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CONSIDERATION OF TEMPORAL TOXICITY CHALLENGES CURRENT DEFAULT ASSUMPTIONS

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According to the 1983 NAS paradigm that serves as the basis for current health risk assessment procedures, risk characterization requires the comparison of an exposure estimate against a dose-response estimate. The types of exposure scenarios required under various regulations can be categorized as acute, subchronic, and chronic. Toxicity testing studies can also be so categorized, but such categories are defined by the exposure duration and not the underlying mechanism of action or its appropriate dose metric. Considerations of underlying mechanisms and temporal relationships of toxicity challenge current default assumptions and extrapolation approaches for derivation of dose-response estimates. This article discusses the duration adjustments used in current health risk assessment procedures and highlights the attendant assumptions. Comprehensive dosimetry model structures integrate mechanistic and temporal determinants of the exposure-dose-response continuum. Analysis of dosimetry model structures is proposed as a way to identify key parameters for development of alternative default duration adjustment procedures.

The various environmental and occupational regulatory statutes and implementation activities under such laws as the Clean Air Act Amendments of 1990 (CAAA), the Safe Drinking Water Act (SDWA), the Clean Water Act (CWA), the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), the Resource Conservation and Recovery Act (RCRA), and the Occupational Safety and Health Act (OSHA) require risk characterization and risk management of exposure scenarios that range in duration from a few minutes to lifetime. The 1983 National Academy of Science/National Research Council (NAS/NRC) report on risk assessment and risk management presented a paradigm[1] for this process that serves as the basis of most health

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[1]The NAS recommended that the scientific aspects of risk assessment should be explicitly separated from the policy aspects of risk management. Risk assessment was defined as the characterization of the potential adverse health effects of exposures to environmental hazards, and consists of four steps: (1) hazard identification: the determination of whether a chemical is or is not causally linked to a particular health effect; (2) dose-response assessment: the estimation of the relation between the magnitude of exposure and the occurrence of the health effects in question; (3) exposure assessment: the determination of the extent of human exposure; and (4) risk characterization: the description of the nature and often the magnitude of human risk, including attendant uncertainty.

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assessment procedures and regulatory programs in various federal agencies (NRC, 1983). In order to characterize health risk for these different scenarios so that risk management decisions may be made, dose-response estimates for toxicity that are comparable to these exposure scenarios must be derived. The definition of comparability between exposure and toxicity estimates, however, has usually been based on the comparability of the exposure duration of the objective exposure scenario to that of the experimental exposure in the laboratory test species (or to various dose surrogates commonly used in occupational epidemiology). In most cases, these definitions do not take into account the mechanistic and temporal determinants of the toxicity nor account for the species differences in such determinants.

This article outlines the current dose-response procedures typically used for noncancer toxicity of various durations. The assumptions underlying current procedures for duration extrapolation are discussed and evaluated with consideration of potential mechanistic and temporal determinants of toxicity. Since toxicity depends on the magnitude, duration, and frequency of exposure—which in turn can be affected by the timing of exposure—determination of the appropriate dose metric and duration extrapolation should be dependent on the mechanism of toxicity. Dosimetry models incorporate mechanistic determinants of chemical disposition in order to characterize the relationship between exposure concentration and target tissue dose. Because these disposition determinants include both concentration- and time-dependent processes, analysis of dosimetry model structures is proposed as a way to identify key parameters and to define limiting conditions for development of alternative default duration extrapolation procedures.

EXPOSURE SCENARIOS AND TYPES OF TOXICITY DATA AVAILABLE

As mentioned earlier, various regulatory statutes and implementation activities require health risk characterization of different exposure scenarios as the basis of risk management programs. As shown in Table 1, these exposure scenarios range from minutes to lifetime, and are often categorized as acute, subchronic, and chronic. Certain of these scenarios have default assumptions incorporated in their definition. For example, default consumption values of 24-h continuous inhalation exposure (at a rate of 20 m^3/day) and 2 L/day for water intake are assumed for a 70-kg person (male). Eight-hour, time-weighted averages are often used as exposure surrogates for occupational scenarios. A daily (24-h) average exposure may be used as an exposure surrogate for "acute" ambient exposures whereas the annual average is calculated as a surrogate for "chronic." "Lifetime" or "chronic" exposures for humans are assumed to be 70 yr, and 10% of this lifetime (7 yr) defines the lower cutoff for "subchronic" exposures. Exposures are usually assumed to be at a constant concentration, whereas the actual exposure is a profile dependent on numerous factors such as production volume, stack height, meteorology, and human activity patterns.

Experimental exposures to animals are typically divided into four categories: acute, subacute, subchronic and chronic, as shown in Table 2.

TABLE 1. Exposure Scenarios Requiring Risk Characterization

Acute
15-min Occupational TWA[a] ceiling level
1-h Emergency response planning guidelines
Subchronic
Intermittent startup/shutdown processes
Periodic contaminations
Chronic
8-h Occupational TWA exposure limits for "working lifetime"
Ambient exposures for "lifetime"

[a]TWA, time-weighted average.

Acute exposure is defined as an exposure to a chemical for less than or equal to 24 h. Although usually for a single administration (e.g., 4 h), repeated exposures are sometimes given within the 24-h period. Repeated or continuous exposures are also divided into subacute, subchronic, and chronic categories. Subacute refers to repeated or continuous exposure to a chemical for 1 mo or less (e.g., a 14-day range finding study). Subchronic refers to repeated or continuous exposure for 1–3 mo, usually a 90-day study. Chronic refers to repeated or continuous exposure for longer than 3 mo, most commonly a 2-yr bioassay in rodents.

These categories are defined based on the duration of the exposure and in the absence of any consideration of mechanisms of toxicity or its temporal aspects. Generally, acute toxicity data are used as the basis for derivation of acute toxicity dose-response estimates that are used to compare against acute exposure estimates for risk characterization. Likewise, chronic bioassay data (or subchronic data with application of an uncertainty factor for the effect of duration) are used as the basis for derivation of chronic toxicity dose-response estimates for characterization of lifetime ambient exposure scenarios. Thus, a fundamental assumption of these approaches is that toxicity across different

TABLE 2. Typical Testing Exposure Protocols

Acute
1- to 24-h single inhalation exposures
Single (or few) oral administrations
Subacute
14-day range-finding exposures
Subchronic
90-day exposure studies
Chronic
2-year bioassays

species is a function of lifetime fraction (chronologic) exposed (e.g., a 2-yr "lifetime" bioassay in the rodent is equivalent to a 70-yr human "lifetime" for the purposes of chronic health risk characterization).

The attendant uncertainties and default assumptions of the dose-response estimate should be evaluated in context with those of the exposure estimate (e.g., assumptions of fate and transport modeling or type of sampling and averaging time of a measured exposure) to ascertain whether the two are appropriate to integrate. Table 3 provides a comparison of different assumptions and derivation methods inherent in some common risk assessment and risk management estimates. The intended use of a dose-response or risk management estimate influences its derivation (Jarabek & Segal, 1993). The assumptions and uncertainties of the risk characterization components (dose-response and exposure assessments) must be explicitly communicated to the risk management arena for application to intended scenarios. Often dose-response estimates are compared inappropriately with risk management or regulatory values that are intended for different exposure scenarios and populations or that are derived using additional considerations such as control technology. Because of these differences, the remainder of this article discusses only procedures for dose-response estimation.

DEFAULT DURATION EXTRAPOLATION FOR NONCANCER TOXICITY

Current procedures for dose-response estimation attempt to match the durations of the exposures that are the basis of the toxicity data with the anticipated human exposure scenario. For oral exposures, this assumption applies whether or not the dose was administered as parts per million (ppm) in water, in diet, or via gavage. When the exposure duration of the laboratory animal toxicological study does not match that of the objective human exposure scenario, a linear prorated adjustment of the exposure concentration is typically performed. The default duration adjustments are shown next for acute and chronic inhalation exposures.

For acute (≤24 h) exposures,

$$EL_{ADJ} = EL \times D/H \tag{1}$$

where EL_{ADJ} is the effect level (ppm), such as a no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL), adjusted for duration of experimental regimen; EL is the experimental exposure level (ppm); D is the experimental exposure duration (h); and H is the objective human exposure duration (h). Twenty-four hours is used by the Agency for Toxic Substances and Disease Registry (ATSDR) as the default for the objective acute human exposure duration (H); EPA has proposed not to adjust acute exposures.

For chronic (2-yr bioassay) exposures,

$$EL_{ADJ} = EL \times D \times W \tag{2}$$

this time D is given in hours per 24 h and where W is the weekly frequency of exposure in days per 7 days.

Thus, the default duration adjustments assume that exposure concentration is equivalent to inhaled dose. Further, it is also assumed that toxicity is linearly related to the product $C \times t$ so that equivalent products cause the same toxicity. A notable exception to these duration adjustments is that of developmental toxicity. No duration adjustment is applied to effect levels for this noncancer toxicity. The rationale is that because developmental toxicity can occur within any time window of the gestational period, duration extrapolation is inappropriate.

The assumption in Eqs. 1 and 2, that the resultant human exposure concentration should be the concentration times time ($C \times t$) equivalent of the experimental animal exposure level, is based on "Haber's law."[2] According to this "law," a constant, in this case a fixed effect (i.e., a constant severity and/or incidence) level, is related to exposure concentration and duration by

$$EL = aC^n \times t \tag{3}$$

where EL is the fixed effect level, a is a coefficient defined empirically, C is the exposure concentration, n is an exponent defined empirically, and t is the duration of exposure. Figure 1 is a schematic illustration of the relationship between exposure concentration and duration to a fixed effect level (EL) assuming "Haber's law." The relationship is described by a hyperbola whose arms converge asymptotically toward the axes of the coordinates (Bliss, 1940). Because Haber examined only extremely short durations, a $C \times t$ relationship appeared to hold because concentration was the dominant determinant of toxicity in that limited time window. Bliss and James (1966) showed that such curves could be extrapolated with minimal error only when the time points in the experiment are located on the asymptotic segments of the curve (i.e., high concentration, acute exposures or low concentration, chronic exposures). The rationale when applied to chronic exposures is that the concentration is low and steady state has been reached and thus duration is the dominant determinant.

"Haber's law" is related to the log(time)–log(dosage) curve. When the relationship in Eq. 3 is plotted on log-log paper, all solutions lie on a straight line. When the exponent, n, is equal to 1, the line passes through the two points ($C = 1$, $t = EL$ and $C = EL$, $t = 1$) and has a 45-degree slope. Empirical data have also shown greater or lesser slopes. The smaller the

[2]Apparently the only statement Haber made of what was to be called his rule is contained in a footnote to the last of a series of five lectures that this chemist made during the period 1920 through 1923 (Haber, 1924). The lecture pertained to the history of gas warfare and only brief exposures were considered. Also, at that time, no chemical was known that would not drift away or be diluted to a harmless concentration soon after its release (Hayes, 1975). The concept was actually not original with Haber but was stated first by Warren (1900) in connection with his studies of the effects of different concentrations of sodium chloride on *Daphnia magna*.

TABLE 3. Comparison of Exposure Limits

Organization/ exposure limit	NAS paradigm	Objective exposure scenario	Effect severity
"Less than lifetime" exposure limits			
ACGIH TLV-STEL[b]	Management	15-min time-weighted average exposure that should not be repeated more than 4 times per day	Protect against irritation, chronic or irreversible tissue damage, or narcosis of sufficient degree to increase chances of accidental injury, impair self-rescue or reduce work efficiency
AIHA ERPG[c]-3	Management	1-h Exposure	Protect against life-threatening effects
AIHA ERPG[c]-2	Management	1-h Exposure	Protect against irreversible or other serious health effects that could impair ability to take protective action
AIHA ERPG[c]-1	Management	1-h Exposure	Protect against mild, transient adverse health effects
COT EEGL[d]	Management	1- and 24-h Exposures	Reversible effects acceptable (e.g., headache, irritation, CNS effects)
COT SPEGL[e]	Management	1- and 24-h Exposure	Reversible effects acceptable (e.g., headache, irritation, CNS effects)
COT CEGL[f]	Management	90-day Exposure	Reversible effects acceptable (e.g., headache, irritation, CNS effects)

Note. Adapted from Jarabek and Segal (1993) and Jarabek (1994).
[a]SF, safety factor; UF, uncertainty factor consistently used for explicit extrapolations applied to data.
[b]ACGIH, American Conference of Governmental Industrial Hygienists; TLV-STEL, threshold limit value–short-term exposure level.
[c]AIHA, American Industrial Hygiene Association; ERPG, emergency response planning guideline.
[d]COT, Committee on Toxicology of NAS; EEGL, emergency exposure guidance level.
[e]COT, Committee on Toxicology of NAS; SPEGL, short-term population exposure guidance level.
[f]COT, Committee on Toxicology of NAS; CEGL, community exposure guidance level.

exponent, the steeper the slope. Based on 1-h lethality studies, ten Berge et al. (1986) found that 19/20 substances showed a value for n in Eq. 3 to be in the range of 1.0–3.5. The one exception had a value of 0.8. If 4-h exposure level is extrapolated to shorter durations using the $C \times t$ assumption and a value of 1 for n, the resultant estimate is considerably higher than

SF or UF[a]	Population	Derivation/database
Minimal SF used; no systematic application	Healthy worker	Based on best available information from industrial experience, experimental human and animal studies (human data preferred); no systematic basis—derived by expert committee
SF	General population living in immediate areas of release	Acute toxicity data preferred; based upon most sensitive endpoint from human or animal data; all endpoints considered; methods vary on a case-to-case basis
SF	General population living in immediate area of release	Same as ERPG-3
SF	General population living in immediate area of release	Same as ERPG-3
Generally no (unless confidence in database is low or chemical is a carcinogen)	Military personnel, assumed to be healthy and relatively homogeneous	Based on most sensitive endpoint (NOAEL or LOAEL) from human or animal toxicity data (acute toxicity data preferred); all endpoints considered
SF of 2–10 applied EEGL to protect more sensitive subpopulations (SF = 2) or fetuses or newborns (SF = 10)	General population	EEGL divided by a factor of 2–10 to protect more sensitive subpopulations
SF of 10–100 applied to EEGL based on pharmacokinetics (i.e., ability to be rapidly bio-tranformed or to bioaccumulate)	General population	EEGL divided by a factor of 10–100 to account for pharmacokinetic considerations

(*Table continues on next page*)

that estimated using a value of 3.5 for n. Based on this analysis, ten Berge et al. (1986) concluded that estimates of the $C \times t$ relationship for derivation of extrapolation procedures should be developed using chemical-specific information. Data to construct log(time)–log(dosage) plots are available for relatively few chemicals and most are lethality data. Establishing an extrap-

TABLE 3. Comparison of Exposure Limits (*Continued*)

Organization/ exposure limit	NAS paradigm	Objective exposure scenario	Effect severity
"Lifetime" exposure limits			
ACGIH TLV-TWA[g]	Management	8 h/day; 40 h/week for a working lifetime (40 yr)	No adverse effect
NIOSH REL[h]	Management	Up to 10 h/day; 40 h/wk; undefined working lifetime duration; appropriate control and surveilance methods	No adverse effect
OSHA PEL[i]	Management	8 h/day; 40 h/wk; 45-yr working lifetime duration; appropriate control and surveillance methods	Protect worker against a wide variety of health effects that could cause material impairment of health or functional capacity
ATSDR MRL[j]	Dose-response	24 h/day, 70 yr	NOAEL or LOAEL with UF
EPA RfC	Dose-response	24 h/day, 70 yr	NOAEL or LOAEL with UF

[g]ACGIH, American Conference of Governmental Industrial Hygienists; TLV-TWA, threshold-limit value–time-weighted average.
[h]NIOSH, National Institute for Occupational Safety and Health; REL, recommended exposure level.
[i]OSHA, Occupation Safety and Health Agency; PEL, peak exposure level.
[j]ATSDR, Agency for Toxic Substances and Disease Registry; MRL, minimum risk level.

olation procedure based on lethality data may not be appropriate for milder effects such as a NOAEL or LOAEL used in risk assessment, especially for extrapolation to a shorter duration, because mechanistic determinants may be different for severe versus milder effects.

Figure 2 illustrates an example of the potential inaccuracies in the prorated linearized extrapolation approach to either shorter or longer durations. The vertical dashed lines at 1 h and 8 h indicate typical exposure durations required for estimation. If the single 4-h experimental concentration was extrapolated to a 1-h exposure estimate, assumption of Haber's law (B) results in an overestimate of exposure when compared to an estimate assuming concentration alone (A) is the dominant determinant of toxicity. Extrapola-

SF or UF[a]	Population	Derivation/database
Minimal SF used; no systematic application	Nearly all workers; personal protective equipment may be factored	Based on best available information from industrial experience, experimental human and animal studies (human data preferred); no systematic basis—derived by expert committee
Minimal SF used; no systematic application	Nearly all workers; personal protective equiment may be factored	Based on best available information from industrial experience, experimental human and animal studies (human data preferred); no systematic basis—derived by expert committee
Same as above	Same as above	Same as above; in addition, technological feasibility is considered in establishing a PEL
UF	General population including susceptible	Occupational, experimental human and animal
UF	General population including susceptible	Occupational experimental human and animal; dosimetry adjustments applied

tion to the longer 8-h duration results in the converse relationship between exposure estimates—in this case the estimate derived assuming Haber's law (B) is conservative in comparison to the estimate based on concentration as a constant (A).

Extrapolation of an exposure based on Haber's law versus keeping concentration a constant regardless of duration could be based on consideration of what the mechanism of action is believed to be. Extrapolation keeping EL = C could be appropriate for irritants, so that no matter the duration, the effective concentration level remains the same. In this case, concentration alone is used as a dose metric. If either the chemical or its damage accumulates with duration, the exposure level given by extrapola-

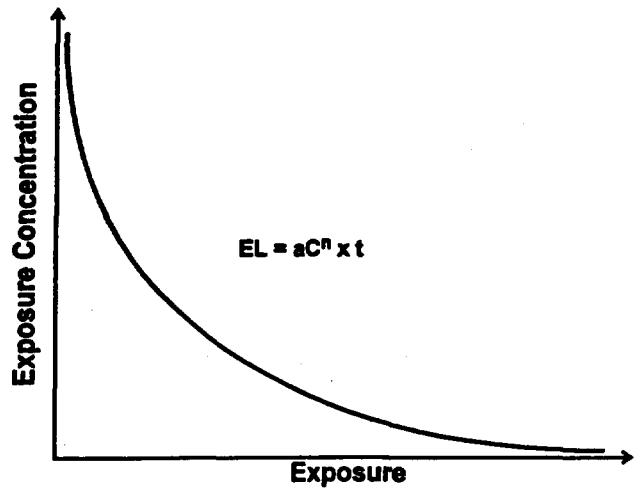

FIGURE 1. Schematic of relationship between exposure concentration (C) and duration (t) to fixed effect level (EL) of toxicity assuming "Haber's law."

tion using Haber's law would be more appropriate because duration (*t*) is an explicit determinant. Andersen et al. (1987a) suggested that toxicity for most industrially important gases and volatile liquids would probably be related to the area under the blood curve (AUBC) rather than to peak blood concentrations, so that the use of C × *t* in the absence of sufficient mechanistic data might be an acceptable way of extrapolation because the

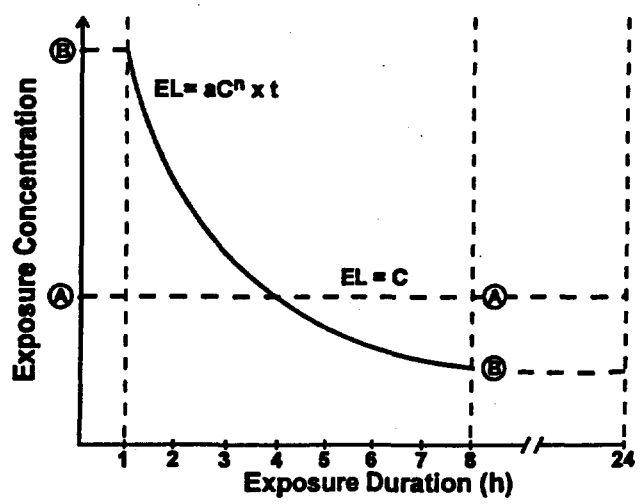

FIGURE 2. Schematic of relationship between exposure concentration (C) and duration (t) to fixed effect level (EL) of toxicity assuming "Haber's law" (solid line) versus concentration as the major mechanistic determinant (horizontal dashed line). Resultant effect levels calculated by extrapolation from a 4-h exposure to a 1-h and 8-h exposure are shown for both.

AUBC would be a similar estimate. Some dose-response methods qualitatively take mechanistic data into account and caveat the use of the preceding default duration adjustments (U.S. EPA, 1994). Consideration of cases where the $C \times t$ assumption may not hold is encouraged (e.g., when concentration may be the dominant determinant). For example, the inhalation reference concentration (RfC) for 2-chloro-1,1,1,2-tetrafluorethane (HCFC-124) did not use the duration adjustment because the data suggested the reversible narcotic effect was due to parent compound concentration only and it had a short half-life. For most effects, however, the "true" dose metric is not determined, and in all likelihood, extrapolation for many toxicants should lie somewhere between the two lines.

MECHANISTIC DETERMINANTS AND TEMPORAL ASPECTS OF TOXICITY

Toxicity can depend on the magnitude, duration, and frequency of exposure. Timing in turn can affect these parameters (e.g., different windows within gestation have different susceptibility). Mechanistic determinants of chemical disposition (deposition, absorption, distribution, metabolism, and elimination) of a chemical include both time- and concentration-dependent processes. In general, fractionation of the dose reduces the effect. If detoxifying biotransformation or elimination occurs between successive doses, or if the damage produced is repaired between successive doses, then a single dose may produce more toxicity than that same amount fractionated into many smaller doses given at intervals. Chronic effects occur if the chemical accumulates, if it produces irreversible effects, or if there is insufficient time for the target tissue to recover from the damage within the exposure frequency interval. Acute toxicity may or may not resemble that manifest after prolonged repeated exposures. For many chemicals, the critical toxic effects following a single high-concentration exposure are quite different from those produced by repeated low-level exposure (e.g., the acute toxic manifestation of high-concentration benzene exposure is central nervous system depression, but chronic low-level exposure can result in blood dyscrasias and leukemia). Acute exposure can also produce delayed toxicity. Conversely, chronic exposure to a toxic agent may produce some immediate (acute) effects after each exposure in addition to the long-term chronic effects. Thus, to truly characterize the toxicity of a specific chemical, information is needed not only on acute and chronic effects but also for exposures of intermediate duration.

The choice of an appropriate measure of "dose" must be defined by the nature of the pathogenesis process (i.e., defined according to the mechanism of action) for the effect under consideration. For example, the appropriate dose metric for the central nervous system (CNS) depression of acute high-concentration benzene exposure could be the parent compound blood concentration, whereas the area under the tissue concentration curve for toxic metabolites would be more appropriate to characterize the erythroid precursor pertubations of chronic low-level exposures. Examples of other

TABLE 4. Potential Dose Metrics

Exposure concentration of parent chemical
Blood concentration of parent chemical
AUBC of parent chemical
Tissue concentration of parent chemical
AUTC of parent chemical
Tissue concentration of metabolite
AUTC of stable metabolite
AUTC of reactive metabolite

Note. AUBC, area under blood concentration curve; AUTC, area under tissue concentration curve.

potential dose metrics are provided in Table 4 and illustrated in Figure 3. Because tissue dose of the putative toxic moiety for a given response is not always proportional to the applied dose of a compound, emphasis has been placed on the need to clearly distinguish between exposure concentration and dose to critical target tissues. The term exposure-dose-response assessment has been recommended as more accurate and comprehensive (Andersen et al., 1992).

The process of determining the exposure-dose-response continuum is achieved by linking descriptions of the mechanisms of critical biological factors that regulate the occurrence of a particular process and the nature of the interrelationships among these factors. The iterative process of linking descriptions at various stages along the continuum is shown in Figure 4. It is ultimately desirable to have a comprehensive biologically based dose response model that incorporates the mechanistic determinants of chemical disposition, toxicant–target interactions, and tissue responses integrated into an overall model of pathogenesis. Dosimetry models can be linked to pharmacodynamic models that address the mechanistic determinants of the toxicant–target tissue interaction and tissue response, respectively. Biologically

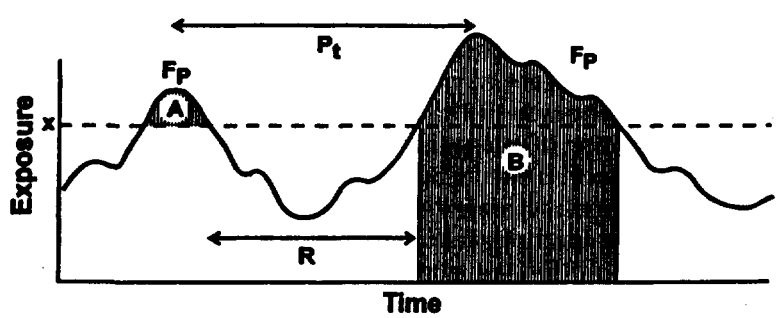

FIGURE 3. Effective exposure causing toxicity depends on the magnitude, duration, and frequency of exposure. Potential dose profile metrics are illustrated. A, area over the threshold, x; B, summation of all dose when x is exceeded. P_t, time between peaks over x; R, respites between peaks over x; F_p, the frequency of peaks over x. Integrated dose and average dose could also be calculated.

based dose-response models refine the designation of response. The tissue dose is linked to determinants of target–tissue interaction (e.g., critical mechanistic events such as cytotoxicity and rebound cellular proliferation), which, in turn, may then be related via other mechanisms to the ultimate production of lesions or functional changes that are typically defined as the disease (pathogenesis) outcome. To the extent that these intermediate events are explanatory of the disease outcome, they can be used to quantitate important nonproportionalities or as replacement indices of the response function. For example, the amount of cytotoxicity from a low-level exposure to a chemical known to cause cellular proliferation and subsequent neoplasia could be used to evaluate risk using mechanistic models rather than estimation of risk based on tumors from high concentration exposures.

Current dose-response assessment methods are essentially based on characterization of the exposure-dose-response continuum at the first, "black-box" level and necessarily incorporate large uncertainty factors to ensure that the estimates are protective in the presence of data gaps that are often substantial. Use of "Haber's law" can be viewed as falling in this first "black box" tier. Interestingly, Hayes (1975) restated the relationship of "Haber's law" in recognition of its limited applicability to address dosimetry considerations as

$$[(CV_m) - De]tR/w = D \tag{4}$$

where D is the dosage (mg/kg) received during time t, C is the concentration of toxicant (mg/m^3), V_m is the minute volume rate of respiration (m^3/min), De is the detoxification rate (mg/min), t is the time (min) of exposure, w is body weight (kg), and R is the retention coefficient expressed as a decimal fraction. The equation shows that a sufficiently high rate of detoxification would negate prolonged exposure to a sufficiently low concentration. It thus expresses quantitatively the limitation on the rule when applied to easily detoxified materials. It is also seen in Eq. 4 that the dosage, D, is not necessarily a constant for all combinations of concentration and time that produce the same effect, since the detoxification rate and perhaps the retention coefficient may vary with dosage.

Equation 4 is actually an attempt to account for potential mechanisms of toxicity and a dose other than the exposure concentration as a metric. Unfortunately, most of the parameters in Eq. 4 are not determined routinely in toxicological studies, nor would they be available for humans. Since the formulation of this equation, dosimetry models[3] have evolved into particu-

[3]Although the term physiologically based pharmacokinetic (PBPK) modeling is often used in a general sense, dosimetry modeling is used in this article as a more comprehensive term to capture not only model structures used to address volatile organic chemicals but also irritant gases and particles. Mathematical modeling is defined as the use of the physical laws of mass, heat, and momentum conservation to quantify the dynamics of a system of interest (e.g., particle deposition and clearance in the respiratory tract). Dosimetry modeling is defined as the application of mathematical modeling to characterize the determinants of exposure-dose-response.

larly useful tools for predicting chemical disposition differences between species.

APPLICATION OF DOSIMETRY MODELS

Dosimetry models that account for mechanistic determinants of the disposition of a parent compound and/or its metabolites, such as physiologically based pharmacokinetic (PBPK) models, have been useful in describing the relationships between exposure concentration and target tissue dose. Because pharmacodynamic data (data on toxicant-target tissue interactions including differences in response due to sensitivity) are the least available, the majority of dosimetry models have restricted structures to describe chemical disposition. Scaling of mechanistic parameters, such as metabolic rates, provides for accurate extrapolation to humans.

Default dosimetry adjustments using a limited number of key parameters and based on mathematical reduction of more comprehensive dosimetry model structures have been developed for different types of inhaled chemicals (particles and various categories of gases) (U.S. EPA, 1994). Use of these default dosimetry adjustments for interspecies extrapolation has moved the U.S. EPA's inhalation reference concentration (RfC) methods to the second tier within the framework shown in Figure 4 (Jarabek, 1995). Because the mechanistic determinants of chemical disposition (deposition, absorption, distribution, metabolism, and elimination) include both time- and concentration-dependent processes, similar analysis of dosimetry model structures to identify key parameters and processes may serve to provide alternatives to the duration extrapolation based on the $C \times t$ assumption of "Haber's law" (Jarabek & McDougal, 1993). Figure 5 outlines various parameters and processes that determine the dominant mechanisms at each interface for progression from exposure to response. The parameters outlined have been incorporated in various mathematical models for specific chemicals.

Figures 6 and 7 illustrate model simulations of the rate of metabolite formed per gram liver tissue via the mixed-function oxygenase system at each of three different $C \times t$ products for dichloromethane (DCM) and perchloroethylene (PERC) (Jarabek & McDougal, 1993). Each of the lines connects output from seven different simulations that have an equivalent $C \times t$ exposure product. For example, a 0.5-h exposure at 400 ppm, a 4-h exposure at 50 ppm, and an 8-h exposure at 25 ppm are simulations that have an equivalent $C \times t$ exposure product of 200 ppm-h. If "Haber's law" held, the plot of equivalent $C \times t$ products versus t would be a straight horizontal line.

DCM and PERC were chosen because they differ in both key physicochemical parameters (e.g., fat–blood partition coefficients of 19.4 vs. 121.0 for DCM and PERC, respectively) and metabolic parameters (e.g., V_{max} of 11.54 vs. 0.180 mg/h/kg, for DCM vs. PERC, respectively). For DCM, concentration is the dominant factor on the rate of metabolism since

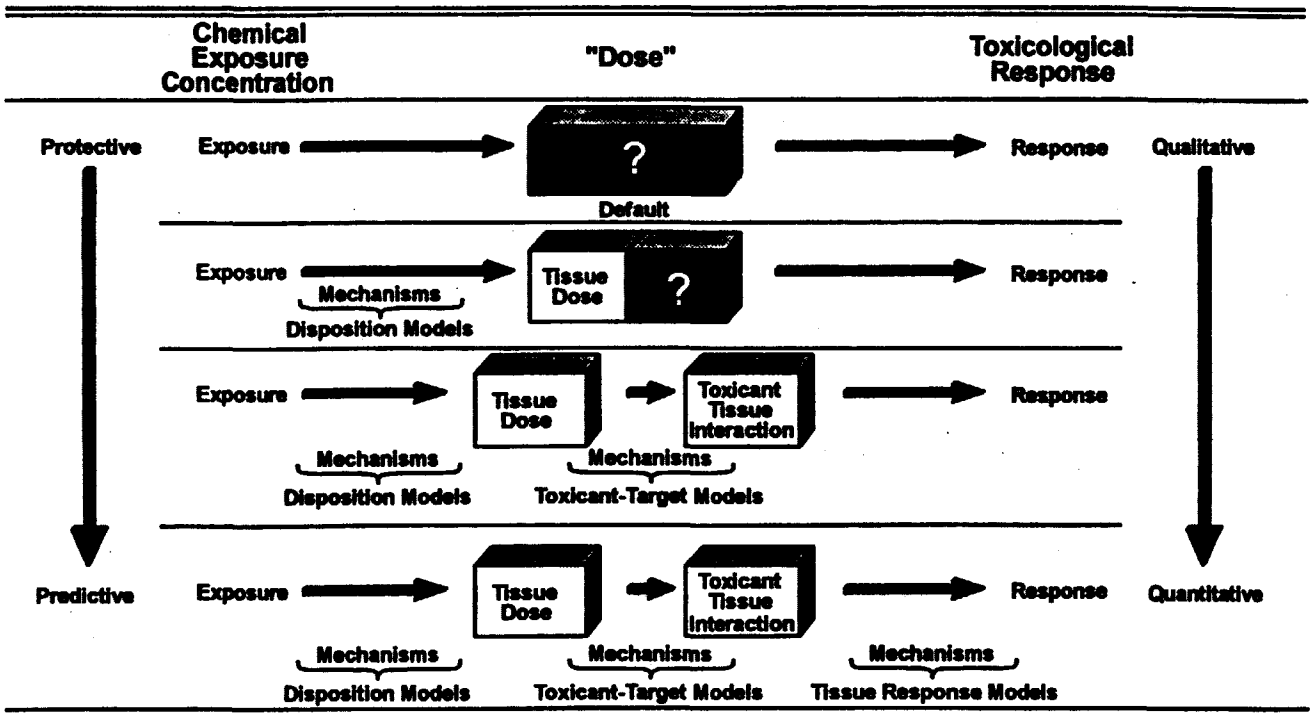

FIGURE 4. Schematic characterization of comprehensive exposure-dose-response continuum and the evolution of protective to predictive dose-response estimates. Adapted from Andersen et al. (1992).

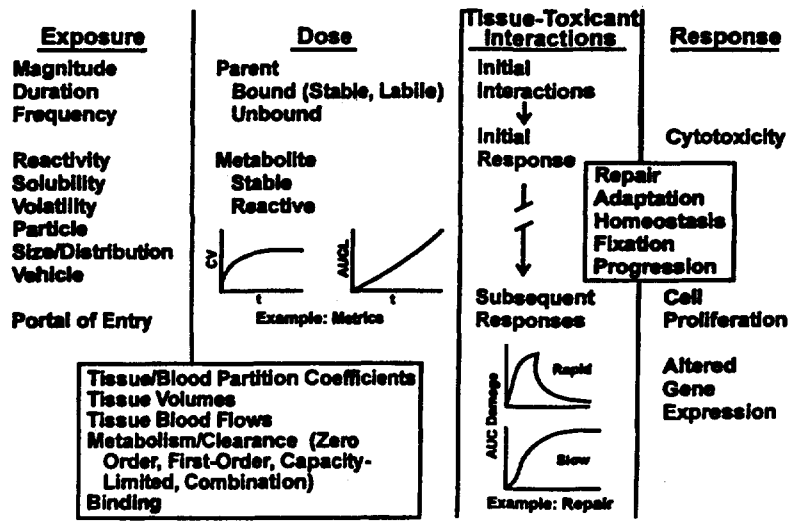

FIGURE 5. Schematic of parameters important to defining interfaces of exposure-dose-response continuum.

this chemical has the greater V_{max}. At 50 ppm the system is not yet saturated. For PERC, time is the more dominant factor on this dose metric since essentially all three C × t products are above saturation. Differences in other dose metrics, such as venous concentration or area under the liver curve, are also exhibited (Jarabek & McDougal, 1993). Similar differences in profiles could be anticipated for oral exposures also. Dosimetry models have shown

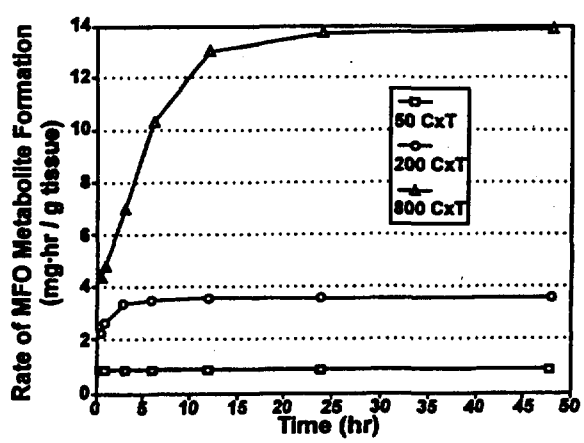

FIGURE 6. Model simulations of the rate of metabolite formed per gram liver tissue via the mixed function oxygenase system in the rat simulated at each of three different C × t exposure products for DCM. Each of the lines connects output from seven different simulations that have equivalent C × t exposure products (e.g., a 0.5-h exposure at 400 ppm, a 4-h exposure at 50 ppm, and an 8-h exposure at 25 ppm). The PBPK model used was that published by Andersen et al. (1991). Parameter values used are available elsewhere (Jarabek & McDougal, 1993).

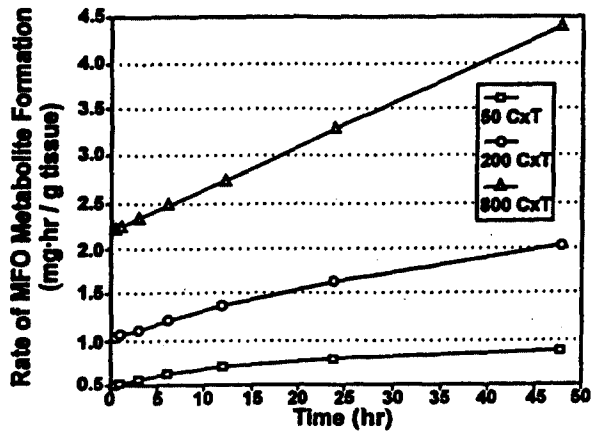

FIGURE 7. Model simulations of the rate of metabolite formed per gram liver tissue via the mixed function oxygenase system in the rat simulated at each of three different C × t exposure products for PERC. Each of the lines connects output from seven different simulations that have equivalent C × t exposure products (e.g., a 0.5-h exposure at 400 ppm, a 4-h exposure at 50 ppm, and an 8-h exposure at 25 ppm). The PBPK model used was that published by Ward et al. (1988). Parameter values used are available elsewhere (Jarabek & McDougal, 1993).

major differences in resultant dose metrics after gavage in oil versus water and in comparison to administration in drinking water (Corley & Reitz, 1990).

Figure 8 illustrates model simulations of different dose metrics of inhaled DCM at equivalent C × t exposure products of 200 ppm-h. These different dose metrics would be appropriate to characterize different toxicities, depending on the choice of an assumed mechanism. For example, parent compound venous concentration (CV) and percent of carbon monoxide (CO) bound to hemoglobin (HbCO) could be chosen as the dose metrics for the neurotoxicity observed with DCM, because these effects have been attributed both to a nonspecific narcotic action of the parent and to the hypoxic effect of its oxidative metabolic byproduct, CO (Winneke, 1981). Note that the profile for CV approximates a hyperbola on this plot, indicating that concentration is the major determinant (i.e., a plot of $C \times t^n \times t^m$ or $C \times t^{n+m}$ approximates the same shape as a plot of $C \times t^n$). For chronic toxicity, the amount of metabolite formed per gram liver tissue via the glutathione (GST) pathway might be considered the appropriate metric, since hepatic tumor incidence in mice has been shown to correlate well with the area under the curve for parent concentration in the liver and the amount metabolized via the GST pathway (Andersen et al., 1987b).

Although Figures 6–8 illustrate simulations of equivalent C × t exposure products only for the rat, dosimetry models could be used to simulate the temporal profile of different dose metrics (e.g., those in Table 4) for interspecies extrapolation. The model would be exercised according to the experimental and objective scenarios for the laboratory animal species of interest

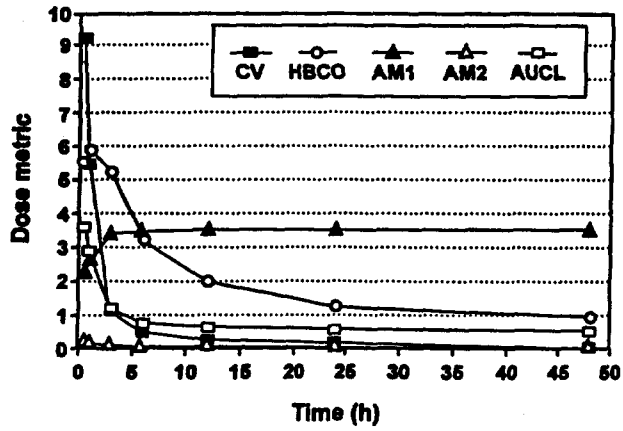

FIGURE 8. Model simulations of different dose metrics in the rat of inhaled DCM at equivalent C × t exposure products of 200 ppm-h. The PBPK model used was that published by Andersen et al. (1991). Parameter values used are available elsewhere (Jarabek & McDougal, 1993). CV, venous parent concentration (mg/L); HbCO, percent of carbon monoxide bound to hemoglobin (%); AM1, amount of metabolite formed per gram liver tissue via the mixed-function oxygenase system (mg-h/g); AM2, amount of metabolite formed per gram liver tissue via the glutathione system (mg-h/g); and AUCL, area under the curve for parent compound concentration in the liver (mg/L-h).

(e.g., intermittent exposure regimen for rats and continuous exposure for humans), and the human equivalent concentration for a given observed effect in the laboratory animal would be estimated as the exposure concentration that results in an equivalent intensity of a chosen dose metric to that achieved with the experimental animal exposure from which the observed toxicity is extrapolated (U.S. EPA, 1994). Dosimetry model templates can be developed using default physiologic parameters (e.g., minute volume, blood flows) for the common laboratory animal species and humans. Chemical-specific physicochemical parameters (e.g., partition coefficients and metabolism rates) can then be used in these default templates. General categories for solubility of gases based on ranges of air:water partition coefficients (e.g., >500, 10–500, <10) could be used to develop models. A gas categorization scheme based on reactivity and water solubility has been used recently to generate default model structures (U.S. EPA, 1994; Jarabek, 1995). Limiting conditions for interspecies extrapolation could be defined by exercising the models to simulate extremes of key parameters and for different dose metrics. For example, models could be exercised to estimate exposures that result in equivalent parent and metabolite dose metrics (e.g., CV, AUBC, AUTC) between rat and human simulations for the extremes of high and low blood–air partition coefficient with high and low metabolic rates as bounds. O'Flaherty (1989) presented a similar framework with which to organize consideration of appropriate measures of delivered dose. Interspecies conversion of kinetically equivalent doses was proposed, based on systematic species dependencies of simple kinetic relationships between administered and delivered doses.

Because dosimetry models incorporate concentration- and time-dependent processes (e.g., rate of metabolism), time is explicitly accounted for and the default adjustment based on "Haber's law" is obviated. These models also allow for development of interspecies relationships for different dose metrics. These dose metrics can be chosen on the basis of plausible mechanisms of action. The use of dosimetry models may therefore also provide revised definitions for "acute" verus "chronic" toxicity that take into account the dynamics of chemical disposition and damage. These models could also be used to simulate toxicity due to intermediate "less than lifetime" and intermittent exposures.

SUMMARY

Various environmental and regulatory statutes require risk characterization for exposure scenarios that range in duration from a few minutes to lifetime. Developing a dose-response estimate for such scenarios requires the use of available acute, subacute, subchronic, and chronic toxicity data and often the use of extrapolation procedures to different durations. The basis of current duration extrapolation procedures on "Haber's law" and its attendant assumptions have been presented. Toxicity depends on the magnitude, duration, and frequency of exposure. Choice of the appropriate dose metric and duration extrapolation should depend on the mechanism of toxicity. Dosimetry models integrate mechanistic and temporal determinants of the exposure-dose-response continuum. Analysis of the limiting conditions for different mechanisms and dose metrics by chemical class categories is suggested as a promising approach to development of alternative extrapolation procedures.

REFERENCES

Andersen, M. E., MacNaughton, M. G., Clewell, H. J. III, and Paustenbach, D. J. 1987a. Adjusting exposure limits for long and short exposure periods using a physiological pharmacokinetic model. *Am. Ind. Hyg. Assoc. J.* 48(4):335–343.

Andersen, M. E., Clewell, H. J. III, Gargas, M. L., Smith, F. A., and Reitz, R. H. 1987b. Physiologically-based pharmacokinetics and the risk assessment process for methylene chloride. *Toxicol. Appl. Pharmacol.* 87:185–205.

Andersen, M. E., Clewell, H. J. III, Gargas, M. L., MacNaughton, M. G., Reitz, R. H., Nolan, R. J., and McKenna, M. J. 1991. Physiologically based pharmacokinetic modeling with dichloromethane, its metabolite, carbon monoxide, and blood carboxyhemoglobin in rats and humans. *Toxicol. Appl. Pharmacol.* 108:14–27.

Andersen, M. E., Krishnan, K., Conolly, R. B., and McClellan, R. O. 1992. Mechanistic toxicology research and biologically-based modeling: Partners for improving quantitative risk assessments. *CIIT Activities* 12(1):1–7.

Bliss, C. I. 1940. The relation between exposure time, concentration and toxicity in experiments on insecticides. *Ann. Entomol. Soc. Am.* 33:721–766.

Bliss, C. I., and James, A. T. 1966. Fitting the rectangular hyperbola. *Biometrics* 22:573–602.

Corley, R. A., and Reitz, R. H. 1990. Dose-route extrapolation in quantitative toxicology: Physiologically based pharmacokinetics and pharmacodynamics of chloroform. In *Principles of route-to-route extrapolation for risk assessment, Proceeding of the workshops, March and July, Hilton Head, SC and Durham, NC*, eds. T. R. Gerrity and C. J. Henry, pp. 195–216. New York: Elsevier.

Haber, F. 1924. Zur geshichte des gaskrieges. In *Fünf Vorträge aus den Jahren 1920–1923*, pp. 76–92. Berlin: Julius Springer.

Hayes, W. J. 1975. *Toxicology of pesticides*, pp. 51–105. Baltimore: Williams and Wilkins.

Jarabek, A. M. 1994. Inhalation RfC methodology: Dosimetric adjustments and dose-response estimation of noncancer toxicity in the upper respiratory tract. *Inhal. Toxicol.* 6:301–325.

Jarabek, A.M . 1995. The application of dosimetry models to identify key processes and parameters for default dose-response assessment approaches. *Toxicol. Lett.*, in press.

Jarabek, A. M., and McDougal, J. N. 1993. Duration-adjustment of effect levels: Comparison of physiologically-based pharmacokinetic (PBPK) models with default approach. *Toxicologist* 13(1):282 (abstr. 1069).

Jarabek, A. M., and Segal, S. A. 1993. Noncancer toxicity of inhaled toxic air pollutants: Available approaches for risk assessment and risk management. In *Toxic air pollutant handbook*, ed. D. R. Patrick, pp. 100–127. New York: Van Nostrand Reinhold.

National Research Council. 1983. Risk assessment in the federal government: Managing the process. Washington, DC: National Academy Press.

O'Flaherty, E. J. 1989. Interspecies conversion of kinetically equivalent doses. *Risk Anal.* 9:587–598.

ten Berge, W. F., Zwart, A., and Appelman, L. M. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. *J. Hazard. Mater.* 13:301–309.

U.S. Environmental Protection Agency. 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. EPA report EPA/600/8-90/066F, October. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office.

Ward, R. C., Travis, C. C., Hetrick, D. M., Andersen, M. E., and Gargas, M. L. 1988. Pharmacokinetics of tetrachloroethylene. *Toxicol. Appl. Pharmacol.* 93:108–117.

Warren, E. 1900. On the reaction of *Daphnia magna* (Straus) to certain changes in its environment. *Q. J. Microsc. Sci.* 43:199–224.

Winneke, G. 1981. The neurotoxicity of dichloromethane. *Neurobehav. Toxicol. Teratol.* 3:391–395.