

Exposure Estimation and Interpretation of Occupational Risk: Enhanced Information for the Occupational Risk Manager

Martha Waters,¹ Lauralynn McKernan,² Andrew Maier,³ Michael Jayjock,⁴ Val Schaeffer,⁵ and Lisa Brosseau⁶

¹Division of Applied Research and Technology, National Institute for Occupational Safety and Health, Cincinnati, Ohio

²Education and Information Division, National Institute for Occupational Safety and Health, Cincinnati, Ohio

³Department of Environmental Health, University of Cincinnati, Cincinnati, Ohio

⁴Jayjock and Associates, LLC, Langhorne, Pennsylvania

⁵Occupational Safety and Health Administration, Washington, DC

⁶Environmental & Occupational Health Sciences, University of Illinois at Chicago, Chicago, Illinois

The fundamental goal of this article is to describe, define, and analyze the components of the risk characterization process for occupational exposures. Current methods are described for the probabilistic characterization of exposure, including newer techniques that have increasing applications for assessing data from occupational exposure scenarios. In addition, since the probability of health effects reflects variability in the exposure estimate as well as the dose-response curve—the integrated considerations of variability surrounding both components of the risk characterization provide greater information to the occupational hygienist. Probabilistic tools provide a more informed view of exposure as compared to use of discrete point estimates for these inputs to the risk characterization process. Active use of such tools for exposure and risk assessment will lead to a scientifically supported worker health protection program. Understanding the bases for an occupational risk assessment, focusing on important sources of variability and uncertainty enables characterizing occupational risk in terms of a probability, rather than a binary decision of acceptable risk or unacceptable risk. A critical review of existing methods highlights several conclusions: (1) exposure estimates and the dose-response are impacted by both variability and uncertainty and a well-developed risk characterization reflects and communicates this consideration; (2) occupational risk is probabilistic in nature and most accurately considered as a distribution, not a point estimate; and (3) occupational hygienists have a variety of tools available to incorporate concepts of risk characterization into occupational health and practice.

Keywords dose-response relationship, environmental variability, exposure estimation, exposure sampling, hazard quotient, overexposure

This article not subject to U.S. copyright law.

This is an Open Access article. Non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly attributed, cited, and is not altered, transformed, or built upon in any way, is permitted. The moral rights of the named author(s) have been asserted.

Address correspondence to Martha Waters, National Institute for Occupational Safety and Health, 4676 Columbia Parkway, MS R-2, Cincinnati, Ohio; e-mail: mwaters@cdc.gov

INTRODUCTION

For an occupational health and safety professional to make risk-based decisions regarding an occupational exposure scenario, workplace exposure concentrations may be compared to a health-protective exposure limit. This occupational health risk assessment decision process has two primary components:

- 1) exposure assessment: an expression of the exposure concentration in the workplace, and
- 2) risk characterization: a method for comparing the exposure assessment to toxic potency of the chemical involved and translating the result into a risk of adverse health outcomes.

Judgments about risk are often complicated because the exposure estimates are not single values—rather they represent

a range of values due to both variability and uncertainty. The probability of adverse health effects will change with exposure concentration and measures of exposure are distributions; thus, a characterization of risk is most accurately reflected as a probability distribution, not a point estimate. In practice, most occupational risk assessments do not fully address the concepts of risk in a quantitative manner. Comparison of measured or estimated exposure concentrations to the reference occupational exposure limit (OEL) provides insight as to relative exposure acceptability, but does not provide full information of the likelihood or severity of adverse effects as exposure exceeds or is below the OEL. Interpretation of the comparison of workplace exposure concentrations with an OEL (i.e., risk characterization) is important when making decisions about effective exposure control strategies (i.e., risk management measures). Such information will be the driving input for decisions such as identification of processes where engineering controls are necessary, new work practices may be introduced or respiratory protection may be needed. Risk management decisions often depend on the anticipated amount of risk reduction among exposure control alternatives.

This article highlights the basis for key ingredients in an occupational exposure assessment, focusing on important sources of variability and uncertainty that can be useful for characterizing occupational risk in terms of a probability rather than a binary decision of “acceptable risk or unacceptable risk.”

This article highlights current methods related to the characterization of exposure. Considerations are also described for interpreting exposure assessments in the context of exposure or dose-response relationships as an essential aspect of estimating occupational health risks. The primary points of emphasis are:

- Occupational risk is probabilistic in nature and is associated exposure distributions and imprecise OELs, not precise point estimates.
- Exposure estimates and exposure limits are impacted by both variability and uncertainty—a well-developed risk characterization reflects and communicates these considerations.
- Occupational hygienists have a variety of tools available to incorporate probabilistic concepts into risk assessments. Active use of these tools leads to a more robust occupational health program by initiating exposure sampling campaigns, medical surveillance programs, or use of personal protective equipment.

Health and Science Policy Basis for Establishing OELs

The term occupational exposure limit (OEL) is a general term to reflect an airborne exposure concentration that has been recommended as guidance or promulgated as a regulatory control limit for the protection of worker health. The definitions and bases for establishing OELs vary among organizations (Table I). One way to categorize different types of OELs is to denote those that are based solely on considerations

related to the expected concentration-response behavior of the agent (i.e., health-based OELs) vs. those that are derived with the additional considerations of technical feasibility and cost-benefit analyses. However, even beyond such a simple dichotomy, there are additional levels of science and policy decision making that ultimately affect the final OEL (Figure 1).

Describing Exposures

Exposure estimation starts with a definition of the population of exposures to be characterized. Examples include the average exposure of a group of workers performing the same work on a given day, the highest 1-min average exposure generated during a specific work task, or the average daily exposure of an individual worker over a year. Estimation may be based on measurements or on a non-measurement approach such as modeling.

When measuring exposures, resource limitations typically prevent all exposures from being measured, and stratification or grouping is often used to simplify the measurement effort. The sampling unit is defined by the population, group, individual, or task to be characterized; location; exposure agent of interest; exposure averaging period; and possibly additional descriptors of the exposure scenario. Measurements based on the sampling unit definition are then collected from a pre-defined portion of the population or group.

For the exposure characterization to have meaning beyond a single characterization effort, such as the basis for predictions about future exposures, random sampling within a group or strata should be conducted. Inference is also only possible when the exposure distribution being characterized is stationary or not fundamentally changing over time, i.e., there are not changes in factors that modify exposures such as a process change or installation of exposure controls. When such changes occur, a new target group is defined and the new exposure distribution must be characterized separately. When a specific scenario is being evaluated for a specific purpose, i.e., evaluating the use of engineering controls or specific work practices, then a sampling scheme that focused on “worst case” sampling could be employed. The purpose of the sampling campaign is uniquely tied to the decisions on how and where to sample.

Variability and Uncertainty in Exposure Estimation

Fully descriptive exposure information can be quite complex since workplace exposures can vary spatially and over time. This intrinsic variability cannot be reduced but can be characterized with sufficient information and proper survey design. Although not always interpreted as such, exposure concentrations are stochastic. The fullest description of exposures is usually in the form of a statistical exposure distribution for a defined set of exposure scenario descriptors. The exposure distribution is also termed an “exposure profile” within the profession of occupational hygiene.⁽¹⁾

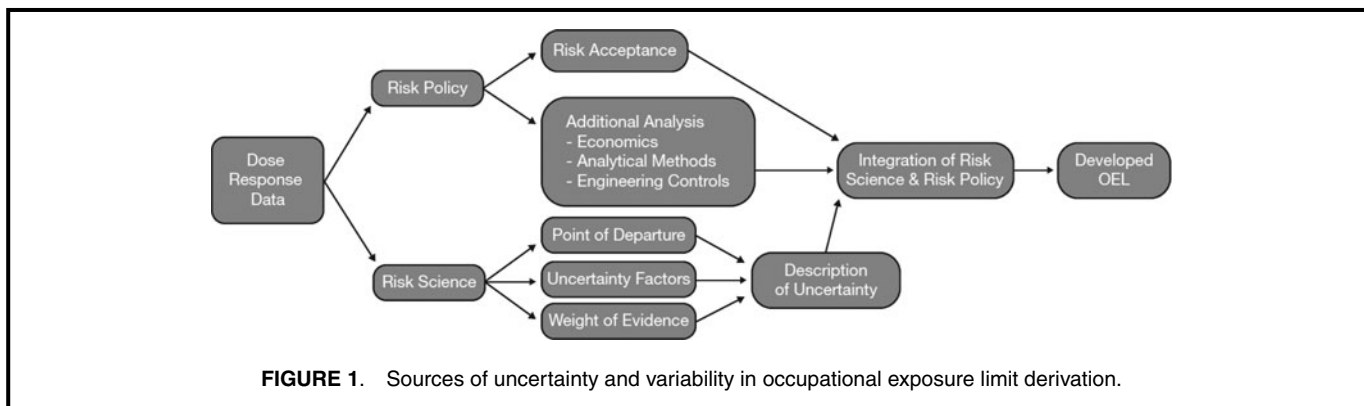
TABLE I. Occupational Exposure Limits (OELs) Developed by Various Organizations^A

| OEL ^B | Definition | Health Basis | Analytical Feasibility | Economic Feasibility | Engineering Feasibility |
|-----------------------------|--|--------------|------------------------|----------------------|-------------------------|
| ACGIH TLV | Threshold Limit Values (TLVs) refer to airborne concentrations of chemical substances and represent conditions under which it is believed that <i>nearly all</i> workers may be repeatedly exposed, day after day, over a working lifetime, without adverse health effects. TLVs are developed to protect workers who are normal, healthy adults. They are not fine lines between safe and dangerous exposures, nor are they a relative index of toxicology. | Yes | No | No | No |
| AIHA-OARS ^C WEEL | The Workplace Environmental Exposure Levels (WEELs) are health-based airborne chemical OELs established to provide guidance where other OELs are not available. The WEELs provide guidance for protecting most workers from adverse health effects related to occupational chemical exposures. WEELs are expressed as either time weighted average or ceiling limits. | Yes | No | No | No |
| DFG MAK | The MAK-values are daily 8-hr time-weighted average values and apply to healthy adults. MAKs give the maximum concentration of a chemical substance in the workplace. | Yes | No | No | No |
| EC SCOEL | The SCOEL 8-hr time weighted average exposures represent levels to which an employee may be exposed via the airborne route for 8 hr per day, 5 days per week over a working lifetime which will not result in adverse effects on health of the worker or their progeny. | Yes | No | No | No |
| NIOSH REL | RELs are occupational exposure limits recommended by NIOSH as being protective of worker health and safety over a working lifetime. The REL is used in combination in engineering and work practice controls, exposure and medical monitoring, labeling, posting, worker training, and personal protective equipment. This limit is frequently expressed as a time-weighted average (TWA) for up to a 10-hr workday during a 40-hr workweek. | Yes | Yes | No | Yes |
| OSHA PEL | OSHA sets enforceable permissible exposure limits (PELs) to protect workers against the health effects of exposure to hazardous substances. PELs are regulatory limits on the amount or concentration of a substance in the air. OSHA PELs are based on an 8-hr time weighted average (TWA) exposure. | Yes | Yes | Yes | Yes |

^AFocusing primarily on full-shift time-weighted averages and excluding biological exposure limits and skin notations. Note that the TLVs have traditionally applied a non-probabilistic approach based on non-cancer and cancer endpoints. For OSHA, probabilistic approaches have been more common. PEL development has focused more on carcinogens, and chemicals with large epidemiology databases. Some organizations such as the MAK Commission and NIOSH have historically not set quantitative limits for carcinogens but have provided control-based recommendations.

^BACGIH TLV - American Conference of Governmental Industrial Hygienists (US) Threshold Limit Values; AIHA OARS-WEEL - American Industrial Hygiene Association and Occupational Alliance for Risk Science Workplace Environmental Exposure Levels; NIOSH REL - National Institute for Occupational Safety and Health (US) Recommended Exposure Level; OSHA PEL - Occupational Safety and Health Administration (US) Permissible Exposure Level; DFG MAK - Deutsche Forschungsgemeinschaft (German Research Foundation) Maximale Arbeitsplatzkonzentrationen (Maximum Airborne Concentration); EC SCOEL - European Commission Scientific Committee on Occupational Exposure Limit Values.

^CThe WEELs were originally developed and published as a committee under the auspices of the American Industrial Hygiene Association. In 2013 The AIHA signed an agreement to transfer the updating and development of new WEEL values to Toxicology Excellence for Risk Assessment under the Occupational Alliance for Risk Science.



Variability of Occupational Exposures

Variability is heterogeneity in a well-characterized population. It is a property of nature and the combination of physical mechanisms creating the exposure. Variability is not reducible by collecting better or more data; it is only more fully characterized. Thus, variability from day to day and worker to worker is unavoidable despite efforts to define groups of workers having similar exposures. Exposure is a random process with many sources of variability that interact multiplicatively and jointly produce very wide ranges of exposures. Due to the multiplicative nature of factors affecting exposures, exposure distributions are skewed and usually well defined by the lognormal distribution.^(2,3) The lognormal distribution also reflects that exposure measurements cannot be below zero, while low-frequency high-exposure results are also present. While variability cannot be changed, it can be measured or estimated with appropriate sample survey design including repeated measurements. A repeated measurement campaign would include assessing an individual's exposure on a prescribed number of days (i.e., three days or more) to assess how much variability is present in exposure characterization.

Uncertainty in Exposure Estimation

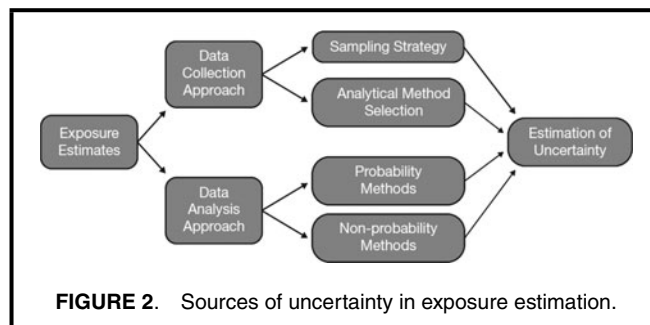
Uncertainty is lack of perfect information about the exposure being characterized. Uncertainty depends on the quality, quantity, and relevance of the data available and can sometimes be reduced by further or better measurement. When predictive models, either empirical or deterministic, are used to estimate exposures, the relevance and reliability of the models, input parameters, and model assumptions influence uncertainty. Additionally, assumptions associated with statistical models such as distributional form, independence of data or homogeneity of variance within group or strata also contribute to uncertainty. Perhaps the largest source of uncertainty associated with deterministic exposure models is a lack of data or specific information on the predictor values. In the absence of empirical data, assumptions must be used regarding the distributional parameters and shapes of these critical drivers.⁽⁴⁾

The magnitude of uncertainty describes the difference between the estimated (i.e., calculated) and the true value. The most common method of reducing uncertainty is to collect additional information and in the case of exposure

measurement, to collect additional measurements. The International Programme on Chemical Safety (IPCS)⁽⁵⁾ published a comprehensive review of uncertainty in exposure assessment with case studies of both qualitative and quantitative uncertainty analyses. Figure 2 summarizes sources of uncertainty in exposure estimation.

Uncertainty in exposure assessment is categorized into scenario, parameter, and model uncertainty. An exposure scenario includes all the assumptions, descriptors, and boundaries about the exposure situation to be analyzed. Scenario uncertainty is due to missing, incorrect or incomplete information about the descriptors and determinants of exposures, and may come from spatial or temporal approximations, homogeneity assumptions, lack of representativeness, errors in professional judgment, incomplete analysis of information available, and insufficient information such as whether the exposure controlling factors are continuous or intermittent and whether exposures are far-field (larger sources releasing to the general environment) or near-field (sources close to the worker). Thus, the exposure scenario defines the exposures for a specific population or group performing a specific job, activity, or task.

For *measurement* surveys, scenario uncertainty is reduced through clear identification of purpose and an appropriate associated survey design, collection of sufficient information, evidence-based judgments, and validation of assumptions. In measurement surveys, exposure uncertainty is based on measurement errors, unless exposure levels are below the limit of detection. Reduction in uncertainty associated with measurement requires more measurements and more sensitive



analytical methods. The uncertainty due to statistical sampling variability is represented by the standard error on the mean and stems from “variability” of occupational exposures. When *modeling* exposures, scenario uncertainty is reduced by using appropriate exposure distributions and models, improving the quality of the information used to define the scenario, and validating the assumptions.

The other sources of uncertainty, parameter, and model also need consideration. Parameter uncertainty with respect to exposure modeling is the imperfect knowledge of the true value of all model inputs. Additionally, model uncertainty exists because models are imperfect representations of truth. The accuracy of model assumptions, the range of applicability of the model, and whether model predictions have been extrapolated beyond the model’s useful range and the degree to which the model reflects the complex forces governing exposure distributions also play a role. Model validation incorporating the distributional nature of exposures is essential to determine the latter.

Methods for Estimating Exposures

Both measurement and exposure modeling are used to estimate the extent of human exposure, although retrospective exposure assessment may utilize additional or hybrid methods. Exposure models follow the general form:

$$\text{Exposure Intensity} = f(\text{Predictors of Exposures}). \quad (1)$$

Ideally, exposure estimation by modeling accounts for the intrinsic variability and the uncertainty of quantitative predictors of exposure and the impact of these on model predictions and the breadth of possible modeled outcomes. Although exposure variability can be quite high, (e.g., geometric standard deviation (GSD) of 3 or higher) uncertainties associated with multiple predictors of exposure in a model will compound and may dominate, causing the estimated exposure range to be quite large. At the simplest level uncertainty can be computed deterministically by propagation of each individual source of uncertainty. Deterministic methods use point values to represent random variables.

Resource limitations often prevent all worker exposures from being estimated. A significant amount of professional judgment is used to identify the exposure scenarios expected to pose the greatest risk, to deem other exposure scenarios as acceptable and therefore exempt from further consideration, to group workers or tasks into similar exposure groups (SEGs), and to designate exposure scenarios as unchanging over time. If worst case measurement or modeling is used, judgment is used to select the worst case. Hybrid approaches combining judgment with exposure measurements are also used, such as when SEGs are defined based on prior exposure measurements rather than observationally. Uncertainty associated with judgment is usually qualitative and based on the accuracy of the knowledge base available about the exposure scenario as well as the experience, training, and objectivity of the occupational hygienist.^(6–9)

Measurement-Based Approaches to Occupational Exposure Estimation

Exposure measurement is usually preceded by workplace observation, formation of similar exposure groups or tasks, prioritization, and review of past data if extant, followed by sampling survey design and one or more measurement campaigns. Exposure measurement may involve both sampling and analysis or simultaneous sampling and detection with direct reading instruments. Sampling and analytical errors are normally distributed and have uncertainties that depend on the agent and the sophistication of the sampling and analysis methods used. A sample survey design is specified or implicitly assumed, ranging from a single worst case sample measurement to a stratified random sampling plan with multiple measurements. Uncertainty may result from judgments used in grouping, prioritization and designing the survey. Sampling and analysis errors are usually much smaller than the natural variability of exposures, i.e., typical sampling analytical errors are often less than $\pm 25\%$ whereas the use of a few samples to estimate the mean or high-end percentile of the exposures of a group of workers can lead to uncertainties of 2–4 fold (200–400%).^(3,10)

Modeling Approaches to Occupational Exposure Estimation

Exposure modeling methods range from simple deterministic physical models such as the single zone box model of a well-mixed room, to complex models with stochastic input parameters.^(11–13) Indeed, the simplest method to characterize overall uncertainty and variability is to conduct boundary analyses with input parameter values from the upper and lower end of the ranges that provide the “worst case” and the “best case”, which are easier to appreciate than other statistics like the mean and standard deviation.⁽¹⁴⁾ Bounds may be estimated from physical limits, detection limits, historical data, and analogy to other exposure agents the expert is familiar with. When the exposure model has multiple input parameters, the end-of-range values that maximize and minimize the exposure prediction are used for each parameter. The primary advantage of this approach is that it provides upper and lower exposure estimates that reflect the exposure level uncertainty.

Probabilistic methods are often used in computer simulations of physical and mathematical systems or models and are commonly used to quantify uncertainty. Monte Carlo methods are computational algorithms that rely on repeated random sampling from the probability distribution associated with each input parameter to compute their results. Exposure estimates are calculated repeatedly by resampling, and then aggregated, yielding a distribution of the predicted exposures with associated point estimates of exposure levels and interval estimates of the propagated uncertainty. Correlations between the input random variables are not quantified in most occupational hygiene applications in practice.

In 1999, Cullen and Frey⁽¹⁵⁾ summarized situations in which probabilistic analyses are useful (Table II). Probabilistic methods can be used to conduct sensitivity analyses when modeling

TABLE II. Exposure Assessment Cases in Which Probabilistic Uncertainty Analyses are Useful (modified from Cullen and Frey⁽¹⁵⁾)

- When consequences of poor or biased exposure estimates are unacceptably high.
- When screening exposure estimates indicate potential risk, but the estimates have substantial uncertainty.
- When it is uncertain whether the collection of additional samples or information will improve the quality of the decision to be made.
- When uncertain information stems from multiple sources.
- When comparing potential interventions with different costs and differential impacts on workers.
- When ranking or prioritizing exposure levels, exposure groups or exposure agents are important.
- When exposure reduction costs are high.

exposures by exploring the variation in model output caused by specific model inputs. Thus, sensitivity analysis can indicate which input variable(s) contribute most to variation in the model outputs and aid model development.⁽⁵⁾ Probabilistic methods can be used either with exposure measurement or exposure modeling. When used with exposure measurement, the measured values are used to simulate the idealized probability distribution that most likely would have generated the observed values. With modeling, one or more input parameters are assumed to be random variables represented by probability distribution functions. In general, even the most sophisticated exposure models may have significant uncertainty.

In 2002, Nicas and Jayjock⁽¹⁶⁾ developed a framework for the comparison of uncertainty associated with the long-term mean exposure levels estimates made by modeling vs. monitoring. The authors showed for a sample size of three or fewer workdays, mathematical modeling rather than air monitoring should provide a more accurate estimate of the mean exposure. They argue that directing research funding to the development and validation of mechanistic exposure models would ultimately provide the most cost effective exposure assessment tools.

Other Approaches to Exposure Estimation With Uncertainty

Probabilistic or Monte Carlo methods have become more common, particularly for environmental exposure estimation.^(6,17) However, when information is sparse and imprecise or imperfect, probabilities are more difficult to define. Also, probabilistic methods do not easily incorporate contradictory information, being based on binary logic.⁽¹⁸⁾ Further, although probabilistic methods work well for stochastic systems of random variables, exposure information may be a collection of evidence with varying degrees of quality associated with each part, ranging from known probability distributions to professional judgment. For these cases, other approaches may be used for uncertainty estimation. These methods include fuzzy sets and Bayesian likelihood methods.^(18,19) These methods use available knowledge as constraints to distinguish what is possible from what is not. They are not point-based and the methods can be more flexible in incorporating different types of exposure descriptor information.

Fuzzy set theory can be used when there is incomplete knowledge about the exposures being modeled and the probability distributions for the model input parameters. Uncertainties are fuzzy membership functions rather than probability distribution functions. Fuzzy set theory describes imprecisely defined classes or sets while allowing the quantification of uncertainty. Set members are grouped into classes that do not have sharply defined boundaries. Fuzzy sets incorporate concepts and techniques for dealing with sources of uncertainty or imprecisions that are non-statistical in nature. In classical set theory, an object either belongs to a set or does not, whereas fuzzy set theory allows an object to have partial membership of a set. Huang et al.⁽²⁰⁾ proposed a fuzzy interval risk assessment methodology for studying the adverse effects in a petroleum-contaminated site. Dahab et al.⁽²¹⁾ developed a rule-based fuzzy set approach for risk analysis of nitrate-contaminated groundwater. Donald and Ross⁽²²⁾ used fuzzy logic for risk management of hazardous wastes. Liu et al.⁽²³⁾ developed an exposure dose model and a fuzzy risk assessment model for petroleum contamination in groundwater.

Interval analysis is related to worst case scenario analysis in that the largest and smallest possible values of input parameters are propagated through the exposure estimation algorithm or model. Similarly, probability boundary analysis uses boundary distributions where the parameter estimates are described by intervals.^(24,25) Upper and lower distributions define what is known as a p-box. These are boundaries of the exposure estimates. Probability boxes are used when the distributions of input parameters are not exactly known and the dependencies between input parameters are not known. P-boxes have been used in environmental risk assessment but have not yet been applied to occupational exposure assessment.⁽²⁶⁾

Ramachandran⁽²⁷⁾ described the use of Bayesian methods to develop retrospective exposure estimates. Hewett et al.⁽²⁸⁾ described the first use of hierarchical Bayesian methods for prospective estimation of occupational exposures using judgment combined with one or more exposure measurements. The result is a set of Bayesian posterior likelihoods of the true exposure falling within four or five exposure categories expressed as fractions of the OEL. Sottas et al.⁽²⁹⁾ developed a unified Bayesian method combining measurements, expert judgment, and exposure model estimates in an empirical

hierarchical Bayesian model. These methods show promise for future occupational exposure estimation for static processes when baseline exposure data exist.

RISK CHARACTERIZATION

Once an OEL has been defined, information about occupational exposure levels in a specific work scenario is compared to the OEL to make a decision about the acceptability of exposures. A number of methods exist for making this comparison.

OEL Interpretation in Risk Characterization

Exposure limits comprise at minimum a limiting concentration, an averaging time over which that concentration applies, and a definition of to whom the limit applies. Averaging time may be an 8-hr day or a short term such as a 15-min time-weighted average (TWA). There may be additional constraints associated with the exposure limit such as a defined number of excursions above the limit permitted within a specific time-period as in case of some short-term exposure limits (STELs). (Concentration limits applied to area or work rooms are not occupational exposure limits; however, they may be used as such if there is a basis for assuming that all workers in the area or room are exposed at or below the level and this assumption is explicitly stated.)

In risk characterization, the OEL cannot be dissociated from the methods used to compare worker exposures to the OEL. The selection of methods can reflect risk policy considerations (e.g., regulatory compliance vs. long-term health surveillance studies). There are additional scientific factors such as propensity for effects from a single exposure that can influence the preferred approach and resulting risk interpretations. These methods range from simple comparison to more complicated methods. In addition to the comparison method itself, factors related to the quality of the worker exposure point estimate directly affect the risk characterization.

Methods for Comparing Exposure Data to OELS

Hazard Quotients

Occupational hygienists use OELs routinely to facilitate risk decisions in the workplace. Together the exposure profile and the OEL will create the Hazard Index or Hazard Quotient as defined by the following equation:

$$\text{Hazard Quotient} = \frac{\text{Exposure Point Estimate}}{\text{Occupational Exposure Limit}} \quad (2)$$

The hazard quotient is termed the “risk characterization ratio” within the European Union. In its simplest form this comparison represents a hazard quotient where the point estimate for exposure is divided by the OEL. This unitless ratio informs the risk manager of the degree to which exposure exceeds or is below the concentration expected to carry little health risk. The hazard quotient does not estimate the likelihood for adverse effects as exposure reaches and exceeds the OEL, although theoretically as the hazard quotient diverges greatly from a

value of unity the potential for adverse effects also increases or decreases, while hazard quotients in the close to or exceeding a value of 1 would suggest the need for closer examination. No uniformly accepted guidelines have been provided for an acceptable distance below a hazard quotient of unity. The hazard quotient value is used to determine regulatory compliance and to determine the need for and type of risk management measures.⁽¹⁾ Such applications are discussed below.

NIOSH and OSHA Compliance Approaches

NIOSH recommends a method for comparing exposure data to an OEL that incorporates the hazard quotient concept based on collection of a single measurement.⁽³⁰⁾ Approaches include collecting samples from the worst case exposure scenario or randomly from a defined similar exposure group of interest. The measurement is compared to the OEL and is classified into one of three decision categories: clearly below the limit, clearly above the limit, or too close to the limit for an immediate decision. In the last case, a confidence interval (CI) around the measurement is computed based on sampling and analysis uncertainty only without consideration of environmental variability within-worker over time or between similarly exposed workers. If the measurement is over the OEL, the lower end of the CI is compared to the OEL; conversely, if the measurement is below the OEL the upper end of the CI is compared to the OEL. The NIOSH method became the basis for the OSHA compliance approach.⁽³¹⁾ Limitations on these approaches, when they are based on a single measurement and do not address environmental (e.g., weather conditions) variability, have been discussed elsewhere.^(3,32–36) In addition, limited sampling may not generate confidence bounds that reflect the actual process variability, and support the use of lognormal distributions to characterize probability.

AIHA Exposure Assessment Strategy

Following publication of criticisms of the compliance approach to exposure risk decision-making,^(3,32–36) methods were proposed that shifted from a compliance focus using single measurement of a worst-case exposure to a more comprehensive approach applicable to all workers over all work days.^(1,34,37) A committee within the AIHA published an exposure assessment strategy that recommended that TWA OELs be interpreted as upper limits of exposure (e.g., 95th percentile) for each similar exposure group (SEG) and that the exposure distribution profile of each SEG should be controlled so that the 95th percentile exposure is less than the OEL over time.⁽¹⁾ Since the 95th percentile of the presumed lognormal distribution depends on both the mean and the variance of the measurements, this approach sets an upper limit on the entire exposure distribution and goes beyond comparison of a single measurement to the OEL using the hazard quotient. Recommendations include collecting at least six measurements per SEG. This approach is well specified but lacks a formal statistical hypothesis-testing framework.

Frequentist Approaches with Sufficient Sampling

Several authors have proposed a frequentist approach with formal hypothesis testing of exposures compared to an OEL.^(3,38,39) The strategy groups workers, collects measurements from multiple workers and at least two repeat measurements per measured worker, and first assesses goodness of fit to the lognormal model. If the fit is acceptable, the next step uses a Wald-type test to determine if the probability of overexposure within the group is below an *a priori* specified value, e.g., less than 10%. Overexposure is the probability that the mean exposure of a randomly selected worker is greater than the OEL. If exposures are acceptable by this criterion, the effort is complete. If exposures are not acceptable, the within-group variability is then examined for heterogeneity. If exposures within-group vary widely, one or a few individuals have higher exposures than the others and the focus is placed on evaluating and controlling individual tasks and activities. If within-group (between-worker) exposures do not vary much compared to within-worker exposures, the group exposures are homogeneous and exposures are unacceptable for the group as a whole, leading to engineering or administrative controls and re-evaluation. The formal testing structure of this approach is desirable; however, the sample size requirement can be quite large, depending on the overall variability in exposures and how close the exposures are to the OEL. When exposures are far below the OEL, the acceptability decision does not require many samples. The greatest advantage of this approach is the evidence-based guidance for either an individual or group-based exposure control strategy.

Bayesian Methods

Hewett et al.⁽²⁸⁾ proposed a Bayesian updating approach. First, judgment is used to estimate the prior probability that the true exposure will fall within one of five categories, which are based on fractions of the OEL (e.g., 0.0–0.1, 0.1–0.5, 0.5–0.9, 0.9–1.0, or > OEL). Then one or more measurements are combined with the prior probabilities using hierarchical Bayesian updating to obtain the posterior probabilities in each category. A feature of the Bayesian method as specified by AIHA⁽¹⁾ is that the exposure metric used is not the mean but the 95th percentile exposure. The greatest advantage of Bayesian estimation methods is the use of a formal structure for combining non-quantitative information and judgment with a small number of measurements. Clearly, the expertise of the occupational hygienist is key. Research is underway to identify methods for training occupational hygienists to produce better judgments through data interpretation exercises and recalibration of judgments. These methods hold great promise but are in the developmental stages. Similar methods have been incorporated into the Advanced REACH Tool (ART)^(40,41) and a new version of Stoffenmanager, two exposure-estimating and decision-making tools developed in Europe. Sensitivity analyses were used to partially evaluate uncertainty associated with the exposure risk decision during model validation for both of these tools.

Tools for Exposure Estimation and Decision-Making

In occupational exposure risk determination, there is long history of making one or several measurements and an *ad hoc* comparison with an OEL to determine acceptability of exposures. Even in cases where larger exposure data sets exist, quantitative analysis of exposure data is often not performed. Several quantitative exposure data analysis tools exist for evaluating, summarizing, and visualizing exposure measurement data. These include SPEED (The Statistical Program for the Evaluation of Exposure Data) (Version 1, Institute for Risk Assessment Sciences (IRAS), Netherlands),⁽⁴²⁾ IH Stats,^(43,44) and IH Data Analyst (V1.27, Exposure Solutions, Inc., Morgantown, WV).⁽⁴⁵⁾ SPEED is based on the strategy described by Rappaport et al.⁽³⁴⁾ and Lyles et al.⁽⁴⁶⁾ Each of these tools permits visualization of the idealized distribution that best fits the measurement data and, computation of summary descriptive metrics such as the 95th percentile exposure and the exceedance fraction.

DISCUSSION

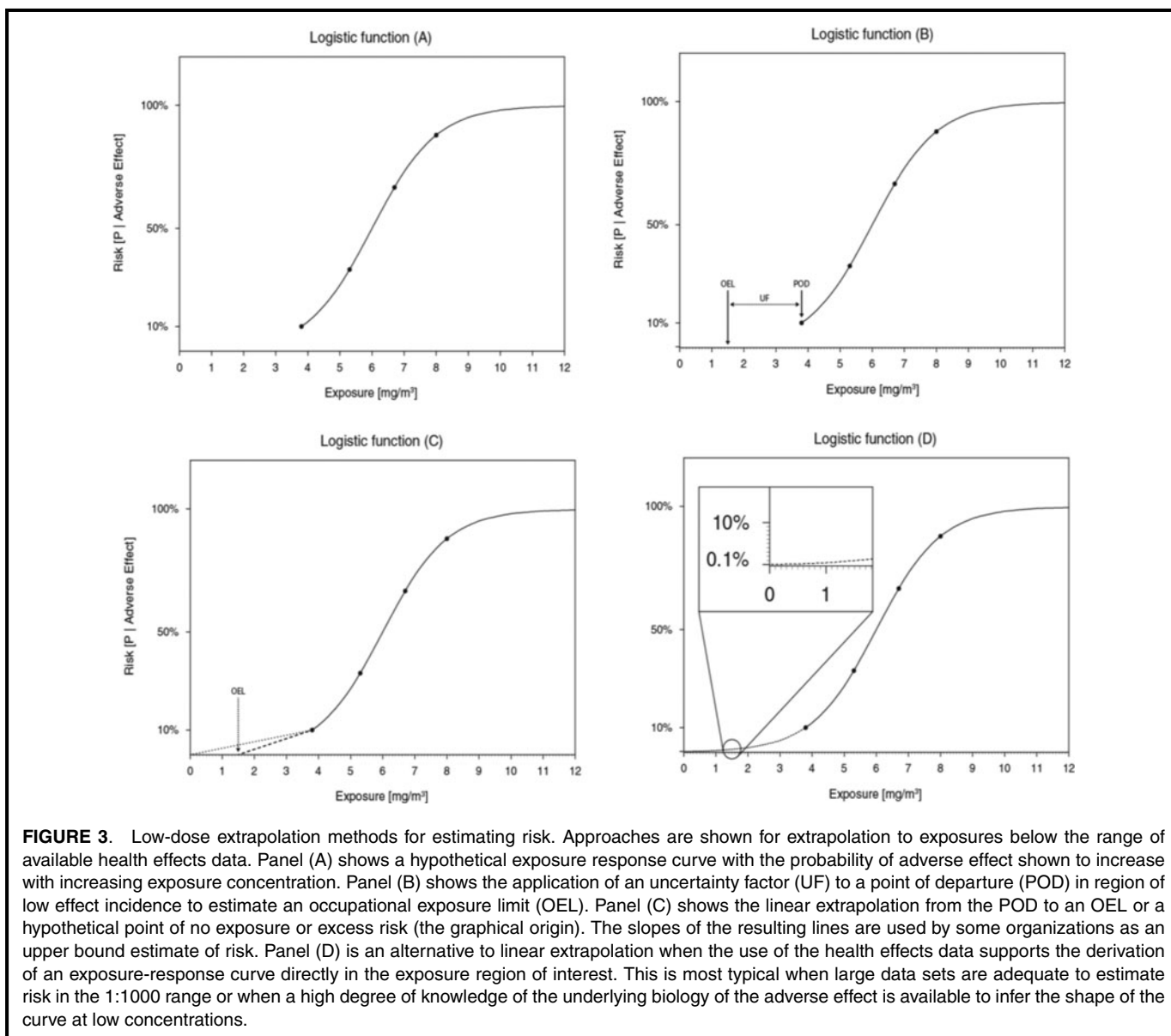
Brief Summary of Findings

In this article we focus on traditional and evolving interpretations of occupational exposure assessment with an emphasis on the probabilistic nature of the risk characterization effort. The tools for risk characterization used most commonly by the occupational hygienist, i.e., OELS and exposure estimates, are not single deterministic values—rather they are estimates with a probability range. Many occupational hygienists do not make full use of the probabilistic nature of these random variables to inform their risk management decisions. Understanding uncertainty could increase the ability to understand variability of exposures and associate them with specific tasks to reduce exposures. This article describes current tools and methods in exposure-response evaluation and exposure assessment that can provide occupational hygienists with greater access to consideration of probability in characterizing health outcomes and designing effective control strategies.

Research Needs and Gaps

Exposure-Response Methods for Estimating Risk at an OEL

In this article, we use the term occupational exposure limit (OEL) as a general term to reflect an airborne exposure concentration that has been recommended as guidance or promulgated as a regulatory control limit for the protection of worker health. The definitions and bases for establishing OELs vary among organizations (Table I). Two practical outcomes that result from the complex series of decisions embedded in an OEL are (1) that OELs are likely to vary in value among different organizations (and possibly appear inconsistent) and (2) OELs derived as a series of complex decisions are imprecise estimates of a safe exposure.⁽⁴⁷⁾ Although imprecise, OELs are not arbitrary with methods applied in their derivation expected to yield protective limits. Since the occupational hygienist will often face a range of potential OEL values, it is critical for



users of an OEL to understand the implications of a particular methodology in applying an OEL to support worker health risk decisions.

Despite the push for increased use and development of risk-based exposure guidance, for most OELs the probability of adverse health effects with increasing exposure is not easily determined. This is because the OELs published by most organizations represent a single value with no clear articulation of the incremental level of risk as exposure reaches or exceeds the OEL. A variety of exposure response analysis methods have been proposed to address this limitation in the context of setting health risk assessment guidelines for environmental or occupational scenarios. The impacts of exposure-response methods⁽⁴⁸⁾ and application uncertainty factors for OEL derivation⁽⁴⁹⁾ are described in detail elsewhere. In addition to these methods, options for specifically addressing the question of

probability of effects in derivation and application of OELs are also being explored.

In 2001, Jayjock and colleagues⁽⁵⁰⁾ provide a rationale using multiple low-dose extrapolation models for the quantitative estimation of the level of residual risk (with resulting uncertainty bands) that is extant at any documented OEL.

Low-dose extrapolation using benchmark dose modeling is one relatively simple method for estimating risk probabilities (Figure 3). Incorporating an early effect biomarker into the exposure-response assessment can also extend the interpolation range of the exposure-response curve to lower doses, as well as help identify lower levels of risk in the data range.⁽⁵¹⁾ Techniques such as categorical or ordinal regression may also be useful for characterizing probability of adverse effects.^(52–55) U.S. EPA has developed a software tool to facilitate the application of categorical regression for

risk assessment applications (CatReg Software, Version 2, U.S. EPA, Research Triangle Park, NC).⁽⁵⁶⁾ As an alternative to these techniques that center on the exposure-response curve, the uncertainty factor (UF) can be characterized using probabilistic methods. Two approaches have grown out of environmental exposure research in this area. The first assumes distributions for each of the commonly applied uncertainty factors and subsequent health-based reference limits.^(57–59) A second approach estimates the hypothesized risks below, at, or above a health-based reference limit^(60–63) based on the use of standard uncertainty factors that estimate the likely human equivalent dose at a given response. The intraspecies and/or interspecies uncertainty factor distribution is used to estimate the likely probability for the critical effect in humans.⁽⁶⁴⁾

As shown above and previously stated, there are many alternative approaches related to the exposure-response assessment techniques in OEL development that provide information on risk probabilities. An issue critical to the integrity and utility of any OEL resides in the appropriateness and transparency of its documentation. The documentation of most OELs does not include estimates of the probability of effects associated with that limit. Transparency of uncertainty in the risk value is an important aspect of appropriate risk characterization.

OEL development based on exposure-response data accompanied by risk level data is needed by occupational risk managers. However, risk-based OELs have yet to see significant application in most IH programs. From an exposure-response perspective, barriers to the full use of probabilistic techniques relate to toxicological data gaps, science uncertainty, and debate surrounding exposure-response behavior at the low range of exposures, and needs for broader education of the occupational hygiene community on the exposure-response tools available for providing a probabilistic view of risk.

As described above, OELs are already derived and applied on a probabilistic basis in some cases, usually where large epidemiology data sets are available with sufficient statistical power to describe changes in risk as a function of exposure concentration. Such data sets reduce the uncertainties related to interspecies as well as low-dose extrapolation. Since epidemiology studies are complex and resource intensive, it is not likely that the expansion of probabilistic concepts for most OELs will come from a fundamental change in the ready availability of large human effects data sets, which are increasingly more difficult to initiate due to resource limitations and difficulty in obtaining occupational exposure information. In the future, greater use of molecular epidemiology tools and approaches based on individualized medicine can be envisioned as one path to address this challenge. Since most OELs are derived on the basis of toxicology studies, changes in the availability of data in this area will also impact developing exposure-response assessments in a way that facilitates better characterization of exposure-response behavior in the low-dose range. The increased focus on early effects and systems biology data⁽⁶⁵⁾ coupled with developments in computational biology are already moving us in the direction of better

characterizations of effects at low levels of exposure. This concept has become a significant emphasis in the toxicology and risk assessment field; an example is the U.S. EPA NexGen Program.⁽⁶⁶⁾ DeBord et al.⁽⁵¹⁾ described the implications of these developments for OEL settings. In the near term, data collection and methods development are recognized as a vital aspect of the problem formulation step of risk assessment. The importance for risk management decision-making at low exposures helps to prioritize the necessary research based on the value of the new information. Value-of-information concepts are growing as an integral part of risk assessment.^(60,67)

Exposure Assessment

Challenges remain in occupational exposure assessment. Collecting exposure measurements using a well-defined statistical sampling strategy can be resource intensive, a potential barrier to developing the type of empirical data sets that reduce uncertainty in decision making. As an alternative to such sampling campaigns, exposure modeling or other estimation methods have replaced measurement of exposures in some applications.⁽⁶⁸⁾ The primary repositories of exposure measurements are private companies that are generally reluctant to share data with risk assessors. Exposure modeling has an established history of routine use within the environmental risk assessment realm, but is still expanding within occupational exposure science. Occupational exposure modeling has been greatly expanded within the European Union in the last decade due to the implementation of the Registration, Evaluation and Authorization of Chemicals Directive or REACH.^(40,69) However, uncertainty analyses within these contexts are still rudimentary. Model validation is essential yet not always performed due to lack of data, access, or resources. Further, no universal agreement exists about what constitutes model validation. Indeed, existing models are “useful” but their utility and value as optimally cost-effective tools within any comprehensive risk assessment and management scheme awaits the necessary resources and research to develop them.⁽¹⁷⁾ In addition, software tools are needed to make these approaches more attainable by field practitioners. A few specialized tools exist for analyzing exposure data, visualizing exposure distributions, and comparing exposure estimates to OELs for decision-making: IHSTAT,⁽⁴⁴⁾ SPEED (Version 1, Institute for Risk Assessment Sciences (IRAS), Netherlands),⁽⁴²⁾ IHMOD,⁽⁴³⁾ and IHDA (V1.27, Exposure Solutions, Inc., Morgantown, WV).

Tools for Communicating Uncertainty in the Exposure Assessment and Risk Characterization

In general, there is oversimplification and under-appreciation of true uncertainties associated with exposures and exposure risk decisions due to the skewed nature of exposure distributions and the difficulty in collecting adequate exposure measurements. Therefore, efforts to more fully communicate the basis of uncertainties are needed. For example, IPCS⁽⁵⁾ published a broader definition of data quality in exposure assessment and defined hallmarks of data quality:

TABLE III. Summary of Key Considerations during Phases of Risk Assessment

| Phase of Risk Assessment | Critical Question(s) | Key Resources |
|--|---|--|
| Problem Formulation | What is the occupational exposure scenario under consideration? | <ul style="list-style-type: none"> • NRC: Science and Decisions: Advancing Risk Assessment (2009).⁽⁶⁰⁾ • Bullock, W.H., and J.S. Ignacio: A Strategy for Assessing and Managing Occupational (2006).⁽¹⁾ • IPCS: Uncertainty and Data Quality in Exposure Assessment (2008).⁽⁵⁾ |
| OEL Derivation (Toxicity evaluation and exposure-response) | What are the key sources of variability and uncertainty in the OEL? | <ul style="list-style-type: none"> • Nelson, D.I.: Chapter 9: Risk Assessment in the Workplace In The Occupational Environment: Its Evaluation, Control, and Management (2011).⁽⁷¹⁾ • Haber, L.T. et al: Noncancer Risk Assessment: Principles and Practice in Environmental and Occupational Settings (2012).⁽⁵⁴⁾ |
| Exposure Assessment | What are the methods for characterizing occupational exposures and their uncertainties? <ul style="list-style-type: none"> • Sources of variability • Uncertainties in exposure estimation • Methods for estimating exposures • Measurement-based approaches • Modeling approaches | <ul style="list-style-type: none"> • Rappaport, S.M. and L.L. Kupper: Quantitative Exposure Assessment (2008).⁽³⁾ • IPCS: Uncertainty and Data Quality in Exposure Assessment (2008).⁽⁵⁾ • Cullen, A.C., and H.C. Frey: Probabilistic Techniques in Exposure Assessment (1999).⁽¹⁵⁾ • O’Hagan, A. et al: Uncertain Judgments: Eliciting Experts’ Probabilities (2006).⁽⁶⁾ |
| Risk Characterization | What methods are used to compare exposure estimates to OELs for decision-making about the acceptability of exposures? What tools exist to support risk characterization? | <ul style="list-style-type: none"> • Bullock, W.H., and J.S. Ignacio: A Strategy for Assessing and Managing Occupational (2006).⁽¹⁾ • Rappaport, S.M., and L.L. Kupper: Quantitative Exposure Assessment (2008).⁽³⁾ • AIHA: Exposure Assessment Strategies Committee: IH STAT Excel Spreadsheet Tool. https://www.aiha.org/get-involved/VolunteerGroups/Documents/EASC-IHSTAT-V235.xls. (2014).⁽⁴⁴⁾ • Drolet, D. et al.: Exposure Assessment Strategies Committee: IH MOD Excel Exposure Models Suite. https://www.aiha.org/get-involved/VolunteerGroups/Documents/IHMOD_Korean-AIHA-MathModel209.xls (2014).⁽⁴³⁾ • Hewett, P.: IHDA for Bayesian Decision Analysis. http://www.oesh.com/software.php. V1. 27, Exposure Solutions, Inc., Morgantown, WV (2011).⁽⁴⁵⁾ |
| Risk Management | What problems are associated with this exposure scenario? What actions could be taken? What additional information is needed to evaluate possible risk management options? | <ul style="list-style-type: none"> • NRC: Science and Decisions: Advancing Risk Assessment (2009).⁽⁶⁰⁾ • Bullock, W.H., and J.S. Ignacio: A Strategy for Assessing and Managing Occupational (2006).⁽¹⁾ |

appropriateness, accuracy, integrity, and transparency. These tools and concepts should be applied in designing exposure assessments and assessing data used in risk assessment. Further guidance is provided by the U.S. EPA published guidance

on well-conducted risk characterization that highlights four key elements: transparency, clarity, consistency, and reasonableness.⁽⁷⁰⁾ Such concepts should be applied in communicating risk assessment results. Published tools are needed that

relate the likelihood of adverse effects at a worker's measured exposure levels relative to OELs.

CONCLUSION

Both the exposure-response relationship and exposure intensity are integral to the assessment of occupational health risk when developing and interpreting OELs. We showed in this article that probabilistic approaches applied to exposure estimation are needed to provide a stronger basis for occupational risk management. The integration of these concepts has not been typically applied when making risk decisions. This article highlights the need for more complete use of these concepts in field application of occupational risk assessment. Occupational health and safety professionals can improve risk management practices through the applications of such approaches. Greater education and outreach on the use of these techniques as well as provision of user guides and information would be an important step forward. Table III provides a list of key steps and associated resources to facilitate the use of probabilistic approaches in occupational health risk assessments.

DISCLAIMER

The findings and conclusions in this article are those of the author(s) and do not represent the views of the National Institute for Occupational Safety and Health or the official position of U.S. Occupational Safety and Health Administration. Mention of any company or product does not constitute endorsement by the National Institute for Occupational Safety and Health (NIOSH). In addition, citations to websites external to NIOSH do not constitute NIOSH endorsement of the sponsoring organizations or their programs or products. Furthermore, NIOSH is not responsible for the content of these websites. All website addresses referenced in this document were accessible as of the publication date.

REFERENCES

1. **Bullock, W.H., and J.S. Ignacio:** *A Strategy for Assessing and Managing Occupational Exposures*. Fairfax, VA: American Industrial Hygiene Association, 2006.
2. **Aitchison, J., and J.A.C. Brown:** *The Lognormal Distribution with Special Reference to its Uses in Econometrics*. Cambridge: Cambridge University Press, 1957.
3. **Rappaport, S.M., and L.L. Kupper:** *Quantitative Exposure Assessment*. Raleigh, NC: Lulu Press, 2008.
4. **Jayjock, M., G. Ramachandran, S. Arnold, and E. Dederick:** Uncertainty. In *Mathematical Models for Estimating Occupational Exposure to Chemicals*, C.B. Keil, C.E. Simmons, and T. Anthony (eds.). Fairfax, VA: American Industrial Hygiene Association, 2009. Chapter 10.
5. **International Programme on Chemical Safety (IPCS):** *Uncertainty and Data Quality in Exposure Assessment*. Harmonization Project Document No. 6. Geneva: World Health Organization. (2008).
6. **O'Hagan, A., C.E. Buck, A. Daneshkhan et al.:** *Uncertain Judgments: Eliciting Experts' Probabilities*. West Sussex, UK: John Wiley & Sons, Ltd., 2006.
7. **Logan, P.W., G. Ramachandran, J.R. Mulhausen, S. Banerjee, and P. Hewett:** Desktop study of occupational exposure judgments: Do education and experience influence accuracy? *J. Occup. Environ. Hyg.* 8(12):746–758 (2011).
8. **Vadali, M., G. Ramachandran, and S. Banerjee:** Effect of training, education, professional experience, and need for cognition on accuracy of exposure assessment decision-making. *Ann. Occup. Hyg.* 56(3):292–304 (2012).
9. **Vadali, M., G. Ramachandran, J.R. Mulhausen, and S. Banerjee:** Effect of training on exposure judgment accuracy of industrial hygienists. *J. Occup. Environ. Hyg.* 9(4):242–256 (2012).
10. **Nicas, M., B.P. Simmons, and R.C. Spear:** Environmental versus analytical variability in exposure measurements. *Am. Ind. Hyg. Assoc. J.* 52(12):553–557 (1991).
11. **Jayjock, M.:** Modeling Inhalation exposure. In *The Occupational Environment: Its Evaluation, Control, and Management*, D. Anna (ed.). Falls Church, VA: American Industrial Hygiene Association, 2012. Chapter 10.
12. **Reinke, P., M. Jayjock, and M. Nicas:** Well-mixed rooms with changing conditions. In *Mathematical Models for Estimating Occupational Exposure to Chemicals*, C. Keil, C. E. Simmons, and T. Anthony (eds.). Fairfax, VA: Amer Industrial Hygiene Association, 2009.
13. **Keil, C.B., C.E. Simmons, and T.R. Anthony:** *Mathematical Models for Estimating Occupational Exposure to Chemicals*, 2nd Ed. Fairfax VA: AIHA Press, 2009.
14. **Meyer, M., and J. Booker:** *Selecting from Dispersion Measures in Eliciting and Analyzing Expert Judgment: A Practical Guide*. San Diego: Society for Industrial and Applied Mathematics, 1991.
15. **Cullen, A.C., and H.C. Frey:** *Probabilistic Techniques in Exposure Assessment: A Handbook for Dealing with Variability and Uncertainty in Models and Inputs*. New York: Springer Science & Business Media, 1999.
16. **Nicas, M., and M. Jayjock:** Uncertainty in exposure estimates made by modeling versus monitoring. *AIHA J.*: 63(3):275–283 (2002).
17. **Jayjock, M.A.:** Uncertainty analysis in the estimation of exposure. *Am. Ind. Hyg. Assoc. J.* 58(5):380–382 (1997).
18. **Kerre, E.E.:** The impact of fuzzy set theory on contemporary mathematics. *Appl. Comput. Math.* 10(1):20–34 (2011).
19. **Baudrit, C., and D. Dubois:** Joint propagation and exploitation of probabilistic and possibilistic information in risk assessment. *J. Latex Class.* 1(11):1–13 (2002).
20. **Huang, G., N. Sae-Lim, L. Liu, and Z. Chen:** An interval-parameter fuzzy-stochastic programming approach for municipal solid waste management and planning. *Environ. Model. Assess.* 6(4):271–283 (2001).
21. **Dahab, M., Y. Lee, and I. Bogardi:** A rule-based fuzzy-set approach to risk analysis of nitrate-contaminated groundwater. *Water Sci. Technol.* 30(7):45–52 (1994).
22. **Donald, S. and T.J. Ross:** Use of fuzzy logic and similarity measures in the risk management of hazardous waste sites. 376–382 (1996).
23. **Liu, L., S. Cheng, and H. Guo:** A simulation-assessment modeling approach for analyzing environmental risks of groundwater contamination at waste landfill sites. *Hum. Ecol. Risk Assess.* 10(2):373–388 (2004).
24. **Ferson, S., and L.R. Ginzburg:** Different methods are needed to propagate ignorance and variability. *Reliab. Eng. Syst. Safe.* 54(2):133–144 (1996).
25. **Ferson, S., and S. Donald:** Probability bounds analysis. In *Probabilistic Safety Assessment and Management*, A. Mosleh and R. Bari (eds.). New York: Springer-Verlag, 1998. pp. 1203–1208.
26. **Tucker, W.T., and S. Ferson:** *Probability Bounds Analysis in Environmental Risk Assessment*. Setauket, NY: Applied Biomathematics, 2003.
27. **Ramachandran, G., and J.H. Vincent:** A Bayesian approach to retrospective exposure assessment. *Appl. Occup. Environ. Hyg.* 14(8):547–557 (1999).
28. **Hewett, P., P. Logan, J. Mulhausen, G. Ramachandran, and S. Banerjee:** Rating exposure control using Bayesian decision analysis. *J. Occup. Environ. Hyg.* 3(10):568–581 (2006).

29. **Sottas, P., J. Lavoué, R. Bruzzi, D. Vernez, N. Charrière, and P. Droz:** An empirical hierarchical Bayesian unification of occupational exposure assessment methods. *Stat. Med.* 28(1):75–93 (2009).
30. **Leidel, N.A., K.A. Busch, and J.R. Lynch:** *Occupational Exposure Sampling Strategy Manual*, NIOSH Publication No. 77–173. Washington, DC: United States Department of Health, Education and Welfare, 1977.
31. **Occupational Safety and Health Administration (OSHA):** *OSHA Technical Manual*. Directive TED 01-00-015. Washington, DC: U.S. Department of Labor, 2008.
32. **Rappaport, S.M.:** Assessment of long-term exposures to toxic substances in air. *Ann. Occup. Hyg.* 35(1):61–122 (1991).
33. **Rappaport, S.M., H. Kromhout, and E. Symanski:** Variation of exposure between workers in homogeneous exposure groups. *Am. Ind. Hyg. Assoc. J.* 54(11):654–662 (1993).
34. **Rappaport, S.M., R.H. Lyles, and L.L. Kupper:** An exposure-assessments strategy accounting for within- and between-worker sources of variability. *Ann. Occup. Hyg.* 39(4):469–495 (1995).
35. **Rappaport, S.M., L.L. Kupper, and Y.S. Lin:** On the importance of exposure variability to the doses of volatile organic compounds. *Toxicol. Sci.* 83(2):224–236 (2005).
36. **Tornero-Velez, R., E. Symanski, H. Kromhout, R.C. Yu, and S.M. Rappaport:** Compliance versus risk in assessing occupational exposures. *Risk Anal.* 17(3):279–292 (1997).
37. **Kromhout, H.:** Design of measurement strategies for workplace exposures. *Occup. Environ. Med.* 59(5):349–354 (2002).
38. **Tielemans, E., L.L. Kupper, H. Kromhout, D. Heederik, and R. Houbart:** Individual-based and group-based occupational exposure assessment: some equations to evaluate different strategies. *Ann. Occup. Hyg.* 42(2):115–119 (1998).
39. **Ogden, T., and J. Lavoué:** 2011 William P. Yant Award Lecture: Testing compliance with occupational exposure limits: Development of the British-Dutch guidance. *J. Occupat Environ. Hyg.* 9(4):D63–D70 (2012).
40. **Tielemans, E., N. Warren, W. Fransman et al.:** Advanced REACH Tool (ART): overview of version 1.0 and research needs. *Ann. Occup. Hyg.* 55(9):949–956 (2011).
41. **Schinkel, J., N. Warren, W. Fransman et al.:** Advanced REACH Tool (ART): calibration of the mechanistic model. *J. Environ. Monit.* 13(5):1374–1382 (2011).
42. **Institute for Risk Assessment Sciences (IRAS):** Statistical Program for the Evaluation of Exposure Data (SPEED) (2012).
43. **Drolet, D., T. Armstrong, and M. Jayjock:** “Exposure Assessment Strategies Committee: IH MOD Excel Exposure Models Suite.” Available at https://www.aiha.org/get-involved/VolunteerGroups/Documents/IHMOD_Korean-AIHA-MathModel209.xls.
44. **American Industrial Hygiene Association (AIHA):** “Exposure Assessment Strategies Committee: IH STAT Excel Spreadsheet Tool.” Version 235. Available at <https://www.aiha.org/get-involved/VolunteerGroups/Documents/EASC-IHSTAT-V235.xls>.
45. **Hewett, P.:** IHDA for Bayesian decision analysis. <http://www.oesh.com/software.php>. V1. 27, Morgantown, WV: Exposure Solutions, Inc., 2011.
46. **Lyles, R.H., L.L. Kupper, and S.M. Rappaport:** A lognormal distribution-based exposure assessment method for unbalanced data. *Ann. Occup. Hyg.* 41(1):63–76 (1997).
47. **Maier, A., R. Sussman, J. Mulhausen, and R. Roy:** Characterizing the impacts of uncertainty and scientific judgment. *Toxicologist* 132(1) (2013).
48. **Wheeler, M.W., R. Park, A.J. Bailer, and C. Whittaker:** Historical context and recent advances in exposure-response estimation for deriving occupational exposure limits. *J. Occup. Environ. Hyg.* 12(S1):S7–S17 (2015).
49. **Dankovic, M., B. Naumann, M. Dourson, and A. Maier:** The scientific basis of uncertainty factors used in setting occupational exposure limits. *J. Occup. Environ. Hyg.* 12(S1):S55–S68 (2015).
50. **Jayjock, M.A., P.G. Lewis, and J.R. Lynch:** Quantitative level of protection offered to workers by ACGIH threshold limit values occupational exposure limits. *AIHAJ* 62(1):4–11 (2001).
51. **DeBord, D., L. Burgoon, S. Edwards et al.:** Systems biology and biomarkers of early effects for occupational exposure limit setting. *J. Occup. Environ. Hyg.* 12(S1):S41–S54 (2015).
52. **Dourson, M.L., L.K. Teuschler, P.R. Durkin, and W.M. Stiteler:** Categorical regression of toxicity data: A case study using aldicarb. *Regul. Toxicol. Pharmacol.* 25(2):121–129 (1997).
53. **Hertzberg, R.C., and M.L. Dourson:** Using categorical regression instead of a NOAEL to characterize a toxicologist’s judgment in noncancer risk assessment. 254–261 (1993).
54. **Haber, L.T., J.S. Dollarhide, A. Maier, and M.L. Dourson:** Noncancer risk assessment: principles and practice in environmental and occupational settings. In *Patty’s Toxicology*, E. Bingham and B. Bohrsen (eds.), Hoboken, NJ: John Wiley & Sons, Inc., 2012. p. 5.
55. **Teuschler, L.K., M.L. Dourson, W.M. Stiteler, P. McClure, and H. Tully:** Health risk above the reference dose for multiple chemicals. *Regul. Toxicol. Pharmacol.* 30(2 Pt 2):S19–26 (1999).
56. **U.S. EPA:** *CatReg Software Version 2.3 for Categorical Regression Analysis in Environmental Assessment*. Washington, DC: United States Environmental Protection Agency, 2012.
57. **Baird, S.J., J.T. Cohen, J.D. Graham, A.I. Shlyakhter, and J.S. Evans:** Noncancer risk assessment: A probabilistic alternative to current practice. *Hum. Ecol. Risk* 2(1):79–102 (1996).
58. **Dourson, M.L., and J.F. Stara:** Regulatory history and experimental support of uncertainty (safety) factors. *Regul. Toxicol. Pharmacol.* 3(3):224–238 (1983).
59. **Swartout, J.C., P.S. Price, M.L. Dourson, H.L. Carlson-Lynch, and R.E. Keenan:** A probabilistic framework for the reference dose (probabilistic RfD). *Risk Anal.* 18(3):271–282 (1998).
60. **National Research Council (NRC):** *Science and Decisions: Advancing Risk Assessment*. Washington, DC: The National Academies, 2009.
61. **Price, P.S., R.E. Keenan, J.C. Swartout, C.A. Gillis, H. Carlson-Lynch, and M.L. Dourson:** An approach for modeling noncancer dose responses with an emphasis on uncertainty. *Risk Anal.* 17(4):427–437 (1997).
62. **Hattis, D., S. Baird, and R. Goble:** A straw man proposal for a quantitative definition of the RfD. *Drug Chem. Toxicol.* 25(4):403–436 (2002).
63. **Hattis, D., and M. Lynch:** Empirically observed distributions of pharmacokinetic and pharmacodynamic variability in humans- Implications for the derivation of single point component uncertainty factors providing equivalent protection as existing rfds. In *Toxicokinetics and Risk Assessment*, J.C. Lipscomb and E.V. Ohanian (eds.). New York: Informa Healthcare, 2007. pp. 69–93.
64. **Ginsberg, G., D. Hattis, B. Sonawane et al.:** Evaluation of child/adult pharmacokinetic differences from a database derived from the therapeutic drug literature. *Toxicol. Sci.* 66(2):185–200 (2002).
65. **National Research Council (NRC):** *Toxicity Testing in the 21st Century: A Vision and a Strategy*. Washington, DC: The National Academies, 2007.
66. **United States Environmental Protection Agency:** “NextGen: Risk Assessment.” Available at: <http://www.epa.gov/risk/nexgen/> (2013).
67. **Yokota, F., and K.M. Thompson:** Value of information analysis in environmental health risk management decisions: past, present, and future. *Risk Anal.* 24(3):635–650 (2004).
68. **Rappaport, S.M.:** Assessing workplace exposures: turning to the past for guidance. *Occup. Environ. Med.* 66(7):429–430 (2009).
69. **European Chemicals Agency (ECHA):** Occupational Exposure Estimation. In *Guidance on Information Requirements and Chemical Safety Assessment*. Anonymous. Helsinki, Finland: ECHA, 2009. Chapter R.14.
70. **U.S. EPA:** *Risk Characterization: Science Policy Council Handbook*. EPA-100-B-00-002. Washington, DC: Office of Science Policy, Office of Research and Development, U.S. EPA, 2000.
71. **Nelson, D.I., F. Mirer, G. Bratt, and D.O. Anderson:** Risk Assessment in the Workplace. In *The Occupational Environment: Its Evaluation, Control and Management*. 2nd Edition, S.R. DiNardi (ed.). Fairfax, VA: AIHA Press, 2003. pp. 143–171.