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Current Assessment Practices for Noncancer End Points

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The need for assessing noncancer risks for agents to which humans are routinely exposed indoors arises from the large amount of time spent indoors (i.e., employed persons spend about 60% of their time at home indoors, 30% at work indoors, and 5% in transit). Sources of air pollutants include heating and cooling systems, combustion appliances, personal use products, furnishings, tobacco products, pesticides, bioeffluents from humans and animals, and other microbial contamination such as toxins from molds. The purpose of this paper is to describe current dose–response assessment methods applicable to assessing risk following exposure to indoor air pollutants. The role of structure–activity relationships in hazard identification is also described.

Risk assessments from exposure to indoor air pollutants require exposure assessments and dose–response assessments. Dose–response assessment methodologies include the inhalation reference concentration (RfC), structure–activity relationships, dose–response models, and the decision analytic approach. The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The current RfC method provides guidelines for making the necessary dosimetric adjustments for gases and aerosols. Human equivalent concentrations for no-observed-adverse-effect levels in animals are determined by using mathematical relationships that adjust for regional deposition, solubility, ventilation rate, and blood:air partition coefficients. The RfC methodology exists as an interim methodology. Future scientific advancements are expected to further refine the approach.

Introduction

The need for assessing noncancer risks for agents to which humans are routinely exposed indoors arises from the large amount of time spent indoors. Ott (*1*) has reported that employed persons spend about 60% of their time at home indoors, 30% at work indoors, and 5% in transit. Sources of air pollutants include heating and cooling systems, combustion appliances, personal use products, furnishings, tobacco products, outside pollutants and soil gases, cleaning and maintenance products, pesticides, bioeffluents from humans and animals, and other microbial contamination such as toxins from molds (*2*). Concentrations of some compounds (e.g., volatile organics) may reach concentrations 100-fold higher indoors than outdoors. The purpose of this paper is to describe current dose–response assessment methods applicable to assessing risk following exposure to indoor air pollutants. The role of structure–activity relationships in hazard identification is also described.

The National Research Council (*3*) has summarized risk assessment and its application to indoor and outdoor air pollutants and air pollution-associated health effects. Four basic steps of risk assessment were outlined as follows: hazard identification, exposure assessment, dose–response assessment, and risk characterization. Hazard identification is the determination of whether a particular chemical is or is not causally linked to particular health effects. Dose–response assessment is the quantitative relationship between the magnitude of exposure and the occurrence of human health effects. Exposure assessment is the determination of the extent of human exposure including evaluation of the exposure and the number of people exposed. Risk characterization is the description of the nature, and often the magnitude, of human risk, including attendant uncertainty. Essentially, risk assessment is an integration of dose–response assessment and exposure assessment. While the National Academy of Science has described the four components of risk assessment as separate entities, hazard identification and dose response may be conducted concurrently when dealing with noncancer end points. Developmental, reproductive, and neurotoxicity risk assessment guidelines combine these two components.

Current dose–response assessment methods are described here. The interim inhalation reference concentration method is expanded in greatest detail (*4*). Also described are methodologies for performing dose–response assessments by modeling dose–response relationships and using the decision analytic approach (*5*).

Inhalation Reference Concentration

The U.S. EPA has chosen the reference concentration (RfC) methodology to clarify aspects of risk assessment formerly covered by the acceptable daily intake (ADI). The RfC is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The

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requirements for estimating an inhalation RfC are toxicity data, uncertainty factors, and possibly a modifying factor. The RfC is determined as

$$RfC = NOAEL/(UF \times MF)$$

where NOAEL = no-observed-adverse-effect level; UF = uncertainty factor; and MF = modifying factor.

The operating assumption in RfC development is that a dose threshold exists at or above which an adverse effect will be evoked in an organism if exposure occurs throughout a lifetime. This assumption is well-founded for many compounds that have defined toxicity mechanisms (*6*), though inconsistencies in subpopulation thresholds may make the assumption invalid when considering different populations (*7*). The NOAEL is the first basis for evaluating the RfC. It is derived from toxicity data in which a critical effect having a dose–response relationship is identified. The NOAEL is an exposure level for which no statistically or biologically significant increases in frequency or severity of adverse effects occur in an exposed population compared to a control population. All effects that occur are not necessarily adverse. Adverse effects are functional impairments or pathological lesions that may be manifested in the performance of an organism or the organism's response to a challenge.

The NOAEL, rather than the occupational exposure limit (OEL), the frank effect level (FEL), or the NOEL, is used to determine the RfC. OELs are not used for the derivation of RfCs for several reasons: *a*) OELs are not necessarily based on chronic effects of similar severity to the RfC; *b*) OELs are based on intermittent exposure; *c*) some OELs are based on studies that have not been reviewed or published in the open literature, i.e., some corporate studies; *d*) the OEL toxicity data may differ from the data used by the U.S. EPA in weight of evidence; and *e*) OELs are designed to protect the healthy worker, not the most sensitive subgroup (e.g., children). FELs are unsuitable for determining RfCs because mortality and frankly apparent and irreversible functional impairment are far removed quantitatively from chronic NOAELs and LOAELs. Thus, if a frank effect is all that is detected, the database has failed to establish a level at which no adverse effects occur based upon the most sensitive end point. A single NOEL with no other dose–response data is also unsuitable for the derivation of an RfC because it does not identify a level at which no adverse effects occur.

The database used in selecting the critical study from which the NOAEL is determined contributes to the confidence in the resulting RfC. Human data from epidemiological or clinical studies that describe the exposure levels are preferred and give a high confidence in the database because extrapolation from animal studies is not required with its attendant uncertainties. If human studies are not available, high confidence in an animal database requires two mammalian subchronic or chronic toxicity studies in different species, one mammalian two-generation reproductive toxicity study and developmental toxicity studies in different species. A minimum database is a single, well-conducted, subchronic mammalian bioassay.

Whenever possible, the RfC should be based on data from inhalation exposures. However, inhalation data are not always available. If data from other exposure routes are used, then additional uncertainties occur. Portal-of-entry effects in the lung must be ruled out before extrapolating from exposure by other routes. If portal-of-entry and first-pass effects can be ruled out, estimates of equivalent doses can be based on available pharmacokinetic data for both routes, absorption efficiency by each route, comparative excretion when metabolism is equivalent from both routes, and comparative toxicity when effects are equivalent by both routes. However, this information is available for relatively few chemicals. Metals, irritants, and sensitizers should be cautiously used for route-to-route extrapolation. Metals that can provoke immune or hypersensitivity reactions, including asthma, are mercury, gold, platinum, beryllium, chromium, and nickel (*8*). The biologically based models used in route-to-route extrapolations do not account for irritation and sensitization changes that might occur by either oral or inhalation routes.

The UFs are generally order-of-magnitude values based on the chosen critical effect and represent the second basis for the scientific evaluation of the RfC. A 10-fold uncertainty factor is invoked to account for the variation in sensitivity among human subpopulations. Extrapolation of animal data to average, healthy humans also invokes a 10-fold uncertainty factor. When less than chronic NOAELs are used as a basis for the RfC, a 10-fold uncertainty factor is used (unless the critical effect is developmental or reproductive because a single exposure may be sufficient to produce an adverse effect). When the RfC basis is a lowest-observed-adverse-effect level (LOAEL) rather than a NOAEL, a 10-fold uncertainty factor is used. If the database is incomplete (e.g., only a single animal study is available), a 10-fold uncertainty factor is used. The RfC may be altered with a modifying factor (MF) from 1 to 10 if the critical study has scientific weaknesses or uncertainties or 0 to 1 if the critical study has attendant strengths.

The RfC considers the relationship between exposure concentration and dose delivered to the target site. The respiratory tract dosimetry of gases and particles differs across species, though similar respiratory tract regions are considered (*9,10*). The respiratory tract anatomy, physiology, xenobiotic metabolism, and biochemistry (mucous interaction) and the physicochemical properties of the inhaled toxicant account for differences in deposition across the species. Evaluation of dose–response curves across species requires knowing the dose delivered to the target tissue, and the target tissue dose is determined by absorption, distribution, metabolism, and excretion. The RfC process assumes that either absorption is equivalent across species or that the differences in absorption are so minimal that the interspecies uncertainty factor accounts for them along with other pharmacokinetic and pharmacodynamic differences. Use of physicochemical, physiological, anatomical, and biochemical adjustments will minimize the uncertainty of RfC development.

Because of dosimetric differences between the experimental species and humans, NOAELs determined from experimental exposure levels in animals need to be adjusted to human equivalent concentrations (HEC). The calculation of HECs for the NOAEL requires several steps. Figure 1 shows a schematic of the steps for adjusting a NOAEL to a $NOAEL_{(HEC)}$. First, the exposure concentrations in parts per million must be converted to milligrams per cubic meter. Next, the exposure regimen must be converted to a continuous (24-hr) lifetime (70-year) exposure (except for developmentaland reproductive toxicity end points because a single exposure may be sufficient to produce an adverse effect). If the exposure is to a particle, then physical

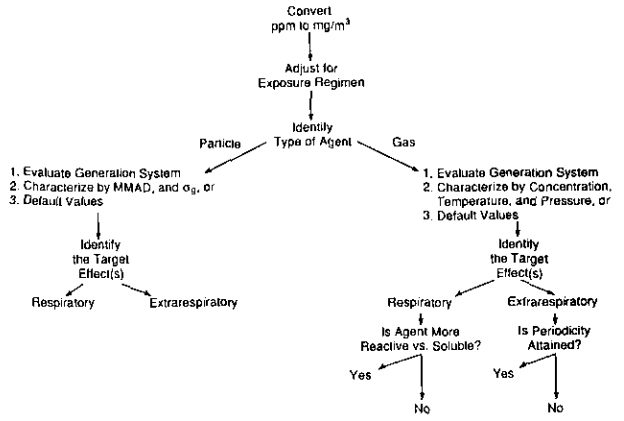

FIGURE 1. Flowchart for calculating human equivalent concentrations. Decision processes for aerosols and gases are shown for respiratory and extrarespiratory target effects.

descriptions of the particles must be obtained to describe the exposure and predict whether a respiratory or extrarespiratory effect is likely to occur. If exposure is to a gas, the temperature and pressure conditions must be determined. Gases may also have respiratory or extrarespiratory effects. Respiratory effects may result from reactive or soluble agents. Extrarespiratory effects of gases depend upon periodicity of the exposure.

Concentration Conversion

If exposure levels are expressed in units of parts per million, then the ideal gas law can be used to convert from parts per million to milligrams per cubic meter using Eq. (1):

$$mg/m^3 = ppm \times g\text{-mole}/22.4\ L \times MW/g\text{-mole} \times 273°/T \times P/760\ mm\ Hg \times 10^3\ L/m^3 \times 10^3\ mg/g \quad (1)$$

where ppm = concentration expressed on a volumetric basis ($L/10^6L$), MW = molecular weight in grams, 22.4 L = the volume occupied by 1 g-mole of a gas at 0°C and, 760 mm Hg, T = actual temperature in degrees Kelvin, and P = actual pressure in mm Hg. Exposures may typically occur at 25°C rather than 0°C. The volume of 1 g-mole of perfect gas at 25°C is 24.45 L, and the conversion is simplified to mg/m^3 = ppm × MW/24.45.

Dose Duration Adjustment

A dose duration adjustment is necessary when developing RfCs because they are based on continuous exposure, and supporting experimental exposure regimens are likely to be discontinuous. Normalization of discontinuous exposure to lifetime continuous exposure is achieved by the following equation for the adjusted NOAEL ($NOAEL_{[ADJ]}$).

$$NOAEL_{[ADJ]}(mg/m^3 = E(mg/m^3) \times D(hours/day/24\ hours) \times W(days/7\ days) \quad (2)$$

where E = experimental exposure level, D = number of (hr exposed/day)/24 hr, and W = number of (days of exposure/week)/7 days.

Duration and solubility effects may affect the accuracy of the simple direct relationship expressed in Eq. (2). Ideally, the exposure duration should include the period of time during which toxic effects sharply change (*11*). Tissue concentrations of a gas also vary with lipid solubility. Gases with high blood-to-air partition coefficients are lipid soluble. First-order kinetics of uptake and elimination are also assumed by Eq. (2).

Human Equivalent Concentrations

After the NOAEL is adjusted for duration of exposure, HECs for either particles or gases must be calculated. The respiratory anatomy, ventilation characteristics, and biochemical and metabolic reactions of the exposed species significantly influences the HEC of an inhaled particle or gas.

Anatomical and physiological differences in humans and animals affect air flow in the respiratory system. The three regions of the respiratory system, nasopharyngeal, tracheobronchial, and pulmonary, are characterized by different structure, size, and function, and the anatomy, physiology, and clearance mechanisms of these regions determine the retained dose of particles in the respective regions. The nasopharyngeal region, also referred to as the extrathoracic region, consists of the anterior nares and extends back and down to the level of the larynx. This region is characterized by a lining of vascular mucous epithelium. Filtration, humidity and temperature changes, and absorption of inhaled gases also occur in the nasopharyngeal region. The trachea, bronchi, and bronchioles are the conducting airways that compose the tracheobronchial region. The upper airways (trachea and bronchi) of this region are lined with a ciliated epithelium coated with a thin layer of mucus. The mucociliary escalator of the conducting airways clears particles from the deep lung to the oral cavity, and the mucus can react with or absorb gases, thereby changing the dose to the epithelium. The airway branching patterns and dimensions are critical in determining particle deposition and gas absorption. The pulmonary region consists of first-order respiratory bronchioles, alveolar duets, and alveolar sacs. This region is the primary site of gas exchange between the environment and the blood.

Particle Effects

The deposition of insoluble particles in various parts of the respiratory system are shown in Figure 2*A* for nasal inhalation and in Figure 2*B* for oral inhalation (*12*). Particles greater than 2.5 μm mass median aerodynamic diameter are deposited preferentially in the nasopharyngeal (extrathoracic) region. Compared to nasal inhalation, oral inhalation shifts the deposition of particles to higher fractions for both the tracheobronchial and pulmonary regions.

The HEC calculations for particles also rely on the physicochemical characteristics of particles and temperature and pressure conditions for gases. Physicochemical characteristics affect particle deposition and retention within the respiratory tract, translocation within the respiratory system, distribution to other tissues, and toxic effects. The sizes of most particles approximate a log-normal distribution. Assuming a log-normal function, the size of particles may be described by the mass median aero-

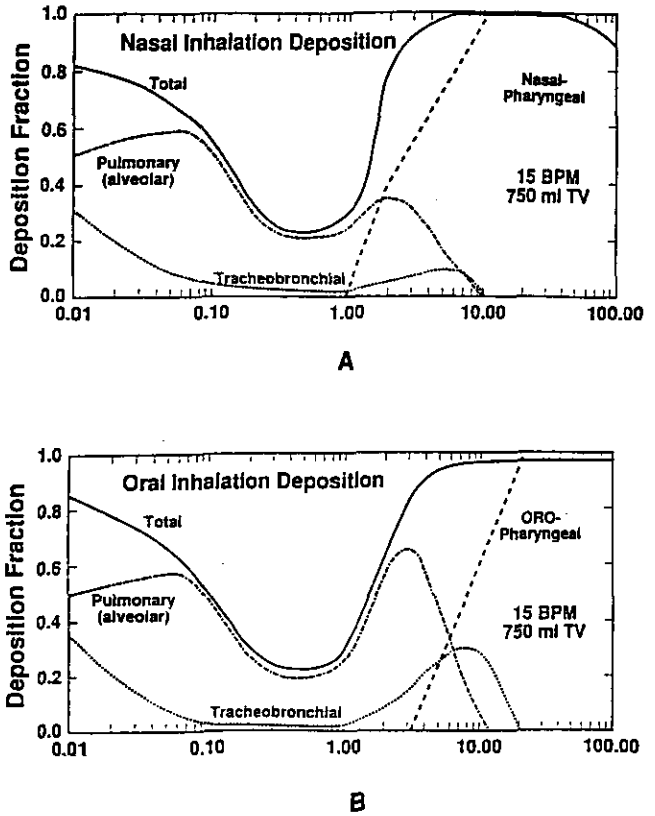

FIGURE 2. (*A*) Diameter of spherical particle with density of 1 g/cm³ (μm). Total and regional deposition fractions for aerosols entering the nose for various sizes of inhaled, airborne spherical particles with physical density of 1 g/cm³ in the human respiratory tract as calculated by the International Commission on Radiological Protection (ICRP) Task Group on Lung Dynamics (*23*) for nasal breathing at a rate of 15 breaths per min (BPM) and tidal volume (TV) of 750 mL. (*B*) Total and regional deposition fractions for aerosols entering the mouth for various sizes of inhaled, airborne spherical particles with physical density of 1 g/cm³ in the human respiratory tract as calculated by the International Commission of Radiological Protection (ICRP) Task Group on Lung Dynamics (*23*) with the head airway deposition function given by Raabe (*24*) for oral breathing at a rate of 15 BPM and TV of 750 mL.

dynamic diameter (MMAD). If particles are nonspherical in shape, then they should be treated as equivalent spheres, and their aerodynamic diameter taken into account. The aerodynamic diameter is the diameter of a unit density sphere having the same terminal settling velocity as the particle whatever its size, shape, and density. Aerodynamic diameter should be considered for the particles deposited by impaction and sedimentation. Since the toxic effect to the lower respiratory tract will increase as the mass of the particles penetrating to the deep lung or alveolar region increases, the MMAD becomes important. Since the particle population is known to have a log-normal distribution, it can also be characterized by the geometric standard deviation (σ_g). Monodisperse aerosols have σ_g values less than 1.2. The ability of particles to take on water (hygroscopicity) may also affect their size and, therefore, their deposition.

Some adjustments and assumptions may be required when using available data to calculate an RfC. Older studies that do not provide MADD and σ_g values should be suspect for use in calculating RfCs. Aerosol-generating equipment in use before the late 1970s could not produce aerosols consistently less than 3 μm (*13*). By taking the particle diameter less than or equal to 3 μm and the distribution characteristic for the given generation system that yields the most conservative HEC, the $NOAEL_{(HEC)}$ can be derived. If count median diameter is given rather than MMAD, the Hatch-Choate equations can be used for conversion (*14*). Adjusting deposition efficiency for nonhygroscopic particles is recommended because models indicate such an adjustment would overestimate deposited dose for the smaller diffusion-dependent hygroscopic particles.

HEC for Respiratory Effects from Particles

Deposition efficiency and particle distribution information can be used to calculate the deposited dose of exposure particles when these particles exist as an insoluble aerosol. The deposited fraction for any region of the respiratory system is a function of deposition efficiency and particle mass fraction. Integration across all particle sizes will give the mass deposition in a particular region. Deposition in a particular region for a given species is obtained from the product of the fractional deposition, ventilation rate, and exposure level divided by the regional surface area. Thus, assuming the equivalent dose across species is the aerosol mass deposited per regional surface area, the regional deposited dose (RDD) for the extrathoracic region is determined as in Eq. (3).

$$RDD_{ET} = \frac{10^{-6} Y V_T f}{S_{ET}} \sum_{i=1}^{n} P_i E_i \qquad (3)$$

where P_i = the particulate mass fraction in the exposure size distribution (MMAD, σ_g), E_i = the deposition efficiency of that size distribution (MMAD, σ_g) in the extrathoracic region for the species of interest, i = size range, n = number of size ranges, Y = exposure level (mg/m³), V_T = tidal volume (mL), f = breathing frequency (breaths/min), and S_{ET} = surface area of the extrathoracic region (cm²).

Deposition of only one size range (i) of particles for one region (extrathoracic) is shown in Eq. (3). Toxic effects in other regions necessitate use of parameters defining the affected region. Summation over multiple (n) particle ranges and multiple regions (extrathoracic, tracheobronchial, pulmonary, thoracic, or total) is possible using the same expression and knowledge of the respective surface areas (S), particulate mass fractions (P), and deposition efficiency (E).

The RDD can be calculated for each species of interest using the same MMAD and σ_g. The regional deposited dose ratio (RDDR) is used to convert the adjusted NOAEL to the human equivalent concentration as follows:

$$NOAEL_{[HEC]}(mg/m^3) = NOAEL_{[ADJ]}(mg/m^3) \times RDDR \qquad (4)$$

where $NOAEL_{[HEC]}$ = the NOAEL human equivalent concentration, $NOAEL_{[ADJ]}$ = the NOAEL adjusted for duration according to Eq. (2), and RDDR = $(RDD_{ANIMAL})/(RDD_{HUMAN})$, the ratio of regional deposited dose in animal species to that of humans for the region and toxic effect of interest.

Because dosimetric data from rats are available, the RDDR of insoluble particles for rats to humans has been calculated for σ_g of 1.2, 1.4, 1.8, 2.0, 2.2, and 2.4 at MMAD of 0.100 to 10.000 μm

for an extrathoracic, tracheobronchial, pulmonary, thoracic, (tracheobronchial plus pulmonary), or total respiratory (extrathoracic plus thoracic) effect (*4,15*).

HEC for Extrarespiratory Effects of Particles

If the toxic effect of an inhaled particle is outside the respiratory tract, then the effect is extrarespiratory, and the equivalent dose across species is based on the particle mass deposition per body weight. In the absence of data indicating otherwise, 100% of the deposited dose is assumed available for systemic absorption and circulation. However, clearance and distribution data could alter this assumption. Eq. (5) shows the expression for calculating the extrarespiratory (ER) RDD.

$$RDD_{ER} = \frac{10^{-6} Y V_T f}{BW} \sum_{i=1}^{n} P_i E_i \qquad (5)$$

where E_i = the distribution efficiency of that size distribution (MMAD, σ_g) in the entire respiratory tract for the species of interest, BW = body weight (kg), and other variables are as for Eq. (3).

The ratio of the animal RDD to the human RDD is used to convert the adjusted animal NOAEL to a NOAEL as a human equivalent concentration as in Eq. (6).

$$NOAEL_{[HEC]}(mg/m^3) = NOAEL_{[ADJ]}(mg/m^3) \times RDDR_{ER} \qquad (6)$$

where $NOAEL_{[HEC]}$ = the NOAEL human equivalent concentration, $NOAEL_{[ADJ]}$ = the NOAEL adjusted for duration according to Eq. (2), and $RDD_{ER} = (RDD_{ER})_A/(RDD_{ER})_H$, the ratio of the dose available for uptake from the entire respiratory system of the experimental animal species to that of humans.

The RDDR for rats to humans for insoluble particles in a range of 1.2 to 2.0 σ_g and an MMAD of 0.100 to 10.000 μm have been calculated for the extrarespiratory region (*4,15*).

Gas Effects

Interspecies dosimetry of gases and vapors should be determined to extrapolate toxicological effects from animal studies to humans. Physiological modeling may be used to predict effects from reactive gases or metabolically activated gases. Uptake and distribution of metabolically activated gases depend on the blood and tissue solubility and physiological parameters such as ventilation and tissue mass and perfusion. Kinetic parameters of metabolism are important too because toxicity may be related to stable or reactive metabolites of the parent compound. Modeling toxicity based on mechanism of action in comparative species requires much data, which are seldom available. Interspecies dose adjustments will become more precise as soon as anatomic and physiologic parameters of the species and physicochemical determinants of the gases are known. Better definition of exposure concentration and duration conditions will also be required for accurate modeling.

HEC for Respiratory Effects of Gases

Reactive gases may have their toxic effect in the lung. Like the approach for insoluble particles, the toxic effect is related to the mass of toxic agent absorbed by the surface area of the region of interest. The ventilatory rate affects the dose, though not directly. The general term for the regional gas dose (RGD) is shown in Eq. (7).

$$RGD = \frac{10^{-6} Y V_T f}{S} \qquad (7)$$

where S = regional surface area (cm^2) of toxic effect observed, and other variables are as previously defined. The RGD may be simplified from unit of milligrams per minute per square centimeter to milligrams per square centimeter by substituting minute volume rather than tidal volume (V_T) and breathing frequency (f). The ventilation rate of the region of concern (e.g., extrathoracic, tracheobronchial, pulmonary, thoracic, or total) should be used to obtain the effective dosimetry. The RGDs for the appropriate species and humans can be compared to derive the regional gas dose ratio (RGDR), which is used to dosimetrically adjust the experimental NOAEL to a human equivalent concentration, as in Eq. (8).

$$NOAEL_{[HEC]}(mg/m^3) = NOAEL_{[ADJ]}(mg/m^3) \times RGDR \qquad (8)$$

where $RGDR = (RGD)_{ANIMAL}/(RGD)_{HUMAN}$, the ratio of regional gas dose in animal species to that of humans for the region and toxic effect of interest, and other variables are as defined in Eq. (6).

Some gases may be highly soluble in the blood and yet have effects on lung tissue. The lung effect of these gases is indirect, and the dosimetry should be treated like the extrarespiratory effects for gases as described below.

HEC for Extrarespiratory Effects of Gases

The approach to determine HECs for extrarespiratory effects of gas exposures should estimate $NOAEL_{[HEC]}$ values as a function of the average animal exposure concentration, i.e., $NOAEL_{[ADJ]}$. Four methods for achieving these estimations have been studied (*16*). The methods are referred to as proposed, established, similar, and optimal. The proposed method is a simple methodology for extrapolating dosimetry from rat studies to human. This method assumes the effective dose is the arterial blood concentration or its concentration multiplied by time and that the blood:air partition coefficient for the animal (λ_A) is less than or equal to the blood:air partition coefficient for the human (λ_H). The proposed method is more conservative, i.e., gives lower HECs, than other methods, including: *a*) the established method, which adjusts dosimetry simply on the basis of ventilation rate divided by body weight; *b*) a method similar to the optimal model method, which uses human physiological parameters and animal parameters scaled from these; and *c*) the optimal method which uses physiologically based pharmacokinetic (PB-PK) model requiring a complete set of physiological parameters for animals and humans.

Physiologically based pharmacokinetic models may use five compartments, including gas exchange, fat, poorly perfused, richly perfused, and liver/metabolizing tissue groups to describe the body (17). The relevant physiological and biochemical parameters and the agent's mechanism of action are needed to use the PB-PK model approach. However, these data are not available for most gases. The relationship of these methods is

shown in Figure 3 (*16*), which shows that the proposed method produces the most conservative $NOAEL_{[HEC]}$ from the animal NOAEL. Because the blood:air partition coefficients are more readily available than are complete physiological parameter data, a ratio of animal to human blood:air partition coefficients is a simple, conservative default that closely approaches the optimal method.

If the concentration of gas in the arteries leaving the lung is periodic, then the blood:air partition coefficient will control the arterial concentration. Periodicity occurs when consistent and regular exposure to a gas is such that clearance from the blood is inadequate to remove the incremental gas concentration until exposure ceases. Once the exposure resumes, incremental increases in blood gas concentration resume as before. This process recurs at regular intervals. A study demonstrating periodicity is shown in Figure 4 (*16*).

Assuming animal alveolar blood concentrations are periodic for the majority of the experimental exposure duration, the $NOAEL_{[HEC]}$ for extrarespiratory effects of gases is calculated as in Eq. (9):

$$NOAEL_{[HEC]}\ (mg/m^3) = NOAEL_{[ADJ]}\ (mg/m^3) \times \lambda_A/\lambda_H \tag{9}$$

where λ_A/λ_H = the ratio of the blood:air partition coefficient of the chemical for the animal species to the human value, used only if $\lambda_A \leq \lambda_H$, and other variables are as defined in Eq. (6). If the λs are unknown or if $\lambda_A > \lambda_H$ the default value of $\lambda_A/\lambda_H = 1$ should be used.

If periodicity is not achieved for 90% of the exposure duration, the $NOAEL_{[HEC]}$ is modified by the ratio of animal-to-human quotients of ventilation rate divided by body weight as shown in Eq. (10).

$$NOAEL_{[HEC]}\ (mg/m^3) = NOAEL_{[ADJ]}\ (mg/m^3) \times \frac{(V_A/BW)_A}{(V_H/BW)_H} \tag{10}$$

where $(V_A/BW)_A/(V_H/BW)_H$ = the ratio of the alveolar ventilation rate (mL/min) divided by body weight (kg) of the animal species to the same parameters for humans, and other variables are as defined in Eq. (6).

More uncertainty is associated with this method, and a modifying factor should be included. The alveolar ventilation rate should be used to eliminate error associated with the area of the lung that has no gas exchange with the blood.

Dose–Response Modeling

Dose-response modeling is a mathematical description relating exposure to changes (e.g., toxic effects) in a biological system. Dose–response models can use all available data, thereby predicting the toxic effect over a wide range of exposures. However, while yielding precise and reproducible predictions of risk, the mathematical nature of dose–response models can lead to overinterpretation.

Dose–response models should be selected based on the intent of the risk assessment. An empirical curve-fitting model should be used if the risk at a dose within the experimental range is desired, and a mechanistic model should be used to predict risk at a very low level below the range of data points.

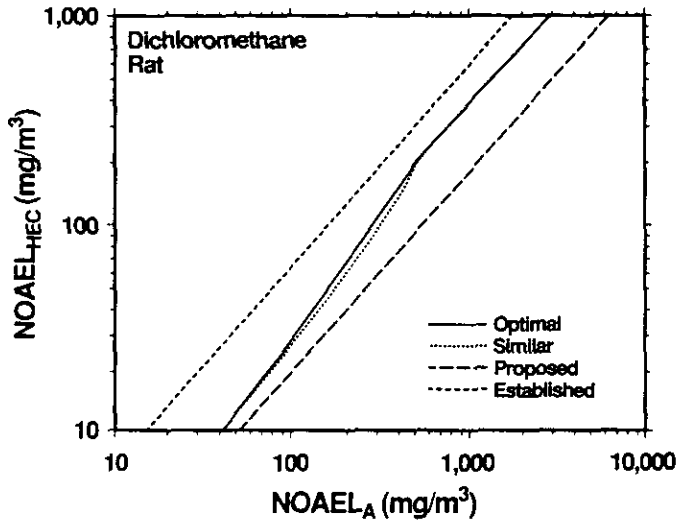

FIGURE 3. Plot of $NOAEL_{HEC}$ versus $NOAEL_A$ for the rat for four possible methods (proposed, established, similar, and optimal) of determining $NOAEL_{HEC}$ estimates for inhaled dichloromethane (*16*).

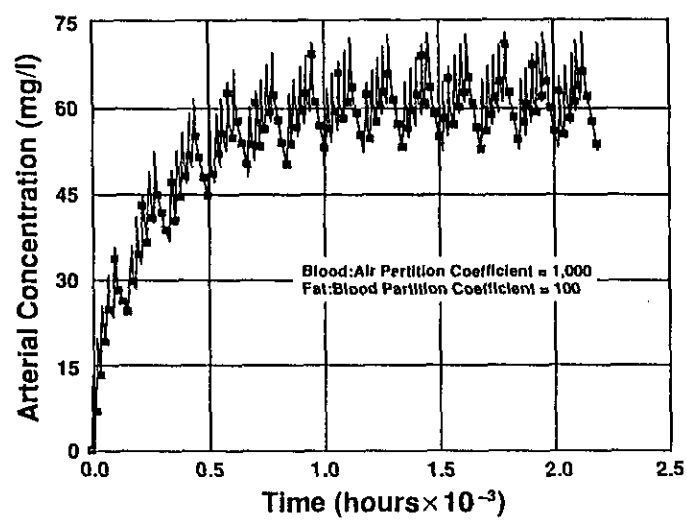

FIGURE 4. Time course of periodicity of a 6 hr/day, 5 days/week exposure (*16*).

The quality and suitability of toxicity data must be evaluated in dose–response models. The data must be described by mathematical constructs. Any nonlinearity in data requires at least three data points (i.e., dose groups) to define the mathematical relationship. When extensive extrapolation is required, the biologically effective dose is the most accurate dosimetry for predicting effects. Less desirable measures of dosimetry in decreasing order are concentration in the affected tissue, circulating blood concentration or absorbed levels, administered dose, and environmental exposure. Pharmacokinetic models can help predict tissue levels from exposure levels, but data for the pharmacokinetic models are not usually abailable. Separate

dose-response models must be evaluated for each affected tissue, and the toxicity data should be similar to the conditions for which the risk assessment is performed, e.g., exposure route, duration, species, age group, preexisting health, and reproductive status.

Models should be selected on the basis of the type of model to be developed and the type of data available. Applications of both the empirical and mechanistic models are described above. Dose-response models use quantal data regarding the presence or absence of an effect and the frequency of that occurrence. These models may be threshold or nonthreshold. Threshold models use dose above a threshold, and nonthreshold models are of the multistage, one-hit, or Weibull type. Tolerance distribution models are dose-response models that describe the probability of tolerances or thresholds in a population. The prevalence of effects such as mortality are usually described in these models.

Dose-intensity models use continuous measurements and assume that deviation from the normal value increases with increasing dose (*18,19*). The numerical value derived from these models is not an indication of hazard. Rather, the measured effect must be compared to control populations. The probability of an effect being adverse may be derived from these models if the probability distribution of normal measurements is derived first.

Dose-severity models are used when dealing with toxicity grouped in severity categories. These models should be used when the general severity of toxic response is the assessment goal. This model, like the RfC, is designed to prevent adverse effects regardless of the target organ. The results of these models can be presented as probabilistic risk.

Statistical methods should be used to estimate model parameters, and sensitivity analyses should be conducted on all possible parameters. Parameter values for empirical models should be based on prior studies in similar species or with similar chemicals. Biologically based and mechanistically based models should use assigned parameter values from control populations.

The quality of the dose-response model is based on its available goodness of fit to the data and an estimate of each parameter's variation by a method such as standard error. A level of statistical significance can be applied to the model based on its variation. If alternative assumptions are required by the model, then the range generated by the model should be defined. When multiple toxic end points are modeled from animal data, those models applicable to the human toxic response should be presented. Sufficient information on mechanism of action, pharmacokinetics, and species differences in tolerance distributions should be given in prevalence models to relate animal response rates to human response rates.

Decision Analytic Approach

The decision analytic approach to dose-response relationships emphasizes the characterization and representation of the major uncertainties in the estimate. Probability is used to quantify the degree of uncertainty. These uncertainties arise because of measurement error, sample size, sampling protocol, and insufficient health effects data. The judgmental interpretation of probability is also known as Bayesian interpretation. The Bayesian viewpoint is that probabilities represent an individual's degree of belief about a given quantity rather than a measured property of the world (*20*).

Decision analysis permits characterization of uncertainties in terms of probability often obtained by eliciting probabilistic judgments from scientific experts. Such an approach has been used for lead (*5*) and ozone (*21*). The approach should be used when a distribution of risk estimates for a defined health end point associated with given levels and conditions of human exposure are desired. The decision analytic approach to dose-response assessment is more data intensive than the RfC approach and often requires an ability to elicit expert judgment and the cooperation of these experts. The scientific experts should be recognized, competent scientists who have done research and published in the area of interest. The experts should represent a range of credible scientific viewpoints.

This process begins with developing an assessment protocol that guides the collection of qualitative and quantitative judgments by ensuring that questions are phrased identically to all experts, that specific assumptions and definitions are common to all experts, and that the encoding process is carried out similarly with all participants. The appropriate health end point must be defined for the expert participants. Exposure conditions, populations of interest, and geographical areas of interest must also be defined for the experts as part of the encoding protocol (*22*).

Probabilistic dose-response relationships are obtained from experts in an interview session. The process is referred to as "probability encoding." Initially, the purpose of the session is established followed by defining the unknown quantity for which judgment will be elicited. The scientific literature relevant to the relationships and possible biases are discussed. After this discussion, values that bound specific probability intervals are determined. Experts are asked to express judgments in probabilistic form. The encoding process establishes upper and lower bounds on plausible response rates at a specific exposure level, i.e, an upper response rate that would be exceeded with probability 0.01 and a lower response rate that would be exceeded with probability 0.99. The median response rate is also determined, which is a response rate such that the true response rate is equally likely to be above or below it. Probabilities for other response rates are also encoded. Encoded probabilities for several exposure levels can be plotted on a graph. Implications of the graph of probabilities are discussed and the experts allowed to make any changes (*22*). These probability judgments are checked for stability and coherence, i.e., the judgments must satisfy the laws of probability such as additivity.

When an adequate database is available, a probabilistic dose-response relationship and an estimate of uncertainty can be obtained. However, since the assessment must be for humans and the population from which the data was drawn is likely to be from animals, extrapolation is required. Probabilistic dose-response relationships can be presented as curves on a graph of dose or exposure versus response rate. The curves can consist of the 0.5, 0.05, and 0.95 fractile distributions. The 0.05 and 0.95 fractile distributions bound the 90% credible interval, i.e., 0.9 probability that the "true" dose-response relationship lies in the designated range. Each expert's 90% credible interval can then be compared to assess a total range for the 0.9 probability of the "true" doseresponse curve.

Structure–Activity Relationships

Structure–activity relationships may be used in the hazard identification step when very little or no test data are available. The approach contains four elements: *a*) evaluating pertinent data on the chemical under study; *b*) evaluating data on an analogous chemical; *c*) using mathematical expressions for biological activity; and *d*) interpretating and integrating available information.

The chemical under study or its potential metabolite must be evaluated and interpreted. This evaluation must include physical and chemical parameters that affect the toxicity of the chemical.

Analogous chemicals must also be evaluated. Two factors are used to define chemicals as analogous: structural, functional, and mechanistic similarities that control the biological reactivity of the chemicals and availability of pertinent toxicologic information on the analogues. An effort should be made to select analogues with similar structural and substructural components that also have similar biological activity. Potential metabolic pathways should be considered to identify key potential metabolites. Once a list of chemicals having similar structure or similar metabolites are identified, these chemicals are searched on an available toxicity database to identify relevant toxicity literature necessary in completing the hazard identification.

Quantitative structure–activity relationships that are mathematical expressions of biological activity are used to estimate physical and chemical properties, e.g., water solubility, partition coefficient, vapor pressure. The water solubility is a key component when considering the dermal, pulmonary, or gastrointestinal absorption of a chemical. Thus, the physical and chemical properties of an analogue in addition to its structural properties may be important in selecting the most similar analogue.

Finally, the available information must be interpreted by scientific assessors. The information developed in the preceding steps on analogous substances and metabolites will likely be limited in some respects and therefore require judgment and integration. The data on analogues should be evaluated based on the similarity to the chemical under study, and metabolites should be evaluated based on their formation and toxicological significance. Parameters to be evaluated are dermal, pulmonary, and gastrointestinal absorption; distribution and excretion; and possible mechanisms of toxicity and the ability of the chemical and its analogues to operate by such mechanisms. The greater the similarity between the chemical in question and its analogues, the more reliable the hazard identification.

Summary

Risk assessments from exposure to indoor air pollutants require exposure assessments and dose–response assessments. Dose–response assessment methodologies have been discussed here. These methods include the inhalation reference concentration, structure–activity relationships, dose–response models, and the decision analytic approach. The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The current RfC method provides guidelines for making the necessary dosimetric adjustments for gases and aerosols. Human equivalent concentrations for no-observed-adverse-effect levels in animals are determined by using mathematical relationships that adjust for regional deposition, solubility, ventilation rate, and blood:air partition coefficients. Physiologically based pharmacokinetic models can also be used in some cases to predict the human equivalent concentration more accurately. Dose–response modeling, although very data intensive, describes the dose–response relationship over the entire range of data and can be modified to address different assessment goals. The decision analytic approach to dose–response assessment can be used to obtain a distribution of risk estimates for a defined health end point by using expert judgment regarding the dose–response relationship. Structure–activity relationships may be used for hazard identification when few or no test data exist, and chemical analogues can be identified which have similar structural, metabolic, and toxic effects as the chemical of concern.

The RfC methodology exists as an interim methodology. Future scientific advancements are expected to further refine the approach. Quantitation and reduction of uncertainty are the subject of current research designed to improve this dose–response methodology. In addition to the analysis of uncertainty for the RfC methodology, physiologically based pharmacokinetic models are being actively pursued for many chemicals. These models will reduce the uncertainty of extrapolation from animals to humans. Research into route-to-route extrapolation will further expand the scope of the RfC procedure. Research into biologically based dose–response models and mixtures are other areas that will reduce uncertainty in dose–response models and, therefore, in indoor air risk assessments in the future.

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