor of 10 for intraspecies variability (i.e., a divisor of 100). Examples of NIOSH applications of UFs are in risk assessments for carbon nanotubes and nanofibers [NIOSH 2013b] and toluene diisocyanate [Daniels 2018].

In general, UFs are conservative approximations meant to protect workers against adverse effects from exposure to an agent by increasing the margin of safety [Dankovic et al. 2015]. UFs are preferred when data are insufficient to derive substance-specific or analogue-specific adjustment factors known as chemical-specific adjustment factors (CSAFs). For example, chemical-specific data on interspecies differences or human variability in toxicokinetics or toxicodynamics are useful for deriving CSAFs [Meek et al. 2002; WHO 2005]. The scientific bases for UFs have been previously described [Dourson et al. 1996; Dourson and Stara 1983; Naumann and Weideman 1995].

6.3.4.1 Animal-to-Human Uncertainty Factor (UF$_A$)

UF$_A$ accounts for the uncertainty in extrapolating laboratory animal data to average healthy workers. When using laboratory animal data to assess the risks to workers, the risk assessor applies UF$_A$ to address the differences in sensitivity between animals and humans, generally assuming that humans are more sensitive to substances than animals. It may be that humans are equally or less sensitive than animals for specific exposures, but unless this is demonstrated with experimental data, a UF$_A$ should be applied.

The UF$_A$ comprises separate factors that account for toxicokinetic and toxicodynamic differences between species. Toxicokinetic differences arise because of differences in body size and metabolic rate. One way to address the toxicokinetic difference is by using an allometric scaling approach. In the absence of cross-species data on chemical-specific metabolism, allometric scaling assumes that physiological parameters and basal metabolic rate are drivers of toxicological effects. As discussed previously in Section 5.6.3.1, risk assessors calculate an allometric scaling factor, or species-specific dosimetric adjustment factor (DAF), by

$$DAF = (BW_a/BW_h)^{0.25}$$

for body weights (BW) of the animal (a) and human (h). Thus, different allometric scaling factors correspond to different species. Allometric scaling is generally applicable in most cases, except when the substances cause toxicity only at the portal of entry, such as can occur for the skin, respiratory tract, or gastrointestinal tract (i.e., not dependent on absorption or metabolic rate), and for the acute lethal effects [EPA 2006b]. Allometric adjustments replace the toxicokinetic portion of the UF$_A$.

Other replacements for the toxicokinetic portion of the UF$_A$ are (1) a DAF that is applied when information is available, describing a more proximal (and presumably more relevant) dose; and (2) compound-related metabolic information that is available on humans and animals in the form of physiologically based pharmacokinetic (PBPK) modeling, provided that the model is validated and applicable to the specific agent.

Different agencies apply different defaults for UF_A. For instance, WHO applies a sub-factor of 4 for toxicokinetics and 2.5 for toxicodynamics [WHO 1994; WHO 2005], whereas the EPA typically uses equal sub-factors of $\sqrt{10}$, or approximately 3 [EPA 2002]. The UF_A of 1–10 should be applied based on available data on toxicokinetics and toxicodynamics. NIOSH risk assessors use the WHO values of 4 for toxicokinetics and 2.5 for toxicodynamics.

6.3.4.2 Interindividual (Human) Variability Uncertainty Factor (UF$_H$)

UF_H accounts for response heterogeneity among the members of worker populations at risk. Like UF_A, UF_H is a result of toxicokinetic and toxicodynamic differences between the average and the most sensitive worker population. NIOSH considers the overall UF_H to be a factor of 10, with the subfactors for toxicodynamics and toxicokinetics each accounting for $\sqrt{10}$ of the variability (often rounded to 3). UF_H is modifiable with chemical-specific toxicokinetic information. For example, one typically adjusts the UF_H to a value of 3 for chemicals that cause respiratory irritation upon inhalation, because irritation is unrelated to metabolism (i.e., a toxicokinetic sub-factor reduced to unity).

Some organizations consider a working population to be less heterogeneous than the general population and use a UF_H of less than 10. For example, the European Chemicals Agency recommends a UF_H of 5 to address interindividual variability in workers and a UF_H of 10 for the general population when establishing derived no-effect levels [ECHA 2008]. However, working populations might also include sensitive individuals such as asthmatics, pregnant women, older workers, and others who may be more susceptible. Therefore, NIOSH typically uses a factor of 10 for the overall UF_H unless chemical-specific information is available to the contrary. Risk assessors must fully explain the rationale for using a factor other than 10.

6.3.4.3 LOAEL-to-NOAEL Uncertainty Factor (UF$_L$)

UF_L accounts for the uncertainty in extrapolating from LOAELs to NOAELs. When the starting point for the exposure level of concern calculation is a LOAEL, an additional UF_L between 3 (for minimal toxicological severity, such as fatty liver) and 10 (for severe effects, such as hepatic necrosis) should be applied to estimate a dose where no adverse effect would occur [Dourson et al. 1996; Dourson and Stara 1983; Naumann and Weideman 1995].

When the starting point is a NOAEL or a BMDL, no additional UF_L is required and the UF_L value should be unity (equal to one). However, risk assessors might apply a UF >1 in certain cases, such as (1) with a poor-quality study in which very few animals and doses are used or (2) when very severe effects occur at the slightly higher next dose, which is the LOAEL.

6.3.4.4 Shorter-Term-to-Longer-Term Uncertainty Factor (UF$_S$)

Ideally, data from long-term (chronic) animal toxicology studies are available to estimate lifetime excess risks of chronic disease in humans. In practice, however, data may be limited to those from shorter-than-lifetime bioassays (e.g., two years for mice and rats). In these cases, a shorter-term to longer-term uncertainty factor (UF_S) may be necessary to adjust for differences in duration of exposure. The UF_S (also known as a subchronic to chronic factor) assumes that an effect observed at subchronic exposure levels will be seen at lower levels of chronic exposure [Dourson et al. 1996]. An exception would be evidence that risk (i.e., the incidence or severity) is unrelated to exposure duration or fully characterized by the shorter-term study. For example, some effects like sensory irritation of the skin/respiratory tract and effects caused by a reactive metabolite may not increase with duration. In these circumstances, additional correction using UF_S >1 may be unwarranted [Dankovic et al. 2015].

Typically, a factor from 3 to 10 is applied for subchronic to chronic extrapolation, with allowance for factor modifications using chemical-specific experimental data. Extrapolation to chronic exposure from subacute (28-day) or acute (<24-hour)

studies is not generally recommended, although prediction of chronic effects from short-term studies is an active area of research.

6.3.4.5 Database Inadequacy (Incomplete Data) Uncertainty Factor (UF_D)

UF_D accounts for the inability of the available toxicity database to address all likely adverse effects in humans. Evaluation of the total toxicological database should address whether the derived exposure level of concern is protective enough against all potential adverse outcomes for the substance.

Risk assessors apply a UF_D (1 to 10) in the absence of sufficient data. For example, if preliminary data indicate some evidence of neurotoxic/immunotoxic effects, then the absence of a detailed study evaluating neurotoxicity and immunotoxicity may be grounds for a $UF_D > 1$. The use of this factor is infrequent; NIOSH has not applied UF_D in any of its risk assessments to date.

6.3.4.6 The Composite Uncertainty Factor (UF_C)

Generally, the product of individual UFs yields the overall composite factor (UF_C). Typically, when a UF of $\sqrt{10}$ is used, convention says that $\sqrt{10}$ is approximately 3.16, which is rounded to 3. However, when multiplying UFs of 3 and 3, the result used should be $\sqrt{10}$ and not 9. A risk estimate incorporating UF_S of all five types should trigger concern over database sufficiency and appropriateness of risk characterization. Multiplying several factors could result in an overly conservative UF_C value because the set of factors may not be independent [Calabrese and Gilbert 1993]. In general, the UF_C value is usually less than 300. A UF_C value greater than 300 should be questioned. In rare instances, the UF_C may be greater than 300 but should not exceed 3,000 when providing a basis for a REL.

6.3.4.7 Alternatives to Uncertainty Factors

In most situations, the use of standardized UF_S provides an appropriately conservative margin of safety against underestimation of the health risk from a hazardous agent. Occasionally, however, the product of several default factors can lead to incongruous overestimation of risk. Alternatives to applying UF_S are available. Most recently, probabilistic methods for adjusting for uncertainty have been proposed [Chiu et al. 2018; Simon et al. 2016; Swartout et al. 1998]. Stemming from its review of the process used by the EPA to derive toxicity values for IRIS, the National Research Council (NRC) of the National Academies recommended a Bayesian hierarchical modeling approach as a means to modernize the use of UF_S in risk assessment [NRC 2014]. In general, the NRC proposed accounting for overall uncertainty by representing UF_C as a Bayesian lognormal prior distribution to combine with a lognormal distribution representing uncertainty in the PoD. Simon et al. [2016] refined the NRC method to allow for simultaneous adjustment of individual factors rather than adjusting the UF_C. Simon et al. [2016] provided several examples that cover most situations risk assessors may encounter. Overall, probabilistic methods tend to reduce the size of uncertainty adjustment compared to the standard UF approach, with the magnitude of the difference depending on the number of UF_S and complexity of the assessment.

6.3.5 Characterizing Multiple Outcomes

Many hazardous agents are associated with more than one adverse effect. In general, NIOSH risk assessment focuses on hazards with the greatest consequences affecting the largest group of workers and that have sufficient data to quantify occupational risk. Candidate endpoints arise from hazard identification and dose-response analyses that provide valid estimates of the utmost unmitigated risk associated with the hazard (e.g., per unit exposure to a hazardous chemical agent). Even so, a clear distinction in risk among some important stressor-outcome relationships may be lacking; therefore, risk characterization can involve comparisons of multiple endpoints that inform risk management

decisions on which stressor-outcome relationship best supports the intended purpose of the risk assessment and end-user needs. NIOSH typically accomplishes this by drawing on the scientific judgement of a multidisciplinary team and through input from stakeholders. In basing a REL, NIOSH generally seeks health endpoints that are: 1) most relevant to risk management goals (i.e., the risk assessment purpose), 2) most specific to the stressor(s) of interest (e.g., the chemical exposure); and 3) most sensitive to apical adverse effects of interest.

As a NIOSH example, recall that the apical health effect for diacetyl exposure is obliterative bronchiolitis (OB). Human data on the association between diacetyl exposure and OB were limited; therefore, NIOSH examined the associations between diacetyl exposure and several different markers of human lung function, assuming each may indicate future onset of OB. NIOSH presented all analyses in its published risk assessment [NIOSH 2016]. For the REL, NIOSH relied primarily on the human data showing significant exposure-associated reductions in the FEV_1/FVC ratio and percent predicted FEV_1 used in multiple outcome definitions. Rather than selecting data from a single outcome, NIOSH considered the range of estimated risk across outcome definitions and determined the REL accordingly.

When multiple outcomes arise from apparently independent mechanistic origins, it may be appropriate to consider aggregating risk to base the REL. To illustrate, Park [2018] estimated excess lifetime risk from occupational exposure to metalworking fluids by combining data from published studies reporting excess cancer mortality from one of 12 tumor sites. Park [2018] reported attributable cancer deaths (assuming 10 years lag) of 0.48 per thousand person-years at age 60 after 40 years of work from 1.0 mg/m³-year exposure to metalworking fluids, with excess cancer in five sites (larynx, esophagus, brain, female breast, and uterine cervix) contributing over 90% of the aggregate risk. Mortality from cancer of the larynx was the largest contributor, resulting in nearly 40% of the attributable risk.

6.4 Special Considerations When Developing a Short-Term Exposure Limit (STEL)

In some cases, the available health effects data may elicit a concern for short-term exposure limits (STELs). For example, if peak exposures increase CNS symptoms, asthma attacks, or other acute-onset health effects, the data may be informative for developing STELs. Risk assessors should consider evidence of peak exposures causing specific health effects when evaluating the need for a STEL. For example, if the 8-hour TWA REL is 1 ppm and peak exposures at 25 ppm cause nasal and eye irritation, it is prudent to consider those data in developing a STEL. A NIOSH STEL is typically defined as a 15-minute TWA exposure that should not be exceeded at any time during a workday. Without a STEL, in this case, workers exposed for 15 minutes to 32 ppm and zero exposure for the remainder of the day are compliant with the REL (i.e., 32 ppm × 0.25 hour/8 hours = 1 ppm) but still receive exposures related to adverse effects. If there is good dose-response data at levels of concern for acute adverse effects, it is possible to conduct a quantitative risk assessment to support a numerical STEL. More often, quantitative data on the effects of peak exposures are not available. In those cases, a concern for acute exposures may be supported by data or a plausible concern may exist based on MoA, analogous chemicals, or other considerations.

A simple way of testing this is to multiply the TWA REL or RML-CA by 32 (8 hours/workday ÷ 0.25 hours). One should estimate a STEL if the resulting exposure would elicit concern for short-term effects. For example, consider a REL based on quantitative risk assessment of 10 ppm. If adverse effects are evident for the same chemical at short-term exposure to 320 ppm, then estimate a STEL. If there are quantitative data showing health effects from short-term exposures (for example, respiratory irritation after exposure to 200 ppm for 10 minutes), that should be used to inform or establish the STEL. Alternatively, if there is a concern for short-term exposures but no data for quantitative assess-

ment, then a STEL may be determined based on industrial hygiene practice (for example, STEL = 5 × 8-hour TWA REL). This provides a maximum peak exposure that serves to both reduce peak exposures and reduce overall TWA exposure.

6.5 Addressing Uncertainty and Variability

NIOSH risk estimates and RELs are most useful when combined with a reasonable understanding of the magnitude of the attendant uncertainty and variability. In risk assessment, the term variability describes the spread of true values of an estimated quantity (e.g., risk per unit dose) within the specified target population, given heterogeneity in the response in that population. Once a population is identified, variability is an irreducible property of the true distribution of the quantity in that population [Nayak and Kundu 2001]. In contrast, "uncertainty" refers to a lack of precise knowledge on the true dose-risk relationship between the agent and the adverse effect caused by the randomness (e.g., sampling error) and incompleteness of data. For example, imperfect knowledge of the relationships among components of a system being modeled (i.e., model uncertainty) is usually a dominant source of estimate uncertainty. Uncertainty and variability are unavoidable consequences in human health risk assessment. Moreover, uncertainty is pervasive in each assessment step; therefore, summed overall, the propagated cumulative uncertainty can become quite large.

Appendix B provides details on common sources of uncertainty in NIOSH risk assessments. Briefly, in addition to model misspecification errors described above, some of the major sources are:

- Measurement error in exposure estimation (how much of the agent workers were exposed to in the study)
- The impact of exposure timing and limits on observation (e.g., projecting working lifetime risk from less than lifetime exposure)

- Errors in health effects ascertainment (how accurate the health effects data are and whether and how the health effects are related to the exposure of interest)
- Extrapolation from animal models or specific populations of workers to the general worker population (i.e., external validity)
- Influence of mixed exposures and other risk factors in the study population.

Risk assessors should evaluate these sources, to the extent practicable, and describe the approach taken to reduce their effects. The description should include an assessment of potential biases in risk estimates resulting from these sources. At a minimum, risk characterization should include an assessment of the analyst's confidence in the estimate (e.g., confidence intervals or qualitative ratings), estimates of the magnitude and direction of potential biases, and areas of future research that will reduce uncertainty and improve risk estimates.

In some situations, NIOSH may conduct detailed quantitative analyses to present a reasonable range of plausible risks at a given dose. Typically, these analyses employ complex statistical methods, such as second-order distributions and two-dimensional Monte Carlo simulation techniques [Burmaster and Wilson 1996; Kelly and Campbell 2000; Nayak and Kundu 2001], to account for variability and uncertainty in data. However, these analyses often require considerable judgment on the distribution of values around true but unknown parameters used to derive risk estimates. There are several statistical techniques for dealing with data imperfections (e.g., latent variable analyses for unobserved variables, missing data imputation methods, and ensemble methods for countering model specification errors); however, there is no perfect remedy for data incompleteness other than obtaining more and better data. Nevertheless, the continued evolution of personal computing constantly improves the field of quantitative analyses; therefore, keeping current with uncertainty analysis methods is paramount to safeguarding best practices in NIOSH risk assessment.

Appropriately communicating uncertainty and variability to risk managers and other stakeholders is challenging [Schulte 2003]. In fact, conveying these concepts can actually act to reduce public confidence in risk assessment findings [Johnson and Slovic 1995]. For example, Johnson and Slovic [1995] examined whether discussing uncertainty in risk assessments reduces the perceptions of risk and increases respect for the risk-assessing institution. They concluded from their findings that

- People are generally unfamiliar with uncertainty in science and in risk assessment.

- People are more likely to recognize uncertainty when simply presented, although graphics had mixed results in communicating uncertainty.

- People's views appear less influenced by uncertainty manipulations than by attitudes toward risk, government, and authority.

- Discussion of uncertainty in risk estimates appears to signal honesty (i.e., improved transparency).

- Discussion of uncertainty in risk estimates may also signal incompetence for some.

- The magnitude of estimated risk levels may affect views of expert knowledge (i.e., confidence in estimates diminishes with decreasing risk levels).

- Although risk communication is beyond the scope of this document, risk characterization requires its consideration. Therefore, NIOSH risk assessors consider the findings above in developing and implementing a strategy for treating and portraying uncertainty and variability.

To reiterate, uncertainty is a property of the risk assessment, whereas variability is a property of the population at risk. For a risk assessment to be informative on decision-making, it is imperative that risk characterization adequately describes the uncertainty and variability in its risk estimates. Whether describing them quantitatively or qualitatively, risk assessors should maintain a distinction between variability and uncertainty to improve risk

communication [NRC 1994]. As practical, risk assessors should describe variability as the extent of actual risks to individuals within the affected population above and below the reference point. Risk assessors should also identify vulnerable populations and specific conditions of vulnerability. This information allows for tailoring risk management strategies to specific conditions or subgroups within a population to account for differences in susceptibility. For example, ionizing radiation exposures are limited in pregnant workers compared to other workers, to protect the more vulnerable fetus. For uncertainty, risk assessors should provide enough information to aid risk managers in judging the robustness or believability of the reference point in decision-making.

Risk characterization should include a discussion on analysis limitations and known or suspected biases. Any discussion on bias, known or otherwise, should clearly describe its source, magnitude, and direction. For example, a common practice is to err on the side of worker protection to create a margin of safety, given incomplete information. For example, selecting a PoD based on the lower 95% confidence limit on the BMD rather than the central estimate is a "protective" practice common to benchmark dose-response modeling. Risk assessors should describe steps to increase the safety margin in enough detail to inform risk managers. Conversely, it may be appropriate to describe a tendency to underestimate risk when comparing workers to other populations without accounting for selection differences (i.e., a bias from healthy worker effects [HWEs]). In summary, risk assessors should make clear to risk managers any tendency to underestimate or overestimate true risks as a part of risk characterization.

6.6 More on NIOSH RELs and RML-CAs

Adequate control of causative agents of occupational illness and disability is fundamental to the health and safety of the American workforce. To that end, NIOSH synthesizes relevant information on occupational hazards to formulate hazard

mitigation strategies, including publication of RELs and RML-CAs as discussed in this report. Preferably, these OELs stem from a quantitative assessment of the occupational risk associated with the hazard, although analytic and technical feasibility is also considered. For example, the NIOSH REL for occupational diacetyl inhalation exposure is 5 ppb and was based primarily on the findings from a quantitative risk assessment using epidemiologic data [NIOSH 2016]. From these data, NIOSH predicted that the risk of significant lung impairment was in the range of a target risk of 10^{-3} excess lifetime risk for workers exposed to 5 ppb over a 45-year working lifetime.

The occupational risk to workers from exposure to a hazard is best characterized by a probability distribution rather than a point estimate, given unavoidable variability in exposure and response. In addition, NIOSH typically integrates both risk science and health policy, such as the feasibility of analytic methods, into deriving RELs and RML-CAs, which introduces further uncertainty (Figure 6-5). OEL development often involves considerable uncertainty and generous professional judgment. Therefore, NIOSH recommends against treating RELs and RML-CAs as "bright lines" between safe and unsafe exposure for all workers. Instead, these OELs are better described as levels on the dose-risk continuum prompting evaluation and control (i.e., risk management).

NIOSH recommends that in adopting a risk management strategy, decision-makers consider its recommendations on exposure levels, including their basis and the magnitude of occupational risk and attendant uncertainties, as well as competing risks from substitution or hazard controls. Fundamental to this strategy, employers should consider continued improvement in controls until exposure levels below the REL or RML-CA are confidently attained. However, actual exposure situations can vary widely; therefore, information used by risk managers in assessing the reasonableness and/or practicality of implementing hazard control strategies can differ by situation. Thus, underlying any

risk management strategy is an assurance that risk mitigation efforts are not disproportionate to the magnitude of the risk involved. In the example case of diacetyl, it is important to understand that the REL protects against an excess risk that is relatively low compared to that faced in everyday life. At these low risk levels, situations can arise in which further reduction can be extremely difficult if not impractical to achieve.

The REL and RML-CA are recommendations based on the best available science; neither places enforceable or binding limits on exposure. Application is solely at the discretion of the end-user. However, NIOSH derives RELs and RML-CAs to be protective for most workers and in most occupational settings; therefore, in the absence of situational risk management, the recommended level can serve as an appropriate control level. As such, many industries have voluntarily adopted NIOSH RELs and RML-CAs as a part of their risk management practices. Moreover, regulatory agencies have considered available NIOSH recommendations and supporting information when setting enforceable limits on exposure to some agents (e.g., coal dust and silica). NIOSH RELs and RML-CAs are determined exclusively for worker protection; therefore, these recommendations are not directly applicable to the protection of consumers or members of the public. However, the science behind these recommendations is likely to be useful for deriving similar public health standards.

In forming its recommendations on exposure, NIOSH identifies uses and manufacturing operations for the given hazard to recognize effective control strategies and describe engineering achievability. NIOSH may also indicate when the nature of job activities presents a challenge to meeting the REL or RML-CA. NIOSH has considered feasibility when setting RELs; however, engineering achievability is no longer considered in setting RML-CAs [NIOSH 2017]. Although routine attainment of exposures below the NIOSH-recommended limits may not occur in all work settings initially, it does represent a reasonable objective that employers can work to achieve through modification of work or

the introduction or improvement of engineering controls. In this way, the REL and RML-CA encourage technological improvements to limit exposures. For some operations, additional protective measures such as administrative controls and personal protective equipment may be necessary to achieve risk mitigation goals.

Finally, NIOSH RELs and RML-CAs facilitate hazard communication, as NIOSH urges employers to disseminate related information to workers and customers and encourages manufacturers to convey this information to downstream users. NIOSH also requests that professional and trade associations and labor organizations inform their members about workplace hazards. This communication should include a description of NIOSH recommendations and the risk associated with exposures at controlled levels. In communicating these risks, it may be helpful to include context, such as risks from other sources encountered in the human experience.
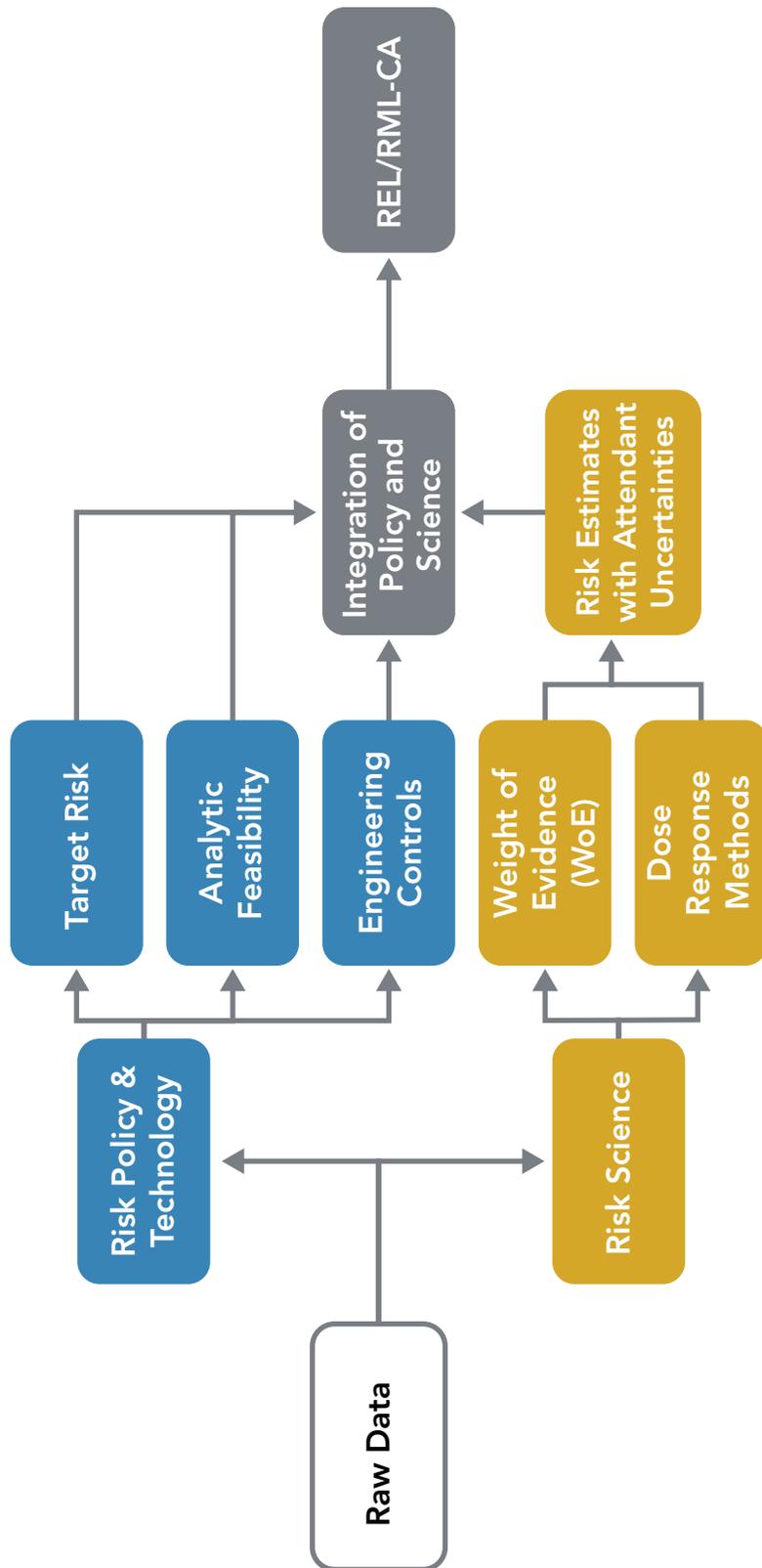
Figure 6-5. NIOSH process for deriving a Recommended Exposure Limit (REL) or Risk Management Limit for Carcinogens (RML–CA). The gold boxes indicate occupational risk assessment. The blue boxes indicate other inputs to risk management decisions. The grey box indicates risk management decisions. Each step in the process induces uncertainty and variability in the selection of the exposure limit. Adapted from Waters et al. [2015].

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7 Conclusions

Integrating all the pieces of a risk assessment requires careful attention to the purpose of the risk assessment. It is important to thoroughly investigate the robustness of key assumptions used and provide transparency for both the main analysis and analyses of alternative modeling strategies and defaults. If innovative or unusual modeling or analytical strategies are used, it is critical that these be presented in a clear manner, drawing the reader's attention to departures from past practice. Ideally, novel or unusual methods would be published in the peer-reviewed scientific literature before they are used to develop NIOSH policies expressed in a NIOSH numbered publication, although this may not always be possible. One set of questions from the risk assessment plan at the beginning of this document deserves attention:

- How will risks be expressed and, if in quantitative analysis, what are the target risk levels used?

- What is the support for those decisions, and are there reasonable alternatives?

- How would using any reasonable alternatives influence the conclusions of the risk assessment?

Among completed NIOSH quantitative risk assessments, most have examined the risk from occupational carcinogens. The risk assessment assumptions regarding cumulative exposure and chronic expression of cancer are well supported and have numerous NIOSH precedents. Non-cancer risk assessments, on the other hand, have diverse health impacts and exposure profiles. These require thoughtful discussion of the assumptions in the dose-response analysis. Although harmonization of cancer and non-cancer risk assessments is a desirable goal, it is critical to keep in mind the differences in MoA and natural history of disease when using the risk assessment information to derive a REL for non-carcinogens.

NIOSH risk assessors must take care that the resulting risk assessments are a rational and clear portrayal of the available information. Risk assessors must thoroughly and accurately characterize uncertainties in risks caused by any level of exposure to the agent. If the risks at low doses cannot be determined with high accuracy, precision, and confidence from current information, then the uncertainty characterization step of the risk assessment process should clearly reveal this fact. Results of uncertainty and sensitivity analyses should be presented that highlight the value of specific additional pieces of scientific information in resolving or reducing current scientific uncertainties about low-dose risks. When data are uncertain, risk assessors tend to make protective assumptions; however, they should be mindful that an overestimation of risk could lead to unnecessary actions that can be detrimental to occupational health. Thus, the potential for bias in either direction must be clearly identified to inform risk managers. Above all, the risk assessment must balance the protection of workers with the strength of the data to ensure that all the NIOSH recommendations are supported by sound science.

Risk assessment science is continuously evolving, given a wide array of uncharacterized hazards and a large community of risk assessment practitioners in academia, industry, and government. NIOSH risk assessments, although purposed for worker protection, can have relevance outside of the workplace. Similarly, activities intended for characterizing risks in other populations can also inform worker risks. Given these conditions, overlapping activities are anticipated among multiple agencies or risk assessment programs. For example, a recent review by the United States Government Accountability Office (GAO) examined overlap among federal and state chemical toxicity assessment programs [GAO

2014]. The GAO findings suggest there was ample room for improvement in risk assessment through shared resources. Thus, routine exchange between NIOSH and the risk assessment community, both home and abroad, is paramount to ensuring best practices are followed, including improved efficiency and effectiveness by reducing duplication of effort. For these reasons, NIOSH maintains active collaborations within the risk assessment community and coordinates its risk assessment activities with stakeholders and the public.

Methods currently under development provide additional, powerful tools to assess risks to workers on the basis of limited data. Validation of these approaches is a critical need. Occupational risk assessment should move forward and embrace new methodologies, but with caution and deliberate evaluation of new techniques and approaches. Appendix C shows examples of methods currently under development. As these methods are validated and demonstrate their utility for occupational risk assessment, it is anticipated that NIOSH risk assessors will adopt them.

8 References

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APPENDIX A

Glossary

Terms	Definitions
absolute risk	The probability that a disease-free individual will develop a given disease over a specified time, given age and other risk factors, and in the presence of competing risk.
adverse effect	Changes in the morphology, physiology, growth, development, reproduction, or life span of an organism, system, or population that result in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences.
adverse outcome pathway	A conceptual construct describing a sequential chain of causally linked events at different levels of biological organization leading to an adverse effect.
aerodynamic equivalent diameter	The diameter of a sphere with a standard density of one gram per cubic centimeter ($1 \ g/cm^3$), having the same terminal velocity when settling under gravity as the particle under consideration.
agent	A chemical, biological, or physical entity that contacts a target.
allometric scaling	Adjustment of data to allow for differences and making comparisons between species having dissimilar characteristics (e.g., in size, shape, and metabolism). Allometric scaling commonly refers to the relationship between metabolic rate and body size among mammalian species (e.g., the metabolic scaling between a laboratory rat and human).
aneuploidy	A change in chromosome number from the species' normal diploid or haploid number, other than an exact multiple of the haploid number (polyploidy).
associative causation	Causal discovery based on relative risk or similar statistical measures of association. It is used in most papers that assert causal relationships and is often interpreted and applied by using Hill's guidelines or similar qualitative weight-of-evidence criteria.
apical effect	An observable outcome in a whole organism, such as a clinical sign or pathologic state, that is indicative of a disease state resulting from exposure to a toxicant.

Terms	Definitions
asymptotic relative efficiency	The relative quality of two estimators as the sample size increases to infinity. This concept is best described with an example. Suppose an unknown parameter, θ, is to be estimated by using data $y_1, y_2, \ldots, y_n$ and that two estimators, $\hat{\theta}_i = \theta_i (y_1, y_2, \ldots, y_n)$; $i = 1, 2$, are to be compared. If the quality of each estimator is inversely proportional to its mean squared error $\text{MSE}(\hat{\theta}_i) = E\{(\hat{\theta}_i - \theta)^2\}$, then the MSE efficiency of $\hat{\theta}_1$ relative to that of $\hat{\theta}_2$ is $\text{MSE}(\hat{\theta}_2)/\text{MSE}(\hat{\theta}_1)$ which is a function of the sample size η and the asymptotic relative efficiency is given by $\lim_{\eta \to \infty}\{\text{MSE}(\hat{\theta}_2)/\text{MSE}(\hat{\theta}_1)\}$. The asymptotic relative efficiency from performing conditional logistic regression on sampled risk-sets, with m controls matched to each case, relative to the full risk-sets is $m/(m+1)$.
attributable risk	The risk that is regarded as being caused by exposure to the agent; also referred to as risk difference, excess risk, or added risk.
benchmark dose (BMD)	A dose or concentration that produces a predetermined change in the response rate of an adverse effect, relative to the background response rate of the effect.
benchmark dose lower limit (BMDL)	The statistical lower confidence limit on the benchmark dose, which is typically used as the point of departure in dose-response analyses. The BMDL is usually set at the one-sided 95% lower confidence limit on the BMD.
benchmark response (BMR)	A predetermined change in the response rate of an adverse effect relative to the background response rate of the effect.
biomarker	Indicator of changes or events in biological systems. Biomarkers of exposure refer to cellular, biochemical, analytical, or molecular measures that are obtained from biological media such as tissues, cells, or fluids and are indicative of exposure to an agent.
chronic exposure	A continuous or intermittent long-term contact between an agent and a target. (Other terms such as "long-term exposure" and "protracted exposure" are also used.)
clastogenicity	The disruption or breakage of chromosomes, leading to sections of the chromosome being deleted, added, or rearranged.
confounding	The mixing of the effects from the exposure of interest with the effects from other factor(s) on the risk of the adverse effect.
cytotoxicity	The harmful effects to cell structure or function that ultimately lead to cell death.
dichotomous	Dividing or branching into two parts. For example, dichotomous data can have only two values.

Terms	Definitions
dose	Total amount of an agent administered to, taken up by, or absorbed by an organism, system, or (sub)population. Dose is also described as the amount of agent that enters a target after crossing an exposure surface. The term is often used interchangeably with exposure.
dose-response	The relationship between the amount of an agent administered to, taken up by, or absorbed by an organism, system, or population and the change developed in that organism, system, or population in reaction to the agent. In NIOSH risk assessment, the dose-response is typically described as the conditional probability of the adverse effect in exposed workers at different levels of occupational exposure to the agent, given assumed levels for other direct causes of the adverse effect. Related term: exposure-response.
dose-response assessment	The analysis of dose-response association between exposure to the agent and adverse effects. Ideally, the products of the dose-response assessment are unbiased estimates of the risk per unit dose that are used in risk characterization.
dosimetry	The determination or measurement of the amount of an agent administered to, taken up by, or absorbed by an organism, system, or (sub) population (see dose).
ecological fallacy	An erroneous inference that may occur because an association observed between variables on an aggregate level does not necessarily represent or reflect the association at an individual level; a causal relationship that exists on a group level or among groups may not exist among the group's individuals.
etiology	The science of origins, causes, or causality of diseases or conditions.
excess relative risk	A measure of association equivalent to the relative risk -1.
exposure	Contact between an agent and a target. Contact takes place at an exposure surface over an exposure period.
exposure assessment	The process of estimating or measuring the magnitude, frequency, and duration of exposure to an agent, along with the number and characteristics of the population exposed. Ideally, it describes the sources, pathways, routes, and uncertainties in the assessment. The use of this term is reserved for the description of risk assessments by the National Research Council [NRC 1983].

Terms	Definitions
exposure duration	The length of time over which continuous or intermittent contacts occur between an agent and a target.
exposure event	The occurrence of continuous contact between an agent and a target.
exposure frequency	The number of exposure events in an exposure duration.
exposure index	A measured or estimated quantity of exposure or dose.
exposure model	A conceptual or mathematical representation of the exposure process.
exposure pathway	The course an agent takes from the source to the target.
exposure route	The way in which an agent enters a target after contact (e.g., by ingestion, inhalation, or dermal absorption).
exposure scenarios	A combination of facts, assumptions, and inferences that define a discrete situation where potential exposures may occur. These may include source, exposed population, period of exposure, microenvironment(s), and activities. Scenarios are often created to aid exposure assessors in estimating exposure.
exposure-response	The relationship between the intensity, frequency, or duration of exposure to a stressor or agent and the intensity, frequency, or duration of the subsequent biological response of the organism. Given varied use of the terms *dose* and *exposure* in many settings, exposure-response and dose-response are often used interchangeably. Related terms: concentration-response, dose-response.
external validity	The degree to which study findings may apply, be generalized, or be transported to populations or groups that did not participate in the study.
extra risk	The measure of the proportional increase in risk of an adverse effect, adjusted for the background incidence of the same effect.
genotoxicity	A general description of all types of DNA or chromosome damage, such as breaks, adducts, mutations, aberrations, and aneuploidy.
hazard	A condition or a set of circumstances that present a potential for harm (e.g., occupational illness or injury) to an organism, system, or population.
hazard function	In survival analyses, the rate of failure at an instant in time, t, given that the individual survives until t.

Terms	Definitions
hazard identification	Identification of the type and nature of adverse effects that an agent has an inherent capacity to cause in an organism, system, or population. Hazard identification is the initial stage of the risk assessment. The products of hazard identification are definitions of the agent and outcome used in dose-response analysis.
hazard ratio	In survival analysis, the hazard function (rate) of one individual (e.g., the exposed), divided by that of another individual (e.g., the unexposed), typically holding all other predictors constant (i.e., a rate ratio).
hematotoxicity	Adverse changes to the blood, caused by exposure to an agent.
human equivalent concentration (HEC)	The human concentration (for inhalation exposure) or dose (for other routes of exposure) of an agent that is believed to induce the same magnitude of toxic effect as the experimental animal species concentration or dose.
immediately dangerous to life or health (IDLH)	An exposure condition or environment that is likely to cause death or immediate or delayed permanent adverse health effects or prevent escape from such an environment. The IDLH values developed by NIOSH characterize these high-risk exposure concentrations and conditions.
information bias	A bias in the effect estimate that occurs from systematic inaccuracies in the measurement of either the exposure or the adverse effect.
intake	The process by which an agent crosses an outer exposure surface of a target without passing an absorption barrier (i.e., through ingestion or inhalation).
internal validity	The degree to which study findings are free from bias.
interpretation bias	A bias that arises from improper inference or speculation based on a naïve or deliberate lack of impartiality by the interpreter.
job-exposure matrix (JEM)	A cross-classification of jobs/tasks and exposure level spanning a specified period. The JEM is used to estimate exposure indices that vary by job and time.
key event	An empirically observable precursor step that is itself a necessary element of the mode of action or is a biologically based marker for such an element.
knot	The boundary between categories of the regressor in a regression model using a spline function.

Terms	Definitions
limit of detection (LOD)	For an analytical procedure, the lowest amount or concentration of the analyte that is reliably distinguishable from the absence of analyte (i.e., low false-negative rate). For example, for air sampling methods, NIOSH defines the LOD as the mass of the analyte that gives a mean signal that is three standard deviations above the mean blank signal.
limit of quantification (LOQ)	For an analytical procedure, the amount or concentration of the analyte at which quantitative results can be reported with a high degree of confidence. The high degree of confidence is based on a set of acceptance criteria that are assay-specific. For example, for air sampling methods, NIOSH defines the LOQ as the larger of: (a) the mass corresponding to the mean blank signal + 10 standard deviations of the blank signal or (b) the mass above which recovery is ≥75%.
lowest observed adverse effect level (LOAEL)	The lowest dose or concentration at which there are biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group.
manipulative causation	Causal discovery based on the intuition that changing causes also changes their effects. Manipulative causation is implied by mechanistic causation, where given a network of mechanisms that affect the frequency or severity of adverse effects, manipulation of these mechanisms will change the frequency or severity of adverse effects.
measurand	A quantity intended to be measured.
measurement accuracy	The agreement between a measured quantity value and a true quantity value of a measurand.
measurement error	Any discrepancy between the true quantity and the measurand. The true quantity is considered unique and is unknowable.
measurement precision	The agreement between measured quantities obtained by replicate measurements on the same or similar objects under specified conditions.
mechanism of action	The underlying biochemical interactions, usually at the molecular level, that lead to the mode of action at the cellular level and ultimately the expression of the adverse effect. The mechanism of action is a more detailed understanding and description of events than is mode of action.
medical follow-back	A data collection technique in epidemiologic studies where data from one source (e.g., self-report or registry linkage) is verified or augmented by using medical records.

Terms	Definitions
mode of action (MOA)	A sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in the adverse effect.
monotonic	A relationship, sequence, or trend is said to be monotonically increasing if each value is greater than or equal to the previous one and monotonically decreasing if each value is less than or equal to the previous one. Monotonic responses may be linear or nonlinear, but the slope does not change sign.
mutagenicity	The ability of an agent to induce or generate heritable changes (mutations) of the genotype in a cell because of alterations in or loss of genetic material.
no observed adverse effect level (NOAEL)	The highest dose level at which there are no biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control; some effects may be produced at this dose level, but they are not considered adverse or precursors of adverse effects observed.
occupational exposure limit (OEL)	The allowable concentration or intensity of a hazardous agent in the worker's work environment over a period. Generally expressed as an 8-hour time-weighted average or as a short-term exposure limit of 15 or 30 minutes.
occupational risk	The potential and severity of adverse effects in workers from their exposure to workplace hazards.
odds ratio	A measure of association in comparative studies, particularly case-control studies. It is the ratio of the odds that an outcome will occur, given a particular exposure to the odds of the outcome occurring in the absence of that exposure.
parametric model	A mathematical model of association that is wholly dependent on assumptions about the distribution of the data that are represented by a finite set of explicit parameters. For example, a simple linear regression with one variable has two parameters (the coefficient and the intercept), which completely explain the data.
pharmacokinetics	The study of the absorption, distribution, metabolism, and elimination of exogenous chemicals in biological systems.

Terms	Definitions
physiologically based pharmacokinetic (PBPK) model	A multicompartmental mathematical model based on the known physiology of an organism used to quantify the absorption, distribution, metabolism, and elimination of exogenous chemicals following exposure. In this context, the compartments represent actual tissue and organ spaces and their volumes are the physical volumes of those organs and tissues.
point of departure (PoD)	The estimate of dose-response at an exposure in the low range of (or just below) the observable data. Various approaches are available for its estimation; the simplest defines the PoD as the no observed adverse effect level (NOAEL) or the lowest observed adverse effect level (LOAEL) from an animal toxicologic or human epidemiologic study.
pneumoconioses	The group of interstitial lung diseases, mostly of occupational origin, caused by the inhalation of mineral or metal dusts, such as asbestosis, silicosis, coal workers' pneumoconiosis (black lung disease), and chronic beryllium disease.
publication bias	A bias from an editorial preference for publishing particular findings, which distorts inferences made from available evidence.
random error	Variation of results and inferences from the truth, occurring only because of chance. Random measurement error is a component of measurement error that in replicate measurements varies in an unpredictable manner.
rate ratio	A measure of association that quantifies the relationship between an exposure and a health outcome from an epidemiologic study, calculated as the ratio of incidence rates or mortality rates of two groups.
recommended exposure limit (REL)	An exposure limit recommended by NIOSH, expressed as an 8-hour time-weighted average airborne concentration of a chemical during a 40-hour workweek over a 45-year working lifetime. RELs are usually based on a quantitative risk assessment, when available, but may also depend on the limit of quantification of the analytical exposure measurement method. RELs are published in NIOSH Criteria Documents and Current Intelligence Bulletins and are compiled in the NIOSH Pocket Guide to Chemical Hazards.
relative risk	The ratio of the risk (disease probability) observed in the exposed (intervention) group to that observed in the unexposed (control) group; also used as a general term for measures of association on a relative scale, including risk ratio, rate ratio, hazard ratio, odds ratio, standardized incidence ratio, and standardized mortality ratio.

Terms	Definitions
reliability	The extent to which multiple assessments are consistent.
risk	The probability and severity of an adverse effect in an organism, system, or population caused under specified circumstances by exposure to an agent. In NIOSH risk assessment, risk is more narrowly defined as the incidence of the adverse effect (e.g., disease onset) occurring in subject(s) over a specified period of time, given that the subject(s) were disease-free at the beginning of that period. Under this definition, risk is a measure corresponding to an average individual-specific risk (i.e., cumulative incidence).
risk assessment	Determination of the relationship between the predicted exposure and adverse effects, in four major steps: hazard identification, dose-response assessment, exposure assessment, and risk characterization. The NIOSH risk assessment process is limited to occupational exposures and primarily includes hazard identification, dose-response assessment, and risk characterization, while omitting exposure assessment. In NIOSH assessments, exposure data are evaluated as a part of hazard identification.
risk-based decision	A risk management decision using risk assessment as the basis for decision-making.
risk characterization	The qualitative and, wherever possible, quantitative determination, including attendant uncertainties, of the probability of occurrence of known and potential adverse effects of an agent in workers under defined exposure conditions. In NIOSH risk assessment, risk characterization is the culmination of planning, problem formulation, and analysis phases to form a risk basis for NIOSH recommendations on limiting occupational exposure levels.
risk-informed decision	A risk management decision using risk assessment as an input to decision-making.
risk management	The managerial, decision-making, and control process intended to avert intolerable risk.
risk management limit for carcinogens (RML-CA)	An exposure limit for chemical carcinogens that represents a starting place for controlling exposures, preferably based on target risk. For example, NIOSH will set the RML-CA at a risk of one excess cancer case in 10,000 workers in a 45-year working lifetime, when analytically feasible. For more information, see the NIOSH Chemical Carcinogen Policy [NIOSH 2017].

Terms	Definitions
risk ratio	A measure of association that quantifies the association between an exposure and a health outcome from an epidemiologic study, calculated as the ratio of incidence proportions of two groups.
short-term exposure limit (STEL)	Generally, a 15-minute TWA exposure that should not be exceeded at any time during a workday. Some NIOSH STELs are based on a different short-term exposure duration.
similar exposure groups	Workers having the same exposure profile because of similarity and frequency of tasks performed.
spline function	A mathematical function that is used for regression model interpolation or smoothing. The boundary between categories of the regressor are called the knots or joint points of the spline.
standardized incidence ratio (SIR)	The ratio of the observed number of disease cases in the study population to the number of cases that would be expected, based on disease rates in the referent population that are applicable to the characteristics (such as age, race, gender, and calendar period) in the study population.
standardized mortality ratio (SMR)	The ratio of the observed number of deaths in a study population to the number of deaths that would be expected, based on death rates in the referent population that are applicable to the characteristics (such as age, race, gender, and calendar period) in the study population.
stressor	Any physical, chemical, biological, or psychosocial entity that can induce an adverse effect.
systematic error	A component of measurement error that in replicate measurements remains constant or varies in a predictable manner.
target	Any biological entity that receives an exposure or a dose (for example, an organ, an individual, or a population).
tolerable risk	The region in the risk continuum that can, for the time being, be tolerated, assuming that the risk is minimized by appropriate control procedures.
toxicity	The inherent property of an agent having the potential to cause an adverse effect when an organism, system, or population is exposed to that agent. Toxicity is usually defined with reference to the dose, the way the agent is administered and distributed in time (single or repeated doses), the type and severity of injury, the time needed to produce the injury, the nature of the organism(s) affected, and other relevant conditions. In some settings, toxicity refers to the adverse effect.

Terms	Definitions
uncertainty factor (UF)	A "safety" factor ≥1 that is used as a divisor to adjust the safe-dose point of departure downward to account for variation and uncertainty in estimates from experimental or observational data.
underlying cause of death	The disease or injury that initiated the train of events leading directly to death or the circumstances of the accident or violence that produced the fatal injury.
uptake	The process by which an agent crosses an absorption barrier.
validity	The quality of being logically or factually sound; the extent to which the measure describes that which is being measured. It is the degree to which inferences drawn are valid. Study validity comprises internal and external validity.
weight of evidence on toxicity (WoE)	The nature and extent to which the available data support the hypothesis that an agent causes a defined adverse effect (e.g., cancer in humans).

APPENDIX B

Sources of Uncertainty in Risk Estimation

B.1 Validity

Validity is the quality of being logically or factually sound; the extent to which a measure describes that which is being measured; and the degree to which inferences drawn are valid. Study validity comprises internal and external validity [Campbell and Stanley 1963]. The former is the degree to which study findings are free from bias, whereas the latter is the degree to which study findings may apply, be generalized, or be transported to populations or groups that did not participate in the study. The two components of validity are not independent and can entail tradeoffs [Grimes and Schulz 2002].

In general, sound observational and experimental studies are aimed to provide internally valid causal effect estimates from a study sample, rather than estimates of an externally valid causal effect for a target population [Edwards et al. 2017]. Internal validity is the *sine qua non* of research supporting risk assessment; therefore, information on sources of potential bias (e.g., selection, information, and confounding) is the focus of this appendix. External validity has received much less attention, although it can also be an important consideration when applying research findings to assessing risks in a broad population of workers [Steckler and McLeroy 2008]. External validity has been described as generalizability and transportability [Lesko et al. 2017]. In this context, generalizability refers to the quality of inference from a potentially biased sample of the target population to the full target population. Transportability refers to inference in the target population from observations in a partial or completely non-overlapping sample population. In either case, measuring external validity requires data and assumptions beyond those needed for internal validity. Thus, relating a causal effect observed in a single study to the target population can be difficult and, in some cases, impractical. Generalizing and transport methodologies in observational research are sparse [Hernán and Vanderweele 2011; Lesko et al. 2017; Pearl and Bareinboim 2014]. Potential exceptions are statistical methods for combining diverse studies, such as meta-analyses and data pooling [Pearl and Bareinboim 2014]. A general algorithm for the transport of experimental results to populations is provided by Bareinboim and Pearl [2013].

The tendency to conflate statistical generalizability or representativeness with scientific generalizability should be avoided. There are many examples in which representativeness can detract from research goals and ultimately hinder scientific inference [Rothman et al. 2013]. Instead, external validity can be considered as the explanation of the reasons in which the scientific findings are valid beyond a specific study. In practice, evaluation of external validity in risk assessment requires more scientific judgment compared to internal validity.

B.2 Selection Bias

The term *selection bias* is used to describe many biases that are themselves a distortion in the estimate of effect that results from the manner in which the study subjects are selected from the source population [Gail and Benichou 2000]. These include biases resulting in differential follow-up, recall, self-selection, volunteering or non-response, and sampling frames. Selection bias is possible in all observational studies and particularly so in case-control studies, because the outcome is known at study inception. For example, MacMahon et al. [1981] conducted a hospital-based case-control study that reported a strong association between coffee drinking and pancreatic cancer. Controls were selected from "… all other patients who were under the care of the same physician in the same hospital at the time of an interview with a patient with pancreatic cancer" [MacMahon et al. 1981]. This selection process resulted in a large proportion of controls who presented mainly with gastrointestinal disorders; therefore, these patients may have been advised by physicians not to consume coffee [Feinstein et al. 1981; MacMahon et al. 1981; Silverman et al. 1983]. The abnormally low odds of coffee consumption among controls would cause a spurious positive association between coffee intake and pancreatic cancer. This bias may have been avoided by selecting controls

from patients hospitalized for conditions not requiring a change in diet [Silverman et al. 1983]. Primary control of selection bias is managed by study design. The avoidance of selection bias in case-control studies is accomplished by drawing cases and controls from the same study base; therefore, it is imperative that the study base be well-defined before sampling. Other methods include maximizing participation rates, using randomized sampling protocols, and applying sound inclusion/exclusion criteria.

There is often overlap between confounding and selection bias; therefore, secondary control of selection bias can sometimes be achieved by treating identifying factors as confounders in analyses and controlling for confounding accordingly. For example, if union workers are more likely than office workers to participate in a study and be exposed, then partial control of the bias may be realized by including job information as a confounder. Finally, sensitivity analyses using an array of inclusion criteria can help characterize the potential for significant selection bias and define a dataset for use in risk assessment.

The risk assessor should be able to recognize potential sources of selection bias in an evaluation of the study design. The risk assessor should give more weight to studies that have best addressed this source of bias through design, control, and sensitivity analyses. The risk assessor should pay special attention to (non-nested) case-control studies, which are most vulnerable to selection biases.

When reviewing the design of studies for the potential for selection bias, risk assessors should consider the following questions:

- What study design was used and where does this design fall in the hierarchy for WoE? Preferred studies will provide a detailed description of the study design, which includes limitations that are inherent to the design.

- Has the study population been sufficiently described to determine potential differences between study and control groups (i.e., do inclusion criteria differ between groups)? Preferred studies will include a detailed description of the characteristics of the study and control groups.

- What methods were used to select study participants? How could those excluded from study have affected study results had they been included? Preferred studies will include a description of the exclusion and inclusion criteria used for study participation and the methods used to reduce the potential for bias.

- What steps were taken to maximize participation rates? Low participation is indicative of a potential for selection bias.

- Is participation non-differential with respect to exposure? Case-control studies are particularly vulnerable to differential selection to study and control groups with respect to exposure, given that case status is known at enumeration.

- Is there significant loss to follow-up? Loss to follow-up is typically less than 10% in well-designed studies.

B.3 Information Bias

Information bias, sometimes referred to as data collection bias, measurement error, or misclassification bias, is a distortion in the effect estimate that occurs when the measurement of either the exposure or the adverse effect is systematically inaccurate [Gail and Benichou 2000]. In this context, information bias is a study execution bias that is restricted to data on study participants (i.e., the sample population). Information biases may stem from errors in the measurement instrument (instrument bias), data source (data source bias), the observer or investigator (observer bias), and/or the subject (subject bias). Given limitations in available data, observational studies are particularly prone to several sources of information bias. For example, exposure data can be biased when collected with prior knowledge of case status (as in a case-control study). If exposure is self-reported, then a recall bias (a form of subject bias) may result from differential self-reporting of

exposure status among cases and the control group when cases are aware of a potential association between exposure and their disease. If exposure data are collected by interview, then the interviewer must be blinded to case status to reduce the potential for an observer bias. Likewise, if measurement data are collected, then care must be taken to ensure that identical procedures were used for both cases and controls. In general, when assessing the presence of information bias in a study under review, the risk assessor should ask these questions:

- Was the study information obtained in the same way for all comparison groups?

- Was the information on exposure and other explanatory factors collected by persons blinded to case status?

Errors in the data are usually separated by data type, such that the term *measurement error* is reserved for errors in continuous data and the term *misclassification error* refers to errors in discrete data. Measurement error of explanatory variables used in analyses is unavoidable, even in the best-designed studies. Risk assessors should have a firm understanding of the potential effects from these errors in studies selected for dose-response assessment; therefore, a detailed discussion is provided in the following section. This discussion is primarily in the context of errors in measurement of the exposure of interest; however, the concepts presented are shared by all data sources vulnerable to an information bias.

B.3.1 Measurement Error and Misclassification

In the context of exposure, measurement (observation) error refers to any discrepancy between the true exposure, X, and the imperfect measured value, W; thus, it is analogous to exposure misclassification[*]. By this strict definition, measurement

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[*]Although used to describe all measurement error, the term *misclassification* is sometimes limited to errors in qualitative indices and replaced with misspecification when referencing errors in numerical indices.

error comprises both systematic and random components. Random errors are stochastic fluctuations in observed values around the true (but unknown) value, without directional preference. Systematic error or bias refers to inaccuracies in measured values that are inherent to the measurement system.

Systematic error (bias) is a difference between the mean of observed values and the true mean value, for a given true value, and typically arises from inaccuracy in measured or estimated values that are inherent to the measurement process. Bias can be unintentional or deliberate, such as the use of conservative assumptions to increase the margin of safety in a protection system. A common source of systematic error in exposure estimates are methods used to report "nondetects," i.e., measurements below a detection threshold [Helsel 2005]. In these cases, the true value lies somewhere between the null and the detection threshold. In practice, nondetects are typically recorded as zero (likely underestimation of exposure), the limit of detection (LOD, which is a likely overestimation of exposure), or simply omitted (a bias in either direction, depending on the use of the data). Here, the LOD is the lowest amount or concentration of the analyte that is reliably distinguishable from the absence of analyte. For example, in developing air sampling methods, NIOSH defined the LOD as the mass of the analyte that gives a mean signal that is three standard deviations above the mean blank signal [NIOSH 1995b]. Methods to account for nondetects can range from simple substitution (e.g., substituting with LOD/2 or LOD/2$^{0.5}$) to complex parametric and nonparametric statistical modeling [Helsel 2005; NCRP 2010].

Measurement error can be shared or unshared [Hoffmann et al. 2018]. If the error in dose among individuals, groups, and time is independent and identically distributed (a general assumption in most error structure models), the error is unshared. In contrast, correlations in error components between individuals, groups, or time represent shared error. Consider the case in which a set of data from personal air samples used a calibration coefficient that overestimated dose by 20%. This error is shared among workers in the set of data.

In general, measurement error reduces statistical power for trend tests because of added variance and may bias effect measures in dose-response analyses. The influence on risk estimates depends on the combination of error characteristics (Berkson or classical random errors, or shared errors) and model specification, and this influence can range from negligible effects to a strong bias in either direction [Armstrong 1998; Nieuwenhuijsen 2010]. Furthermore, measurement error is often thought of only in terms of the primary predictor; however, risk assessors should be mindful that a dose-response relationship could also be strongly influenced by measurement error in covariates that confound or mediate effects of interest.

Risk assessors should be reasonably assured that the data selected for dose-response analyses are free of a potential for significant bias. This assurance is partly gained through rigorous adherence to estimation methods designed to avoid bias, such as observance of the data hierarchy, blinding assessors to case status, using and comparing multiple indices, and validating estimates. Well-conducted epidemiologic studies typically pay careful attention to obvious sources of systematic error in exposure estimates, but analyses have been generally conducted without considering residual measurement error effects [Jurek et al. 2006]. This is because assessments of measurement errors often require elaborate tests of reliability and validity, which are infrequently performed, if even feasible. Furthermore, many investigators assume that random measurement error always induces bias toward a null association; therefore, they incorrectly conclude it cannot cause spurious positive findings. Consequently, information needed to account for measurement error in risk analyses may be lacking. When data are available, researchers have suggested methods for adjusting estimates to account for random error or assessing its potential effects in dose-response analyses [Carroll et al. 2006; French et al. 2004; Hoffman et al. 2007; Maldonado 2008; Mallick et al. 2002; Meliker et al. 2010; Schafer et al. 2001; Spiegelman and Valanis 1998; Stayner et al. 2007; Thomas et

al. 1993a]. These methods can involve (1) integrating validation data into regression calibration or likelihood-based methods to produce adjusted estimates [Hoffman et al. 2007; Mallick et al. 2002; Schafer et al. 2001; Spiegelman and Valanis 1998] or (2) using Monte Carlo simulation to predict a range of plausible estimates [French et al. 2004; Meliker et al. 2010; Stayner et al. 2007]. In the former case, risk assessors should be cautious of adjustments made on the basis of inadequate information that could induce a potentially stronger bias relative to unadjusted values.

In summary, there may be few options available to risk assessors regarding limiting the potential effects of measurement error in dose-response analyses. Nevertheless, it is important for risk assessors to have a fundamental understanding of measurement error and its associated effects so that they can better describe and account for the limitations in analyses that support quantitative risk assessment. Seminal works on measurement error and dose-response modeling should be reviewed [Armstrong 1998; Carroll et al. 2006; Fuller 1987; Ron and Hoffman 1999; Thomas et al. 1993b]. Some general concepts are discussed below.

B.3.1.1 Differential versus Nondifferential Error

Exposure measurement error is either differential or nondifferential, contingent on its relation to the dependent variable (e.g., disease status). Error that is independent of case status (and other predictors) is said to be nondifferential. It is commonly thought that nondifferential error results in bias toward a null association, which is a proven condition of binary variables or continuous variables in which the magnitude and direction of the measurement error are independent of the true value (i.e., the classical error model; see Table B-1). However, there are examples of nondifferential error in polytomous and continuous exposure measures that induce bias away from the null [Dosemeci et al. 1990; Greenland and Gustafson 2006; Wacholder 1995].

Table B-1. Direction of bias caused by nondifferential measurement error of the primary predictor variable.

Predictor Scale	Bias Expected
Binary	Biases the effect measure toward a null association
Polytomous	Estimates of trend across adjacent categories are biased downward. Estimates from comparison of categories can be biased in either direction.
Numerical	Classical error biases regression coefficients toward zero. Berkson error (i.e., random error that is statistically independent from the observed variable) leads to little or no bias in coefficients in most regression models.

Differential error can result in serious bias in either direction. For example, workers diagnosed with leukemia may be more apt to report or may have more thorough histories of benzene exposure than workers who are cancer free. In this instance, leukemia cases will appear to have higher exposures, thus biasing the association between benzene exposure and leukemia away from the null. Differential exposure error is unlikely if exposure data are collected prior to the disease outcome or without prior knowledge of the hypothesized association. Therefore, the primary means to avoid differential error is to ensure that exposure estimates were made while blinded to case status and that case ascertainment is, to the extent practical, independent of exposure status. When using data from previous studies, risk assessors should examine the study design for any potential weaknesses that may lead to differential measurement error. Common sources of exposure information that are vulnerable to differential measurement error are self-reports or proxy reports, medical records, and compensation records. Cautious interpretation is also warranted for studies involving case ascertainment by differential diagnoses of "occupational diseases" (e.g., silicosis, asbestosis, malignant mesothelioma, and chronic beryllium disease). In certain situations, nondifferential exposure information can be restructured to induce differential misclassification [Dosemeci et al. 1990; Flegal et al. 1991; Wacholder et al. 1991]. For example, combining categories of a polytomous exposure variable or constructing exposure categories from continuous exposure data can result in differential measurement error.

B.3.1.2 Categorical Indices

Measurement error in qualitative data is typically described as the probability of exposure misclassification. For example, the error in a dichotomous exposure index can be expressed by its probability of correctly classifying an exposed worker (i.e., sensitivity) and the probability of correctly classifying an unexposed worker (i.e., specificity). A matrix of misclassification probabilities can be used to describe errors in indices with more than two levels. Misclassification probabilities are generally determined in validity studies comparing exposure estimates for a sample of workers in the study to estimates derived from another source that is believed to be as precise or better. Random (nondifferential) measurement error in a dichotomous exposure variable will always attenuate its effect, i.e., suggest that the agent under study is less toxic than it truly is. Trends across ordered categories of polytomous exposure variables will also be attenuated by nondifferential measurement error; however, comparisons between categories can be biased in either direction [Armstrong 1998].

B.3.1.3 Error Models for Numerical Indices: Classical versus Berkson Error

Two approaches to modeling random measurement error for numerical data are the classical and

Berkson models. Settings where observations are subject to random variation from factors such as instrument imprecision and recording errors may be amenable to a classical model of measurement error, e.g., $W=X+U$, where measurement error, U, is a random variable with mean zero variance, VAR_u, and is independent of X. The observed exposure is equal to the true (but unobserved) exposure plus some measurement error; therefore, average values obtained from replicate measures are unbiased estimates of the true exposure but will always have greater variability than the true exposure. In contrast, the Berkson error model, expressed as $E(X|W=w)=w$, arises when a single estimate, w, is applied to several individuals who have differing values of the quantity being estimated that average to w. In this model, the true exposure is more variable than the observed exposure. For example, assigning the average measured concentration from an ambient air monitor to the group of workers can be modeled by Berkson error. Modeling of the measurement errors may be approached with the use of additive or multiplicative structures under each of these approaches.

The error form is significant regarding dose-response analyses. For example, consider the simple case of a univariate linear dose-response model: $E(Y)=\alpha+\beta_X X$, where the regression of response variable, Y, on the independent variable, X (with variance, VAR), has parameters α and β. If X is unavailable and exposure measure W with classical additive error (i.e., $W=X+U$) is substituted, then the resulting regression model $E(Y)=\alpha^*+\beta_W W$ has the slope parameter $\beta_W=\beta_X\ VAR_X/(VAR_X + VAR_U)$, where the quantity $(VAR_X + VAR_U)$ is the variance of the measured variable. The ratio of true to measured value variances (referred to by Fuller [1987] as the reliability ratio λ) must be less than unity; therefore, classical error results in attenuation of the observed linear dose-response [Fuller 1987]. The degree of attenuation is relative to the quantity VAR_U / VAR_X, such that smaller measurement error or larger spread of true values reduces bias. For example, the effect of classical error in a cumulative dose estimate is likely less than in a single measurement of the same magnitude, given that the error of the single measurement is larger relative to that of multiple measurements comprising the cumulative dose. In contrast, attenuation of linear regression coefficients does not result from Berkson error. Recall that for Berkson error, $E(X|W)=W$, thus $E(Y|W)=\alpha+\beta_X W$, and therefore the estimator (β_X) is not attenuated [Carroll et al. 2006].

B.3.1.4 Additive, Multiplicative, and Mixed Error Structures

Error structures (for numerical values) are generalized by two limiting cases: additive error, in which the variance is constant for different magnitudes of the measurand; and multiplicative error, in which the variance increases with increasing values of the measurand. The classical multiplicative error model can be expressed by $W=Xe^U$, such that there is additivity on the logarithmic scale [i.e., $\ln(W) = \ln(X)+U$]. Measurement error can be modeled by using additive, multiplicative, or a combination of each, resulting in a mixed error structure. Replicate measurements of several occupational agents have shown a multiplicative error structure. As in the additive measurement error model, the increased variance from multiplicative error attenuates the observed dose-response; however, the effect is larger at higher exposures, resulting in the appearance of downward curvature with increasing values of the error-prone measurements of exposure [Carroll et al. 2006]. An attenuated response at higher exposure levels has been observed in numerous occupational studies and in simulations [Carroll et al. 2006; Stayner et al. 2003; Steenland et al. 2015]. Nevertheless, there is considerably less literature on accounting for multiplicative or mixed error structures in predictor variables of dose-response regression models. The subsequent effects on these models vary by structure; therefore, some notion of the error structure is important for understanding subsequent model limitations.

B.3.1.5 Errors in Confounders and Effect Modifiers

As a general rule, random measurement error in a confounder in which the error is not correlated

with other measures or the exposure of interest tends to increase confounding from that covariate [Armstrong 1998]. This means that the effect measure of interest is likely to lie between the unadjusted value (crude measure) and a value obtained under complete control of confounding (i.e., residual confounding from incomplete control). The directionality of induced bias depends on the direction of the confounding effect. The amount of bias depends on the strength of the confounder and the reliability ratio. As in confounding, random measurement error in an effect modifier tends to attenuate its effect modification; therefore, the ability to observe risk difference among groups is diminished [Armstrong 1998].

B.3.1.6 Errors in Adverse Effect Definitions

Information bias is also plausible from misclassification or measurement error in the adverse effect. For example, consider a cancer incidence study of U.S. workers in which cases in the exposed population are ascertained from a single state registry. If incidence rates in the exposed group are compared to standardized national rates, then the resulting effect measure (e.g., SIR) is likely biased from underascertainment of cases due to some migration out of the state by the workforce. Thus, cancer incidence studies within the U.S. are improved with ascertainment involving multiple states. In this case, the misclassification is differential and the bias is likely toward a null association. As a similar example, consider a case control study in which the study population and adverse effect data are drawn from electronic health records (EHRs). As in the previous example, cases may be missed if diagnosed outside of the EHR catchment area (e.g., a single clinic or group of clinics), and the potential for error increases with decreasing catchment area size. In this scenario, the affluent workers in the study have a more flexible health insurance plan; therefore, they are more likely to be diagnosed outside of the catchment area (and be missed). These same workers may have less exposure because of their job assignment. Under these conditions, the misclassification is differential with respect to ex-

posure. As previously discussed, the resulting bias can be in either direction [Wang et al. 2016].

Misclassification can also occur from differences in diagnostic criteria used for defining the adverse effect. These criteria can vary by data source and by time. For example, the ICD published by the World Health Organization has been the standard diagnostic tool used for epidemiology since the late 1940s. Multiple revisions to the ICD have occurred throughout the years, given changes in diagnostic criteria. The definitions of certain diseases (e.g., hematopoietic cancers) have dramatically changed over the course of the ICD; therefore, studies published at different times may not have comparable disease definitions. As another example, consider an adverse effect defined on the basis of data abstracted from medical records. The reliability and validity of data in each individual medical record are vulnerable to different interpretations of different scenarios and often by different observers [Worster and Haines 2004].

Researchers acquire adverse effect data with several different approaches tailored to the response definition, data availability, and study feasibility. Thus, the adverse effect data may stem from direct measurements (e.g., lung function tests), existing health outcome databases (e.g., National Death Index, disease registries, compensation databases), medical records (paper or EHRs), and patient (or proxy) self-reports. These sources are not without error, and the potential for bias is dependent on the magnitude of these errors. For example, EHRs appear to be a promising source of medical information suitable for risk assessment. However, data residing in these systems are inputted by imperfect systems and persons. Sources of misinformation associated with medical records include physician misdiagnoses, flawed laboratory results, and erroneous patient self-reporting [Ash et al. 2004; Burnum 1989; Luck et al. 2000; Worster and Haines 2004]. Thus, data collected prospectively with use of study criteria that were defined beforehand are likely to be superior to data abstracted from EHRs.

In summary, the potential for bias from mismeasurement of the adverse effect is reduced when case definitions and ascertainment are the same among comparison groups. Nondifferential misclassification of the adverse effect with respect to risk factor exposure will likely result in an underestimation of the effect (i.e., bias toward a null association), whereas differential misclassification may result in a bias in either direction. When selecting studies for data synthesis, the risk assessor should confirm consistency in adverse effect definition among comparison groups in data used for risk assessment. Studies with well-defined adverse effects that are consistent throughout observation should be given more weight. For example, data from a compulsory reporting system (e.g., cancer registry) is preferred to information gathered by self-report. Studies with poorly defined adverse effects should be avoided. Risk assessors must also consider limitations that are inherent to the sources of adverse effect data. The risk assessor must consider the potential bias in estimates that may result from errors in the source data and weight the evidence accordingly.

B.4 Confounding

With respect to causal inference, confounding has been described as a mixing of the effects from extraneous factors (confounders) with the effect of interest [Checkoway et al. 2004]. This mixing occurs when the comparison groups (e.g., exposed and unexposed workers) have differing background risks of disease. There are many definitions of confounders; however, perhaps the most complete is that suggested by McNamee (2003), who posited that a factor should be considered a confounder if three conditions are met:

1. The factor is a cause of the disease, or a surrogate measure of a cause, in unexposed people. Factors satisfying this condition are called risk factors.

2. The factor is correlated, positively or negatively, with exposure in the study population. If the study population is classified into exposed and unexposed groups, this means that the factor has a different prevalence in the two groups.

3. The factor is not affected by the exposure (i.e., does not reside on the causal pathway) [McNamee 2003].

Disease risk factors can comprise a wide array, including demographic factors (age, sex, race), lifestyle factors (smoking habits, diet, and alcohol use), or exposures to other agents in the workplace or elsewhere. In study planning, all known or suspected risk factors should be identified, especially those factors most apt to confound dose-response associations. This information is needed to achieve appropriate confounding control and characterize the potential influence on effect measures from residual confounding.

Methods to control for confounding are generally related to study design or analysis. Design methods are meant to ensure that the exposed group is comparable to or exchangeable with the referent group with respect to the potential confounders [Greenland et al. 1999]. Exchangeability is the concept that response distributions in exchangeable comparison groups are identical under the same exposure conditions. These methods include restriction, randomization (i.e., clinical trial), and matching on potential confounders. In practice, there is limited success in finding exchangeable comparison groups in observational studies; therefore, these studies tend to rely on analytical methods for controlling confounding, such as stratified analyses and multiple regression. For example, dose-response analysis in a longitudinal study may use Poisson regression to control for confounding effects of age (an important confounder for most chronic illnesses) on the exposure interest by either background stratifying on age or including age as a covariate in the model. Similarly, a nested case-control study of the same cohort may use conditional logistic regression with age (attained age of the case) as the time scale. Both approaches are used extensively in occupational epidemiology.

In general, reasonable control for important demographic risk factors (e.g., age, sex, and race) and calendar period is achieved in most published epidemiologic studies. However, measures of association

are still vulnerable to confounding effects from incomplete control of measured risk factors or from no control of unmeasured risk factors. Smoking is known to cause several types of cancer and non-malignant disease. If smoking prevalence is also related to exposure status, then smoking might be a confounder. The resultant bias could be in either direction (i.e., positive or negative confounding), depending on the smoking characteristics of the comparison populations. For example, consider that blue-collar workers tend to use tobacco products more than white-collar workers. If blue-collar workers are also more likely to be exposed than white-collar workers (a reasonable assumption in some workplaces), then smoking can be a correlate of exposure [Lee et al. 2004; Stellman et al. 1988]. Under these conditions, smoking could confound the effect of occupational exposure on a smoking-related disease. The expected effect in this case is positive confounding of the exposure effect by smoking, which means the measure of association will be biased away from the null without control for smoking. Unfortunately, information on the smoking habits of workers in most longitudinal studies is rarely available; therefore, direct adjustment for confounding effects of smoking are seldom seen. Instead, researchers might use indirect methods for adjustment [Axelson and Steenland 1988; Richardson 2010]. In the example above, job descriptions could be used as a proxy for smoking. Socioeconomic status is a well-known proxy for many lifestyle factors, including smoking, which may confound a dose-risk relationship [Lantz et al. 1998; McFadden et al. 2008]. One could also examine alternative adverse effects that are strongly associated with the unknown confounder but not with the exposure of interest [Richardson 2010]. An observed (but unexpected) dose-risk relationship between the agent of interest and alternative adverse effects is indicative of residual confounding. At the very least, researchers should provide some information on the potential for significant bias because of incomplete control of known or suspected confounders.

Confounding can also occur in occupational studies that do not account for concomitant workplace exposures. For example, Sathiakumar et al. [2015] examined the relationship between styrene exposure and leukemia in a large pooled study of workers in North American synthetic rubber plants [Sathiakumar et al. 2015]. Styrene-exposed workers were also exposed to 1, 3-butadiene, which is a known human leukemogen [IARC 2012]. Quantitative estimates of cumulative exposure to 1,3-butadiene and styrene were calculated. Statistical analyses used Cox proportional hazards regression models with age as the time scale and adjustment for race, year of birth, and plant. Modest positive dose-response associations between leukemia and cumulative exposures to both agents were observed in separate models; however, the independent effects of styrene exposure could not be determined because of its strong correlation with 1,3-butadiene. Thus, the carcinogenic effects of these agents in combination appear hopelessly entangled in these workers, and the dose-response observed for styrene could be due wholly, or in part, to unmeasured confounding by 1,3-butadiene.

Whether a study is a valid contributor to hazard identification depends on how well the published results address the potential for confounding. In turn, resultant datasets must also inform and support the analytical approaches used in the subsequent dose-response assessment. Thus, the risk assessor should evaluate the adequacy for control of measured and unmeasured confounders in studies under review. When unmeasured risk factors are identified, the risk assessor should evaluate the steps taken by researchers to reduce the potential for significant bias from residual confounding by these risk factors. The risk assessor should also consider the potential for unknown risk factors and assess their potential impact on internal validity. In all instances, the risk assessor should give more weight to studies with measures of association that are least likely to be affected by residual confounding.

B.5 Healthy Worker Effects

Another important potential source of bias in occupational studies is healthy worker effects. These

effects primarily occur from two points of participant selection—into the study at the time of hire and out of the workforce at time of termination—and as such are commonly referred to as the "hire effect" and "survivor effect," respectively [Arrighi and Hertz-Picciotto 1993; Arrighi and Hertz-Picciotto 1994; Fox and Collier 1976]. A third aspect to healthy worker effects is the natural decline in health status with time since hire [Checkoway et al. 2004]. Finally, healthy worker effects do not apply equally to all outcomes or to all groups within a study population (e.g., different races, ages, or demographics). For example, healthy worker effects are generally greater among minority populations compared to Caucasian males because of different class structures in working and referent populations [McMichael 1976]. Given distinct differences in the sources of potential bias and methods available for control, risk assessors should consider these aspects separately as they are discussed in the following sections.

B.5.1 Healthy Worker Hire Effect

The healthy worker hire effect (HWHE) results from increased employment eligibility among healthier persons, which can be exacerbated by hiring practices that screen against poor health (e.g., pre-employment exams). These conditions can result in a group of persons of interest (i.e., workers) who are in better overall health than the comparison group, irrespective of exposure status. HWHE is typically observed in external comparisons (e.g., SMR or SIR studies using the general population as referent); however, some employers have used medical screening information for job placement within the industry, which could bias results from internal comparisons. For external comparisons, the HWHE results in a deficit in risk compared to true effects in some outcomes, particularly in chronic diseases most associated with lifestyle factors (e.g., diabetes mellitus and cardiovascular diseases). An alternative comparison group, such as a similar working population that is unexposed to the agent of interest, may reduce this bias. When job assignment is influenced by medical screening,

the direction of the potential bias depends on the relationship between job assignment and exposure. Risk assessors need to be wary of the potential for a strong HWHE in data from external comparisons.

Unfortunately, there are few options afforded to risk assessors for accounting for HWHE. Risk estimates from external comparisons can be adjusted with use of information on potential biases [Burstyn et al. 2015; Kirkeleit et al. 2013; Park et al. 1991]; however, data availability to support adjustments may be limited. Moreover, adjustments to published SMRs are crude approximations at best and could result in bias themselves. When available, data from internal comparisons should be preferred for dose-response analyses of working populations. When internal comparison data are available, the risk assessor should evaluate the potential for bias from continued medical surveillance.

B.5.2 Healthy Worker Survivor Effect

The healthy worker survivor effect (HWSE) occurs when healthy workers continue to work and unhealthy workers leave employment prematurely or are reassigned to less hazardous work because of their poor health. A potential exacerbating factor is a possible health benefit from employment compared to unemployment, such as the beneficial effect of physical exertion in reducing cardiovascular risk. In any case, exposure is a condition of employment, which itself may be conditional on exposure, health status, or both. The likely effect from these relationships is attenuation of the estimated dose-response.

Methods for mitigating HWSE vary. Control of these effects in longitudinal studies tends to involve one or more factors: age at hire, employment duration, employment status, time since hire, and age at risk [Checkoway et al. 2004]. Methods have typically involved confounding control by restriction, by matching (stratifying), or by covariate adjustment. For example, HWSE controls have included restricting the analysis to participants alive after a minimum length of time since hire; adjusting for employment status as a time-dependent variable;
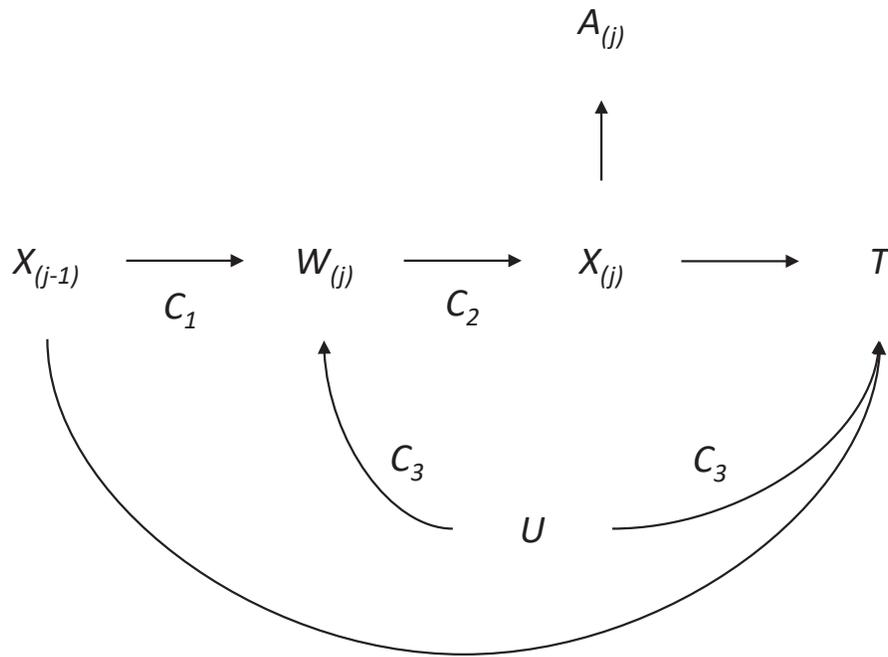
Figure B-1. Directed acyclic graph representing healthy worker survivor effects. Let *j* be index age; *A*, exposure cumulated over follow-up; *X*, continuous exposure; *W*, index employment status; *U*, a common cause of *W* and *T*; and *T*, the index survival time. The three components of survival bias, as expressed by Naimi et al. [2013], are shown as C_1, C_2, and C_3. Adapted from Naimi et al. [2013].

and using time lags (exposure windows). However, it is now recognized that the nature of HWSE may preclude complete control of the effect by standard approaches [Buckley et al. 2015; Naimi et al. 2013]. This is perhaps best explained by the causal diagram in Figure B-1, in which Naimi et al. [2013] described three components of HWSE. Component 1 (C_1) is the association between prior exposure ($X_{(j-1)}$) and employment at age j (W_j), component 2 (C_2) is the association between employment status and subsequent exposure ($X_{(j)}$), and component 3 is the association between employment status and survival time (*T*). If all three components are present, then a standard confounding control that treats employment status as a time-varying confounder in Cox, Poisson, or logistic regression (i.e., standard methods) is inappropriate and may result in bias (Table B-2). When all three components are likely, then the use of more sophisticated nonstan-

dard analytic methods, such as G-estimation, parametric G-formula, and inverse-probability-weighted marginal structural models, is preferred to appropriately control for healthy worker survivor bias [Buckley et al. 2015]. This is because the deleterious health effect from a prior exposure may affect employment status (i.e., violates the third aspect of a confounder).

Of course, a key consideration is whether it is reasonable for exposure to influence employment status. For example, strong survivor effects are much less likely to occur in late-onset adverse effects (e.g., malignant mesothelioma) compared to debilitating effects (or precursor effects) that present during employment years (e.g., occupational asthma). Thus, risk assessors must evaluate the severity and likelihood of survivor effects on the basis of spatial and temporal relationships between employment, exposure, and outcome.

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Table B-2. Associations contributing to Healthy Worker Survivor Effect (as shown in Figure B-1) and recommended analytic methods. (Adapted from Naimi et al. [2013].)

Component			Confounding by employment status?	Employment status affected by prior exposure?	Analysis method*
C_1	C_2	C_3			
1	1	1	Yes	Yes	Non-standard
1	1	0	No	Yes	Standard, employment status unadjusted
1	0	1	No	Yes	Standard, employment status unadjusted
0	1	1	Yes	No	Standard, employment status adjusted
1	0	0	No	Yes	Standard, employment status unadjusted
0	1	0	No	No	Standard, employment status unadjusted
0	0	1	No	No	Standard, employment status unadjusted
0	0	0	No	No	Standard, employment status unadjusted

*Examples of standard analytic methods are logistic, Poisson, and Cox modeling. Non-standard methods are G-formula and G-estimation of a structural nested model.

When there is a potential for strong HWSE, studies have recently employed methods, such as G-estimation [Bjor et al. 2015; Chevrier et al. 2012; Naimi et al. 2014; Picciotto et al. 2016] and G-formula [Cole et al. 2013; Neophytou et al. 2016], in structural nested models or accelerated-failure-time models. Although promising, studies using these methods are currently sparse; therefore, the evidence available for hazard identification will likely be restricted to studies in which residual HWSE is likely when prior exposure affects employment status. Nevertheless, these new methods may be well suited for dose-response modeling in the dose-response assessment.

HWSE may also result from underestimation of prevalent cases in cross-sectional studies when the adverse effect causes persons to leave employment or move to less hazardous jobs. For example, Eisen et al. [1997] identified significant selection bias in estimates of asthma prevalence in a cross-sectional study of workers exposed to metalworking fluids. In that study, workers transferred to a job with less exposure because of the onset of asthma symptoms. This resulted in underestimating disease prevalence in those exposed and subsequently overestimating

prevalence among unexposed persons at the time of the health survey (i.e., a negative dose-response). However, a reanalysis of the data using exposure and disease status at the time of asthma onset instead of time of survey revealed significant excess risk. When evaluating occupational cross-sectional studies for risk assessment, risk assessors should determine whether there is a potential for the adverse effect to influence work status. Studies in which influence is likely should be avoided, unless HWSE has been adequately addressed in the study design and execution.

B.5.3 Length of Follow-up

Although often given less attention, the length that a working population is followed in longitudinal studies is an important consideration when evaluating the potential for healthy worker effects. The strength of HWHE diminishes with increasing time since first employment and is essentially no longer present at post-retirement age. Retirees also lose the survival advantage of continued employment. Collectively, this suggests a decrease in healthy worker effects with increasing follow-up

[McMichael 1976]. Risk assessors should be wary of studies of chronic (or latent) adverse effects that have relatively short follow-up periods. For example, a recent cohort study of mortality patterns among paid Australian firefighters reported a statistically significant deficit in risk of cancer death (SMR = 0.81; 95% CI, 0.72–0.90); however, the average length of follow-up was less than 16 years [Glass et al. 2016]. In contrast, a comparable study of U.S. career firefighters reported excess cancer mortality (SMR = 1.14; 95% CI, 1.10–1.18) in a cohort with average follow-up of 29 years [Daniels et al. 2014]. The relatively short follow-up period in the Australian study is unlikely to counter the selection effects due to pre-employment health criteria for firefighters. In addition to person-years at risk, the percent deceased is a useful indicator of the length and quality of follow-up in cohort studies, especially in examinations of adverse effects that generally occur late in life (e.g., cancer). In the previous example, fewer than 5% of the cohort of full-time Australian firefighters were deceased, compared to over 40% of the U.S. firefighter cohort.

In the previous examples, we discussed the potential for selection bias toward a null association with decreased follow-up. Studies of chronic diseases characterized by a short latent period and short-lived risk after exposure may provide for excess risks that decrease with increasing length of follow-up. For example, leukemia risks that were attenuated with increased follow-up have been observed in follow-on studies of working populations exposed to benzene and ionizing radiation [Boice et al. 2011; Daniels et al. 2013; Rinsky et al. 2002; Silver et al. 2002]. Thus, the risk assessor must also consider effect modification by temporal factors that are associated with the length of follow-up.

B.6 Other Potentially Important Sources of Bias

B.6.1 Model-form Misspecification Error

It is generally understood that any mathematic model of the dose-response is not the "true model"

that generated the observed data; at best, it only approximates truth [Posada and Buckley 2004]. Thus, model-form misspecification results when the mathematical structure of the assumed causal model substantively differs from the true biologic dose-response. The error can be sizeable when the assumptions of the model are not appropriate for the data. Errors in variable selection and/or definition (i.e., variable coding) can lead to spurious dose-response associations. This error is particularly problematic in hazard identification because investigators rarely discuss statistical methods used to counter model-form error. At a minimum, not accounting for this error results in overvaluing estimate precision.

Various methods are available to reduce model-form bias and aid in model selection, such as penalized criteria (e.g., AIC, BIC, and Mallow's Cp), cross validation methods, and model averaging (aggregation) techniques [Arlot and Celisse 2010; Buckland et al. 1997; Burnham and Anderson 2002; Burnham and Anderson 2004; Cox Jr and Ricci 2005; Posada and Buckley 2004; Symonds and Moussalli 2011]. In particular, the use of multi-model ensemble methods (e.g., Bayesian model averaging and simulated inference) that combine results from multiple plausible models typically provides for greater accuracy than that obtained from any single model [Buckland et al. 1997; Raftery et al. 1997]. For this reason, in dose-response analyses NIOSH generally prefers ensemble methods to statistical model selection criteria when data allow. An exception is a case with compelling mechanistic evidence of a specific dose-response function (see section 5.4).

B.6.2 Publication, Interpretation, and Analysis Biases

A publication bias refers to an editorial preference for publishing findings, which distorts inferences made from available evidence. For example, a positive results bias may occur when authors and editors are more likely to publish positive findings rather than null findings. Publication bias can also

occur when there is reluctance to publish disparate or controversial results, or when an emerging issue drives publication such that preliminary data are more likely to be published. Publication bias is plausible in all studies; however, observational and experimental animal studies are more susceptible than randomized clinical trials [Easterbrook et al. 1991]. In all cases, published data can misinform on the consistency of evidence used for hazard identification. Risk assessors should be cognizant of the potential for publication bias and give appropriate attention to all findings, including those from negative studies. Attempts should be made to uncover relevant unpublished works.

Interpretation bias arises from improper inference or speculation based on a naïve or deliberate lack of impartiality by the interpreter. In this case, the interpreters are the study researchers, who interpret their findings at publication, or risk assessors, who translate findings for risk assessment. Research objectivity is always challenged by the ever-present interaction between data and judgement; therefore, interpretation is never completely independent of opinion, notion, or conviction [Kaptchuk 2003]. The potential for significant interpretation bias is likely smaller in the peer-reviewed literature than in trade journals and commercially funded technical reports. Information on potential conflicts of interest or disclosures can be useful in assessing the potential for interpretation bias. A willingness to examine alternative interpretations by investigators and risk assessors alike will lessen the potential for bias. Rigorous peer and public reviews also aid in avoiding interpretation bias.

Analyses bias results for errors in analyzing the data, such as inappropriate analytical strategies (e.g., overmatching, model misspecification, and post hoc analyses). In the course of any study, researchers make several decisions on data collection and analysis, including exploration of analytic alternatives. In some instances, these decisions cannot or are not made beforehand; therefore, they are likely informed by study information. This construct is referred to as "researcher degrees of freedom" [Simmons et al. 2011], which can lead to higher false-positive rates and inflated effect sizes (inflation bias) [Ioannidis 2008; Wicherts et al. 2016]. For example, exhaustive exploitation of study data to achieve significant findings is a source of inflation bias called p-hacking or data dredging [Head et al. 2015; Raj et al. 2017]. As in publication bias, p-hacking results in a conditioning of the literature by presenting only true or false positives. Uncovering the bias can be difficult, in part because many researchers do not recognize it as a real problem. The bias can be reduced by specifying statistical analyses a priori in an analysis plan. In general, post hoc analyses should be avoided. Study designs that are best described as exploratory are most vulnerable to significant bias from p-hacking [Teixeira 2018]. Ideally, studies should be restricted to testing specific hypotheses.

B.6.3 Effect Modification and Interaction

The terms *effect modification* and *interaction* have been used interchangeably in the literature; the former is seemingly preferred by epidemiologists and the latter by statisticians. It has been proposed that, in the strictest sense, these terms describe different phenomena [Vanderweele 2009]. Effect modification is described as a condition in which the exposure-related effect varies by levels of an extraneous factor [Checkoway et al. 2004]. Typically, the extraneous factor is a descriptor of subpopulations (e.g., gender, race); therefore, effect modification may elucidate susceptibility differences in the population. For example, suppose a study reported an association between exposure to agent X and lung cancer in women but not in men. In this case, gender is the effect modifier of agent X for causing lung cancer. There is one intervention (exposure), and the susceptible population is women. In contrast, an interaction specifically refers to the effect of two exposures together to be different (either more or less) than the combination of the two effects considered separately. Thus, an interaction describes the causal effects of the two exposures combined. For example, the joint effects of radon exposure and smoking status on lung cancer differ such that the excess relative risk per unit of radon exposure among nonsmokers is higher than that of smokers

[Lubin et al. 1995a]. In this case, there are two possible interventions (smoking and radon exposure). Interaction effects can range from profoundly antagonistic to strongly synergistic. Unfortunately, most studies available for risk assessment have not examined effect modification by factors other than race or gender, and information is usually insufficient to draw conclusions on potential interactions [Knol and VanderWeele 2012].

B.6.4 Random Error

Random error is the variation of results and inferences from the truth, occurring only because of chance. Effect measures are influenced by random variation in many components of an epidemiologic study. For example, a major contributor to random error in human studies is the process used to select study participants. This process is referred to as sampling, and the random error contribution is known as sampling variation or sampling error [Rothman et al. 2008]. Random variation around true values related to estimates used in statistical models is another source of random error.

The common measure of random error in an estimation process is its variance, and the inverse of variance is a measure of statistical precision of the estimate. Precision can be improved by increasing the sample size, thus reducing the variance. This variance can also be reduced for a given sample size through design improvements; this is referred to as increasing study efficiency [Rothman et al. 2008]. Typically, the random error that is associated with the point estimate reported in a study is reflected by its associated confidence interval or p-value. In hazard identification, more weight is generally given to effect estimates with better precision (e.g., narrower confidence intervals). Nevertheless, estimate precision does not reflect a lack of bias from systematic errors. Moreover, random measurement error can also lead to biased estimates of the dose-response [Carroll et al. 2006]. For example, as previously discussed, when explanatory variables (e.g., dose) are measured with error, the regression coefficient in dose-response models is typically biased toward the null.

Unfortunately, deleterious effects of random error are rarely accounted for in epidemiologic studies, although recently some studies of health effects associated with ionizing radiation have made headway. In particular, regression calibration and Monte Carlo simulation have been used sparingly to account for uncertainty in dose-response analyses in studies relying on complex dosimetry systems subject to shared and unshared measurement error [Fearn et al. 2008; Pierce et al. 2008; Simon et al. 2015; Stram et al. 2015; Zhang et al. 2017].

APPENDIX C

EMERGING PRACTICES

C.1 Occupational Exposure Banding

Occupational Exposure Limits (OELs) play a critical role in protecting workers and emergency response personnel from exposure to dangerous concentrations of hazardous materials [Schulte et al. 2010]. In the absence of an OEL, determining the appropriate controls needed to protect workers from chemical exposures can be challenging. According to the EPA, the Toxic Substances Control Act (TSCA) Chemical Substance Inventory currently contains over 85,000 chemicals that are commercially available [EPA 2015], yet only about 1,000 of these chemicals have been assigned an authoritative (government, consensus, or peer reviewed) OEL. Furthermore, the rate at which new chemicals are being introduced into commerce significantly outpaces OEL development, creating a need for guidance on thousands of chemicals that lack reliable exposure limits. Occupational exposure banding, also known as hazard banding or health hazard banding, is a systematic process that uses both qualitative and quantitative hazard information on selected health effect endpoints to identify potential inhalation-based exposure ranges or categories. The NIOSH occupational exposure banding process seeks to create a consistent, documented process to characterize chemical hazards so that timely, well-informed risk management decisions can be made for chemicals lacking OELs [NIOSH 2019].

The concept of using hazard-based categories to communicate potential health concerns, alert workers to the need for risk management, and inform exposure control requirements is not new. Numerous hazard classification and category-based systems have seen extensive use in the occupational setting. Such systems are deeply embedded in occupational hygiene practice, particularly in the pharmaceutical industry, and are also elements of well-developed, modern hazard communication programs (e.g., United Nations 2013 Globally Harmonized System of Classification and Labelling of Chemicals [2013]). The NIOSH occupational exposure banding process is distinguished from other hazard classification and category-based systems in several ways. These unique attributes of the NIOSH process include (1) a three-tiered system that allows users of varying expertise to utilize the process, (2) determination of potential health impacts based on nine toxicological endpoints separately, (3) hazard-based categories linked to quantitative exposure ranges, and (4) assessment of the process via extensive evaluation exercises to determine accuracy and repeatability.

To apply the NIOSH occupational exposure banding process, it is important to understand the three tiers of the process. Each tier has different requirements for data sufficiency, which allows a variety of stakeholders to use the process in many different situations. The most appropriate tier for banding depends on the availability and quality of the data, how the data will be used, and the training and expertise of the user. Whereas Tier 1 requires relatively little information and modest specialized training, each successive tier necessitates more chemical-specific data and more user expertise to assign an Occupational Exposure Band (OEB) successfully. A primary goal of Tier 1 is to give the user a quick summary of the most important health effects associated with exposure to the chemical of interest and quickly identify extremely toxic chemicals that should be considered for substitution or elimination. Tier 2 requires the user to examine several publicly available databases and extract relevant toxicological and weight-of-evidence data to be used in the NIOSH banding algorithm. Tier 3 employs expert judgment to critically evaluate experimental data and discern toxicological outcomes.

Another important component of the NIOSH occupational exposure banding process is the inclusion of five exposure bands. Occupational exposure banding uses limited chemical toxicity data to group chemicals into one of five bands, ranging from A through E. These bands, or OEBs, define the range of exposures expected to be protective of worker health. Band E is the most protective band for the most dangerous chemicals, whereas band A is the least protective for the least dangerous. One

major benefit of occupational exposure banding is that the amount of time and data required to categorize a chemical into an OEB is significantly less than that required to develop an OEL.

The burden of worker and responder exposure to potentially hazardous chemicals that lack authoritative OELs is considerable, and the need for risk management for these chemicals is clear. Occupational exposure banding is one way to provide this type of guidance. An OEB provides more than a range of exposures that is expected to be protective of worker health. Rather, an OEB can be utilized to identify potential health effects and target organs, inform implementation of control interventions and preparedness plans, inform medical surveillance decisions, and provide critical information quickly.

For more information about the NIOSH occupational exposure banding process and the companion electronic banding tool (e-Tool)), refer to the NIOSH occupational exposure banding safety and health web topic page at: https://www.cdc.gov/niosh/topics/oeb/default.html

## C.2 Emerging Alternatives To Assessing Apical Endpoints

An apical endpoint is an observable outcome in a whole organism, such as a clinical sign or pathologic state, that is indicative of a disease state that can result from exposure to a toxicant [NRC 2007]. For risk assessment, it is typically the final stage of disease progression. Adverse effects are generally related to traditional apical endpoints such as death, reproductive failure, or developmental dysfunction [Villeneuve and Garcia-Reyero 2011]. In some instances, data on the apical effect are not available; therefore, the risk assessment may rely on a non-apical surrogate that lies on the adverse effect pathway (Figure C-1) between the molecular initiating event and the adverse effect (e.g., functional genomics and biomarkers). These sub-organism effects are sometimes referred to as precursor effects.

It has been suggested that the future of risk assessment is likely to shift away from toxicity testing of apical endpoints and move toward research evaluating biologically significant perturbations in toxicity pathways at earlier stages of the disease state. This research is anticipated to use a combination of computational biology and high-throughput *in vitro* tests of human cells and tissues [NRC 2007].

C.3 Biomarkers

A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal physiologic processes, pathologic processes, pharmacologic responses to a therapeutic intervention, or susceptibility [Atkinson et al. 2001; Schulte 1993]. In the context of an adverse effect, the biomarker refers to a biological analyte that predicts the individual's disease state. Biomarkers include conventional measures, such as blood pressure, blood cholesterol, and enzyme levels; however, recent advancements have focused on cellular, genetic, and molecular markers that are sought as screening tools for early diagnosis of a severe disease (e.g., lung cancer and cardiovascular disease). The utility of defining sets of responses based on multiple genomic, transcriptomic, proteomic, and metabolomic markers and processes and/or second messenger and other biochemical pathways is an evolving area of work [Cote et al. 2016].

Risk assessors prefer to measure early indicators of serious health effects rather than wait for frank expression of disease. For example, lung cancer is a rare (<60 cases per 100,000 person-years) and serious (<20% survival after 5 years from diagnosis) adverse effect observed predominantly at ages 65 years or older and at later stages of disease progression [Howlader et al. 2016]. Epidemiologic studies of occupational lung cancer require large populations who are observed over a long period to ensure adequate statistical power for effect sizes typically observed. A biomarker intended for early indication of lung cancer could act to relax some of these design requirements. Research suggests that exhaled breath contains organic compounds from metabolic processes that can vary between healthy subjects and subjects with lung cancer, making it a
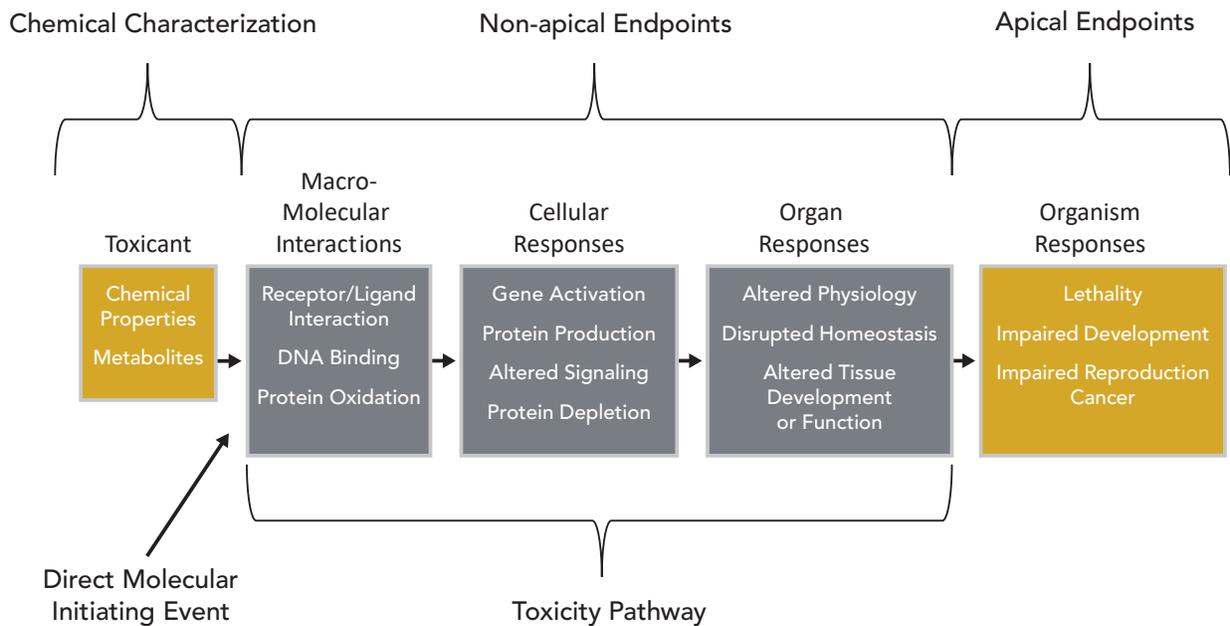
Figure C-1. Diagram of the adverse outcome pathway. A chemical (or its metabolites) interacts with a molecular target to initiate leading a sequence of higher-order effects to produce an adverse effect relevant to risk assessment. Adapted from Ankley et al. [2010].

potentially viable biomarker for early onset of disease [Dent et al. 2013]. If the relationships between dose, the exhaled breath condensate analytes of interest, and lung cancer can be adequately characterized, then exhaled breath condensate may also be a useful response metric in future dose-response analyses of lung carcinogens.

Quantitative risk assessment of biomarkers is an area of active research and development and has been successfully used for risk assessment only in very limited situations [Cote et al. 2016; Poirier 2016]. As such information evolves, the risk assessor must be prepared to consider whether such exposure-biomarker associations are useful relationships to model in occupational risk assessment.

C.4 Use of Genetics and Epigenetics in Risk Assessment

A growing body of literature demonstrates that genetic and epigenetic factors condition biological responses to occupational and environmental hazards or serve as targets of them. Generally, genetic and epigenetic data might be used as endpoints in hazard identification, indicators of exposure, effect modifiers in exposure estimation and dose-response modeling, and descriptors of mode of action (MoA) in characterization of toxicity pathways. Vast amounts of genetic and epigenetic data may be generated by high-throughput technologies. Ideally, these data can be useful for assessing variability and reducing uncertainty in extrapolations and to help identify previously unidentified biological perturbations that may be of interest in risk assessment [Schulte et al. 2015].

One of the most critical areas to understand in the incorporation of genetic and epigenetic information in risk assessment is in the area of gene-environment interactions. The term *gene-environment interaction* can involve a range of interpretations of joint effects, including the risk of a single genotype across a range of environmental exposures, or the risk of exposure across a range of genotypes. Many

of the potential approaches to evaluating the impact of gene-environment interactions are reviewed in Schulte et al. [2015].

Future risk assessments may involve acquired changes in the somatic genome or changes in the epigenetics, which comprise the factors influencing expression of the genome. Techniques for addressing these require deep knowledge of mechanisms of action of toxic agents and well-defined experimental designs to address specific risk assessment questions. The elucidation of perturbations in genetic and epigenetic information on human health is likely to be a rich area for future risk assessment. A framework for organizing the research around these types of risk assessment questions can be found in Schulte et al. [2015]. One area where some progress has been made in developing genetics for quantitative risk assessment is in the use of high-throughput analyses, as described in the next section.

C.5 Molecular Toxicology and High-Throughput Analysis

Because of the lack of full toxicologic data on most chemicals, NIOSH is investigating the utility of high-throughput screening and *in vitro* short-term tests for occupational risk assessment. In the past decade, there has been an exponential increase in the publication of new toxicity data focusing on genomic analysis using high-throughput screening and *in vitro* short-term exposure. The paradigm for assessing chemical risks to human health is rapidly changing because of the availability of this toxicogenomic information and because of increased understanding of the gene-environment interactions.

In 2007, the U.S. Environmental Protection Agency (EPA) requested that the National Research Council (NRC) conduct a complete review of toxicity testing methods and strategies. NRC presented its long-range vision and strategy to advance toxicity testing [NRC 2007]. By recognizing the importance of NRC's vision, several federal agencies (the EPA, National Institutes of Environmental Health Sciences/National Toxicology Program, National Institutes of Health, and Food and Drug Administration) formed a collaborative program known as Toxicity Testing in the 21st Century (Tox 21). This program uses high-throughput screening methods and computational toxicology approaches to screen, rank, and prioritize chemicals for further testing and assessment. The Tox 21 program has screened more than 10,000 chemicals by using approximately 70 *in vitro* cell-based assays with 15-point dose-response at the NIH Chemical Genomics Center, with innovative robotic technology [Kavlock et al. 2009]. In addition to Tox 21, the EPA's Toxicity Forecaster, simply known as ToxCast, has generated data for over 1,800 subsets of chemicals from Tox21 inventory by expanding into more biological endpoints. ToxCast screens chemicals for dose-related changes in at least six doses in over 700 high-throughput assays (both cell-based and cell-free) and 300 signaling pathways that cover a wide range of cell responses [Richard et al. 2016]. The EPA describes in "Next Generation Risk Assessment: Recent Advances in Molecular, Computational, and Systems Biology" how new molecular, computational, and systems biology data and approaches could better inform risk assessment [EPA 2014].

Overall, the screening data generated by these programs are used to predict the toxicity of chemicals and to prioritize the chemicals that need further comprehensive toxicity evaluation. In addition, the results from high-throughput analysis could be used in adverse outcome pathway (AOP) analysis, although the specifics are still being worked out [Tollefsen et al. 2014].

Thomas et al. [2011; 2013] demonstrated a high degree of correlation between the BMD values for transcriptional changes and the corresponding apical endpoint changes in male Sprague-Dawley and F344 rats and in female B6C3F1 mice exposed to various chemicals. The authors went on to suggest that the transcriptional points of departure (PoD) values could be used as potential surrogates for both cancer and non-cancer points of departure. Kuppusamy et al. [2015] and Alyea et al. [2012] demonstrated concordance between the

changes in epigenetics and apical endpoints. In addition, Schulte et al. [2015] discussed the utilization of genetic and epigenetic data in occupational health risk assessment.

Applications of the molecular toxicology approach could include screening out problematic chemicals, identifying critical *in vivo* testing, prioritizing data-poor chemicals, and replacing traditional testing with more efficient alternatives. Although the current effort to use molecular toxicology data looks promising, additional data and methods of analysis are needed. For these efforts to continue, strong collaboration between agencies is needed as well.

C.6 Quantitative Structure-Activity Relationships

The literature on Quantitative Structure-Activity Relationship (QSAR) models is vast (for a review, see Roy et al. [2015]), and the models have been widely applied in pharmaceutical research and risk assessment. In order to predict a response in untested chemicals, QSAR models link chemical, physical, and structural properties to a biological outcome by means of a mathematical model. Currently, no human health risk assessment has been based solely on a QSAR analysis; however, as toxicity testing moves away from animal testing [NRC 2007], such approaches may become more common. Ideally, QSAR approaches can link fundamental chemical properties to adverse outcome pathways and, eventually, whole-organism response (e.g., cancer, death) [Ankley et al. 2010]. Although QSAR modeling in risk assessment is an emerging discipline, general guidelines for its use are outlined below. However, because the science is still in its infancy, an individual approach should be taken in tailoring the guidelines to a given situation.

The first issue in using QSAR modeling in a risk assessment framework is the adverse outcome predicted and its relevance to human health. To date, most QSAR models focus on prediction of single outcomes such as the median lethal dose (i.e., LD_{50}) from chemical structural properties. Such outcomes

are often a gross measure of toxicity and say little about low levels of exposure. Others, which compute the lowest observed adverse effect level (LOAEL), or an equivalent endpoint [Mumtaz et al. 1995], may be directly applicable to the risk assessment but require strong assumptions that should be carefully reviewed. QSAR modeling is under development to predict the entire dose-response curve, which would provide additional information on toxicity. In sum, care should be taken when choosing the endpoint for a risk assessment. If the endpoint is a gross measure of toxicity, then it may be useful to classify a chemical on the basis of its relative toxicity but unreasonable to provide an exposure level in the nature of an occupational exposure limit (OEL). Predicting the entire dose-response curve may have additional applications for quantitative risk assessment. Any QSAR-based risk assessment should start with exploring the limitations of the model and the predicted endpoint *a priori*, and subsequent assessment should carefully consider these limitations.

Once the endpoint/model is chosen, it is important to assess the validity of the QSAR model. This is usually done in a statistical analysis of the prediction in terms of a "leave one out" (or "leave many out") hold-out analysis. Here, the model is fit to a reduced dataset and the held-out data are predicted. Such analyses provide a useful tool to measure the accuracy of the model within the context of the entire dataset tested. Note that chemicals beyond the scope of the dataset will be less likely to behave as predicted. The model should have a high degree of accuracy in prediction for the chemicals of interest, where accuracy is defined relative to the analysis at hand. Further, the model should be validated and a sensitivity analysis (including various plausible assumptions and defaults for the model structure) should be performed. Finally, because the estimates are based upon limited or no data, the preliminary nature of the assessment should be stressed. If new data are made available that suggest the chemical is more or less toxic, the risk assessment should be updated with the new data within a reasonable timeframe.

C.6 Nanomaterials Risk Assessment

C.6.1 Overview

Given the large and growing number of engineered nanomaterials (ENMs) with limited data, as for other emerging and existing substances produced or used in the workplace, alternative test strategies (i.e., toxicological approaches other than primary animal testing) such as high-throughput screening and *in vitro* exposures may help to fill the gaps by providing data that could be used in validated hazard and risk assessment models [Drew et al. 2017; Kuempel et al. 2012].

C.6.2 Dose Normalization *In Vitro* and *In Vivo*

As risk assessments begin to rely largely on *in vitro* data and *in silico* modeling, accurate description of dose both *in vitro* and *in vivo* will be key to evaluating these dose-response relationships and validating alternative test strategies for use in risk assessment [Gangwal et al. 2011; Oberdörster 2012]. Many *in vitro* studies have used doses that are much higher than occupationally equivalent lung doses [Gangwal et al. 2011]. Such studies could be useful for hazard identification and screening evaluations but may overpredict the *in vivo* response. *In vitro* studies are also limited in the cell types represented and interactions among cells.

A challenge in quantifying the dose-response relationships *in vitro* is estimating the effective dose, i.e., the dose that reaches the target cells. The particle surface area doses to cells can differ significantly at a given mass concentration (µg/ml), because of the differences in the specific surface area (m²/g) of particles of different sizes and differences in the sedimentation and diffusion properties of particles in liquid-based systems [Hinderliter et al. 2010]. The *In Vitro* Sedimentation, Diffusion, and Dosimetry (ISDD) model was developed to account for differences in settling velocity in the liquid media based on particle size, density, and specific surface

area [Hinderliter et al. 2010]. Adjusting the *in vitro* dose to estimate the total surface area of nanoparticles that reach cells in the petri dish was shown to better correlate with acute *in vivo* endpoints [Hinderliter et al. 2010; Teeguarden et al. 2007].

C.6.3 Correlation of *In Vitro* and *In Vivo* Responses

Several studies of ENMs have shown good correlation between the *in vitro* and acute *in vivo* inflammation-related responses to poorly soluble particles [Donaldson et al. 2008; Rushton et al. 2010; Zhang et al. 2012]. The dose metric in these studies differed, including comparison of either the total particle surface area to the total cell surface area *in vitro* or *in vivo* (cm²/cm²) [Donaldson et al. 2008], the response per unit particle surface area [Rushton et al. 2010], or the area under the dose-response curve [Zhang et al. 2012]. The steepest portion of the dose-response slope showed the best correlation of *in vitro* with *in vivo* responses [Han et al. 2012; Rushton et al. 2010]. Responses included cell-free generation of reactive oxygen species (ROS), rat lung epithelial cell release of lactate dehydrogenase (LDH) or induction of protein oxidation endpoints, and rat pulmonary inflammation measured as polymorphonuclear (PMN) leukocyte response in bronchoalveolar lavage fluid (BALF) after intratracheal instillation (IT) exposure to different ENMs.

Pulmonary fibrosis *in vivo* (in rodents) and fibrosis-related markers *in vitro* (in rodent or human lung cells) have been shown to be correlated with exposure to some ENMs. Specifically, activation of the NLRP3 inflammasome and pro-fibrogenic endpoints *in vitro* or fibrosis *in vivo* have been associated with exposure to carbon nanotubes [Hamilton et al. 2009; Li et al. 2013; Sager et al. 2014; Wang et al. 2012; Wang et al. 2011]. With further validation, an *in vitro* inflammasome activation assay may be useful for assessing the potential for chronic adverse effects of carbon nanotubes and other ENMs.

C.7 Alternative Methods for Nanomaterials

C.7.1 Comparative Potency Estimation

One promising use of alternative test strategies data is comparative potency analyses between nanomaterials and benchmark materials for use in the development of OEBs [Kuempel et al. 2012]. Benchmark materials can serve as points of reference for comparison to ENMs. Benchmark materials are well-characterized substances within biological MoA categories for which the health hazards are well known and quantitative risk estimates have been (or could be) developed [Kuempel et al. 2012; Nel et al. 2013]. Possible benchmark materials to evaluate inhalation hazards may include fine crystalline silica, asbestos, and ultrafine titanium dioxide and/or carbon black [Oberdörster et al. 2005a]. These comparative toxicity analyses would be conducted *in vitro* for a set of ENMs, along with benchmark particles (including positive and negative controls or references), to which the new materials could be compared. The *in vitro* to *in vivo* dose-response relationships would be validated for the benchmark materials in specific assays. A parallelogram approach [Schoeny and Margosches 1989; Sobels 1977; Sutter 1995] has been used for comparative toxicity and risk estimation and has also been proposed for use in setting provisional OELs of pharmaceutical intermediates, including using *in vitro* data [Maier 2011]. The use of *in vitro* dose-response data to estimate a PoD directly has been proposed; it would involve using methods similar to those used for *in vivo* data, including adjustment of the PoD by uncertainty factors (initially, until more evidence is available) [Crump et al. 2010]. Such comparative approaches could be used in deriving initial OELs or OEBs for individual ENMs or groups of ENMs [Kuempel et al. 2012].

Given the limited data for developing OELs for ENMs, methods have been developed to prioritize or group ENMs based on the available subchronic or chronic dose-response data for benchmark materials

and the utilization of shorter-term *in vivo* data for many ENMs [Arts et al. 2015; Drew et al. 2017; Hristozov et al. 2016]. Several QSAR models have been developed, which describe the important factors influencing the toxicity and allow for hazard grouping and ranking [Burello and Worth 2011; Gernand and Casman 2014; Hristozov et al. 2016; Oh et al. 2016]; however, these models have not been used in human health risk assessment. Still lacking in these frameworks is an integrated methodology to utilize quantitative dose-response data to group EMNs by hazard potency, using biological responses and dose metrics that allow for the estimation of human-equivalent concentration and development of categorical OELs [Schulte et al. 2018]. More comprehensive data across a range of ENMs and experimental designs are needed to develop predictive models using alternative data to the rodent bioassays typically used in risk assessment.

C.7.2 Hazard Classification/ Clustering

NIOSH and others are exploring methods to utilize physicochemical properties—such as particle size, shape, solubility, crystal structure, and chemical composition—as predictors of a material's hazard potency, such as tested in high-throughput cellular studies and validated in limited rodent studies. Potency is the inverse of dose (i.e., higher potency substances are those with a lower dose associated with an adverse effect). In these ongoing analyses, NIOSH is investigating the dose-response relationships and substance-specific physicochemical data, and it is using statistical learning methods such as Random Forests to identify groups of similarly behaving materials with respect to hazard potency [Drew et al. 2017]. The adverse outcomes of interest include pulmonary inflammation, fibrosis, cancer, and systemic effects associated with inhaled nanoscale particles. In current analyses of acute pulmonary inflammation, a set of 16 microscale and nanoscale particles in a training dataset have been grouped into four potency clusters, including three groups for nanoscale particles, which are 4–175 times more potent than a fourth group containing

a microscale reference particle. These analyses illustrate proof of concept for grouping particles by pulmonary hazard potency [Drew et al. 2017].

Next steps are to evaluate an *in vitro* dataset of some of the same materials as in the *in vivo* dataset to investigate the possible utility of *in vitro* studies of cellular responses to particle exposure that are involved in the *in vivo* mechanism of activation of pulmonary inflammation associated with particle exposure, including cytokine, gene transcription, and cell toxicity endpoints. Ultimately, it is envisioned that extended and validated analyses will be used as a framework to develop initial OEL categories or OEBs as hazard inputs into nanomaterial control banding tools [Drew et al. 2017; Kuempel et al. 2012].

C.7.3 Validation

A key challenge to utilizing alternative test strategies data is the development and application of validation criteria. Validation would include evaluation of variability across laboratories and selected assays of reference particles. Such evaluations for ENMs have shown considerable interlaboratory variability in dose-response relationships for the same ENMs across laboratories [Bonner et al. 2013], especially in the *in vitro* assays [Xia et al. 2013].

To facilitate the validation and implementation of alternative test strategies data, standard sets of particle descriptors, dose metrics, and response parameters are needed to compare biological MoA and dose–response relationships across different studies [Kuempel et al. 2012]. *In vitro* data could be used in a tiered toxicology testing such that selected materials (e.g., highest and lowest toxicity within a category) in the *in vitro* assays would go on for *in vivo* testing.

C.8 Non-Chemical and Cumulative Risk Assessment

With the exclusion of ionizing radiation, quantitative risk assessment of non-chemical stressors has received little attention in the risk assessment community. Moreover, risk assessment methods have largely focused on a single stressor, although risks often involve complex exposures to multiple stressors from multiple routes and pathways. Recently, there has been interest in assessing risks from non-chemical stressors separately and in combination with chemical exposures. For example, the National Research Council has recommended that risk assessors consider exposures to both chemical and non-chemical stressors as sources of cumulative risk [NRC 2009]. Such stressors can include physical, operational, and psychosocial domains. Examples include work stress, heat stress, noise exposures, and vibrational exposures.

Research into risk assessment methods for non-chemical stressors and cumulative risks is ongoing [Lentz et al. 2015; Lewis et al. 2011]. For example, NIOSH has developed methods similar to chemical risk assessment to assess some non-chemical hazards, such as ionizing radiation and noise [NIOSH 1987; NIOSH 1998]. Expanding these methods to include other non-chemical hazards, the joint effects of multiple stressors, and the contribution of non-occupational stressors to occupational risk are areas of interest in NIOSH risk assessment.

Concerning cumulative risk, the literature has focused on the potential for interactions among combined chemicals producing synergistic effects [Carpenter et al. 2002; Fox et al. 2017; Hertzberg and Teuschler 2002; Sexton 2012; Sexton and Hattis 2007]. The EPA has developed a series of reports describing its framework for assessing chemical mixtures and conducting cumulative risk assessment [EPA 1986; EPA 2000; EPA 2003; EPA 2007]. These reports provide detailed guidance on cumulative risk that can be adapted to occupational settings. Other frameworks are available [Meek et al. 2011; Moretto et al. 2017]. More recently, an informative report on risk assessments involving combined exposures to multiple chemicals has been published by the OECD [OECD 2018a]. The report provides an overview of the technical aspects, limitations, and uncertainties associated with various approaches and methodologies available to assess health risks from combined exposures to multiple chemicals.
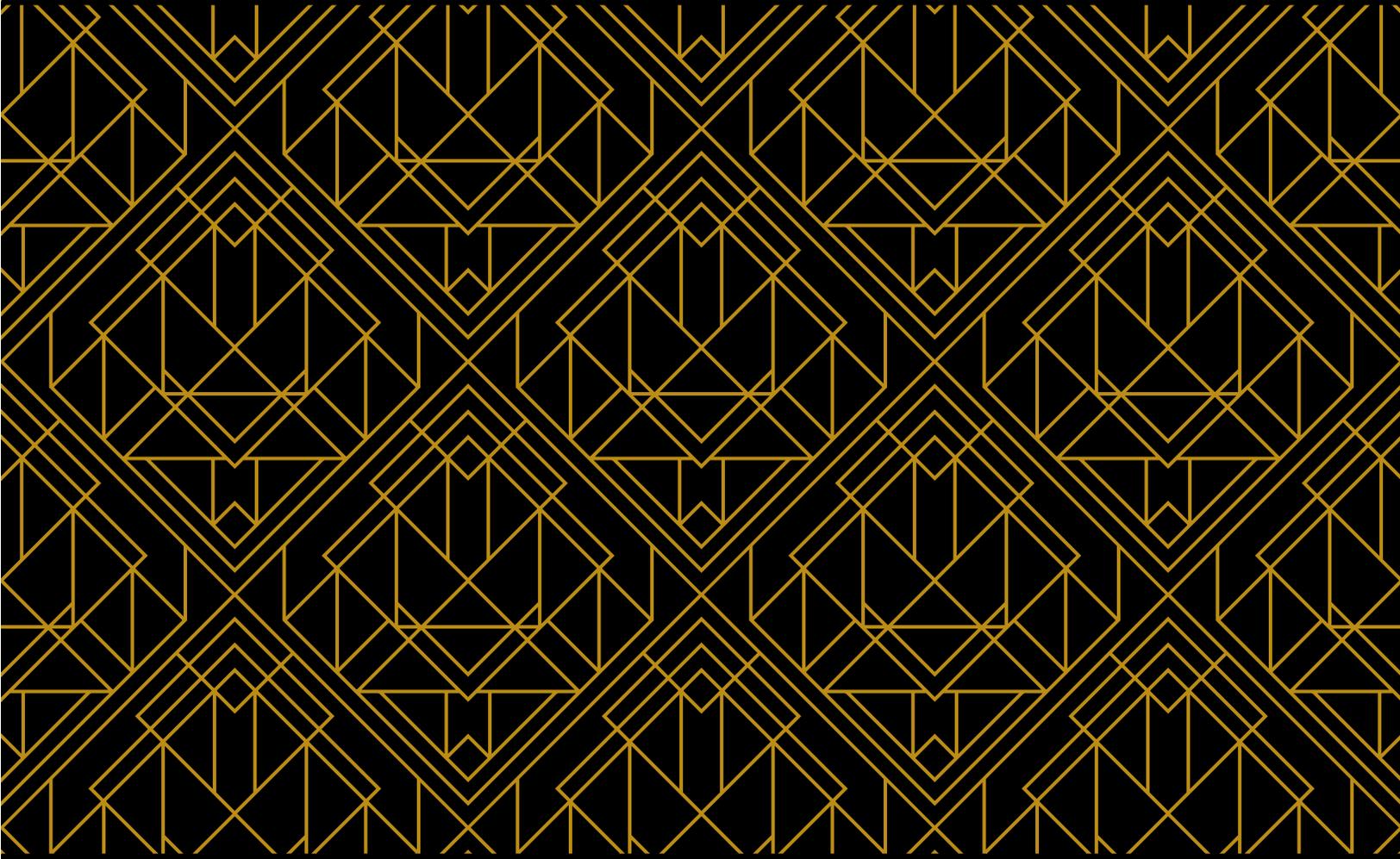
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