The Acute Exposure Guideline Level (AEGL) Program: Applications of Physiologically Based Pharmacokinetic Modeling

James V. Bruckner [a] , Deborah A. Keys [b] & Jeffrey W. Fisher [b]

[a] Department of Pharmaceutical and Biomedical Sciences, Athens, Georgia, USA

[b] Department of Environmental Health Science, Athens, Georgia, USA

Available online: 12 Aug 2010

PLEASE SCROLL DOWN FOR ARTICLE

THE ACUTE EXPOSURE GUIDELINE LEVEL (AEGL) PROGRAM: APPLICATIONS OF PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELING

James V. Bruckner,[1] **Deborah A. Keys,**[2] **Jeffrey W. Fisher**[2]

[1]Department of Pharmaceutical and Biomedical Sciences, College of Pharmacy, University of Georgia, Athens, Georgia, USA
[2]Department of Environmental Health Science, College of Agricultural and Environmental Sciences, University of Georgia, Athens, Georgia, USA

The primary aim of the Acute Exposure Guideline Level (AEGL) program is to develop scientifically credible limits for once-in-a-lifetime or rare acute inhalation exposures to high-priority, hazardous chemicals. The program was developed because of the need of communities for information on hazardous chemicals to assist in emergency planning, notification, and response, as well as the training of emergency response personnel. AEGLs are applicable to the general population, including children, the elderly, and other potentially susceptible subpopulations. AEGLs are the airborne concentrations of chemicals above which a person could experience notable discomfort or irritation (AEGL-1); serious, long-lasting health effects (AEGL-2); and life-threatening effects or death (AEGL-3). AEGLs are determined for five exposure periods (10 and 30 min and 1, 4, and 8 h). Physiologically based pharmacokinetic (PBPK) models can be very useful in the interspecies and time scaling often required here. PBPK models are used for the current article to predict AEGLs for trichloroethylene (TCE), based on the time course of TCE in the blood and/or brain of rats and humans. These AEGLs are compared to values obtained by standard time-scaling methods. Comprehensive toxicity assessment documents for each chemical under consideration are prepared by the National Advisory Committee for AEGLs, a panel comprised of representatives of federal, state, and local governmental agencies, as well as industry and private-sector organizations. The documents are developed according to National Research Council (NRC) guidelines and must be reviewed by the NRC Subcommittee on Acute Exposure Guideline Levels before becoming final. AEGLs for 18 chemicals have been published, and it is anticipated that 40 to 50 chemicals will be evaluated annually.

The AEGL program is a concerted national effort to develop scientifically credible, peer-reviewed emergency exposure levels for hazardous chemicals. The program was undertaken due to the need of federal, state, and local governments, as well the public and private sectors, for guidance on adverse health effects to anticipate upon inhalation of toxic chemical vapors. Agents of concern include industrial chemicals and chemical precursors, pesticides, and

chemical warfare agents. Chemical-specific information is needed for emergency planning, notification, and response, and for prevention.

Emergency exposure limits have been established by different groups for selected chemicals since the 1940s. The National Research Council (NRC) began at that time to develop Emergency Exposure Guideline Levels (EEGLs) for the Department of Defense for chemical exposures of military personnel. During the 1960s and 1970s, the American Industrial Hygiene Association (AIHA) and some companies adopted short-term exposure limits for chemicals of particular interest. Federal, state, and local agencies, as well as industry and other private-sector organizations, became very concerned about hazardous chemicals following the accidental release of methyl isocyanate in Bhopal, India, in December 1984. Approximately 2000 residents living near the chemical plant were killed, and some 20,000 more suffered serious lung and eye injury. This community did not know which chemicals were being used at the plant, whether they were dangerous, or what steps to take in the event of their release. This incident crystallized many governments' realization that they must provide guidance and oversight to prevent such tragedies in the future.

A number of emergency preparedness programs were initiated by the U.S. Environmental Protection Agency (EPA) and private-sector groups after the Bhopal disaster. In 1985, the U.S. EPA organized a chemical emergency preparedness program, under which guidance was provided for development of local community response plans. During this timeframe the Chemical Manufacturers Association (now known as the American Chemistry Council) implemented its own community awareness and emergency response program. Chemical plant managers were encouraged to help community leaders prepare for possible releases of toxic chemicals that were on site. As a part of the Superfund Reauthorization Act of 1986, the U.S. Congress required states to plan for chemical accidents at the local level. As a consequence, the U.S. EPA, as a first step, derived exposure levels of concern (LOCs) for specific chemicals from NIOSH's immediately dangerous to life and health (IDLH) values by dividing IDLH values by 10. This approach was soon refined by the AIHA Emergency Response and Planning Guidelines (ERPG) Committee. One-hour exposure limits were developed for threshold inhalation concentrations for three different adverse health effects per chemical.

Recognition of the need to pool expertise and resources led to formation of a national committee to develop emergency exposure limits for acutely toxic chemicals. The NRC Committee on Toxicology was asked to provide guidance on criteria and procedures for deriving such values. *Guidelines for Developing Community Emergency Exposure Levels (CEELs) for Hazardous Substances* was published by the NRC in 1993. In 1995, the National Advisory Committee (NAC) for Acute Exposure Guideline Levels (AEGLs) was established to formulate guidelines for acutely toxic, high priority chemicals. AEGLs thus replaced CEELs. It was felt that AEGL would convey the broader application of the values for planning, response, and prevention in the community, workplace, transportation, military and hazardous waste site remediation. The NAC for AEGLs is comprised of scientists and other representatives from a number of
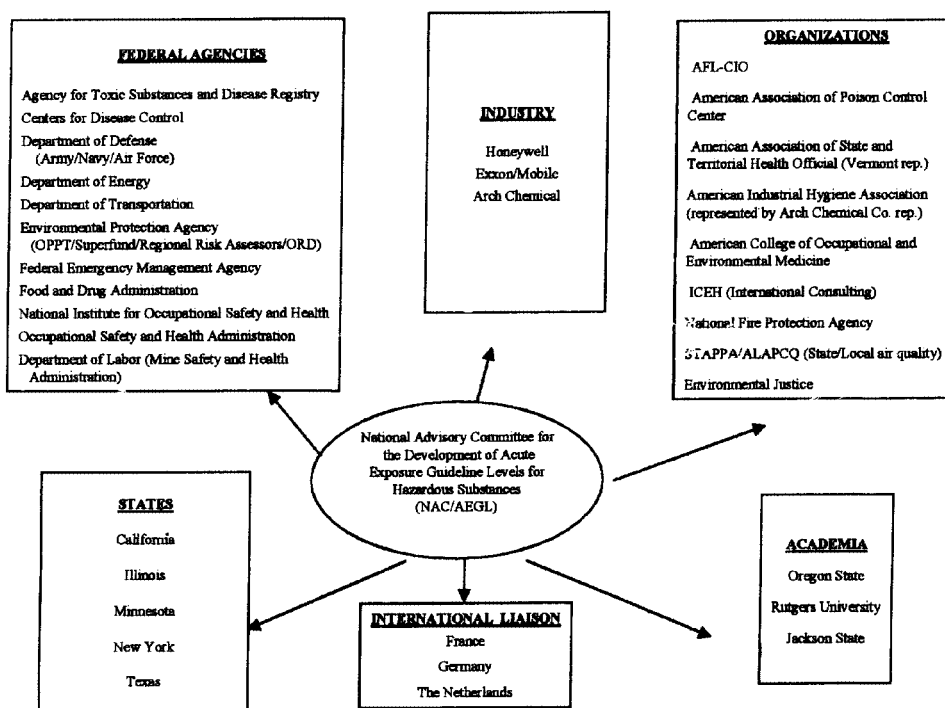
FIGURE 1. Affiliations of members of the National Advisory Committee for AEGLs.

federal departments and agencies, several state agencies, trade and professional organizations, industry, and academia (Figure 1). The Netherlands, Germany, and France currently provide liaison representation. The United Kingdom, Canada, and the European Union are considering participation and support of the program. The organization and function of the NAC have been described by Rusch et al. (2002). Federal organizations that are anticipated to have uses for AEGLs are shown in Figure 2.

THE AEGL PROCESS

AEGLs for selected chemicals are developed by the NAC and reviewed by the NRC subcommittee. The AEGL draft reports are prepared by a team comprised of staff of a contractor (e.g., Oak Ridge National Laboratory) and members of a NAC subcommittee. Each draft report is reviewed by the full NAC. If approved, the report is published in the *Federal Register* for public comments. The comments are considered, and revisions are made as deemed appropriate. The report is then submitted to the NRC subcommittee for evaluation of its comprehensiveness, scientific quality and consistency with the *Standard Operating Procedures* [SOPs] *for Developing Acute Exposure Guideline*
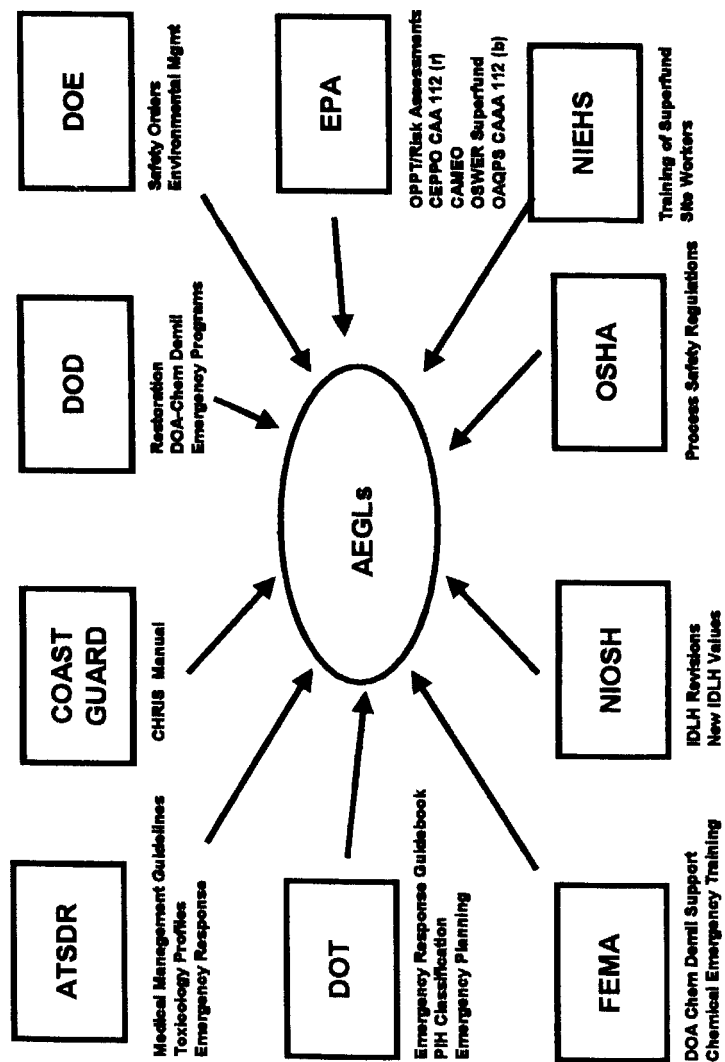
FIGURE 2. Federal organizations with AEGL applications. Acronyms: ATSDR, Agency for Toxic Substances and Disease Registry; CAA, Clean Air Act; CAAA, Clean Air Act Amendment; CAMEO, Computer Aided Management of Emergency Operations; CEPPO, Chemical Emergency Preparedness and Prevention Office; CHRIS, Chemical Hazards Response Information System; DOA Chem Demil Support, Department of the Army Chemical Demilitarization Support; DOD, Department of Defense; DOE, Department of Energy; DOT, Department of Transportation; EPA, U.S. Environmental Protection Agency; FEMA, Federal Emergency Management Agency; IDLH, Immediately Dangerous to Life and Health; NIEHS, National Institute of Environmental Health Sciences; NIOSH, National Institute of Occupational Safety and Health; OAQPS, Office of Air Quality Planning and Standards; OPPT, Office of Pollution Prevention and Toxics; OSHA, Occupational Safety and Health Administration; OSWER, Office of Hazardous Waste and Emergency Response; PIH, Poison Inhalation Hazard.

624

Levels for Hazardous Chemicals (NRC, 2001). The SOP manual is an update and expansion of the 1993 NRC publication. The subcommittee provides written comments for improvement and clarification of each AEGLs report. The NAC revises the documents and presents them at a subsequent meeting of the subcommittee. Once the subcommittee is satisfied with a report, it is published with reports on other chemicals by the National Academy Press. To date, 18 chemicals are included in 4 volumes of *Acute Exposure Guidelines for Selected Airborne Chemicals* (NRC, 2000–2004). The reports for the individual compounds are available online at www.epa.gov/oppt/aegl.

AEGLs represent threshold exposure levels, above which it is anticipated that certain adverse effects may occur (Figure 3). These levels are intended to protect the general population, including potentially susceptible groups (e.g., asthmatics, children, elderly), but not hypersusceptible individuals. AEGLs are developed for each of the following 5 time periods: 10 and 30 min and 1, 4, and 8 h. Inhalation of airborne concentrations lower than AEGL-1 values may result in odor, taste, irritation or certain mild non-sensory effects. AEGL-1 values are those inhaled concentrations above which it is expected that notable discomfort, irritation, or subclinical adverse effects could occur. Such effects are not disabling and are reversible upon cessation of exposure. AEGL-2 values are inhaled concentrations above which there could be impaired ability to escape or serious, long-lasting adverse health effects. AEGL-3 values are inhaled concentrations above which life-threatening effects or death may occur. There
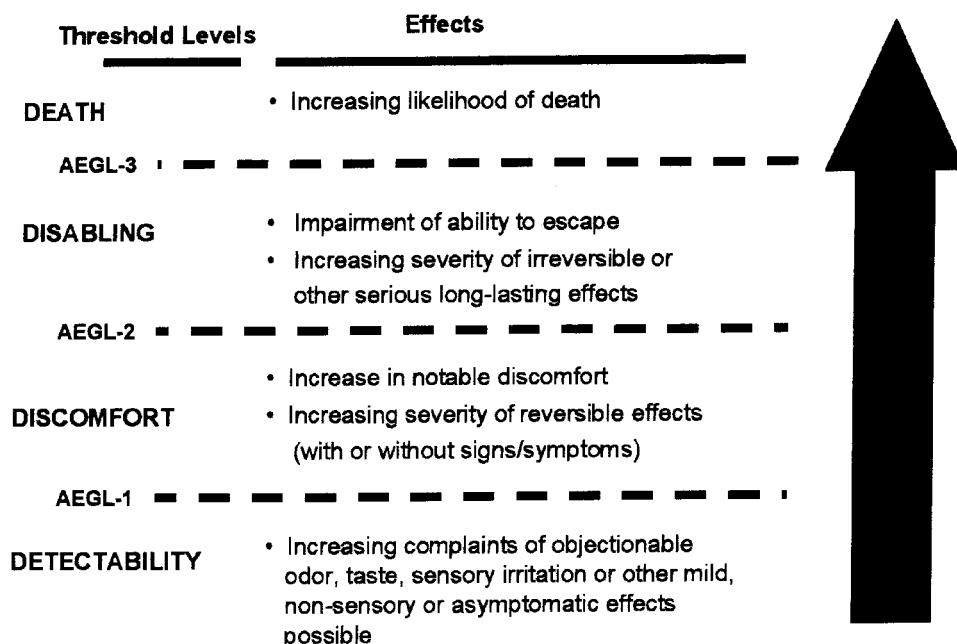

FIGURE 3. Characteristics of AEGLs.

is an increased likelihood of the occurrence and/or severity of effects described for each AEGL level, with increasing airborne concentrations above the AEGL.

AEGL DEVELOPMENT

Development of AEGLs begins with a comprehensive literature search, as well as screening of potentially relevant, unpublished data on the chemical of interest. Results of studies of in vitro toxicity, animal toxicity, carcinogenicity, human occupational and clinical cases, epidemiology, mechanism of action, and toxicokinetics are considered. Human data are preferred. Inhalation toxicology data are most useful, although oral and dermal data can be used as supporting or weight-of-evidence information. Route-to-route extrapolations are not commonly performed. Physiologically based pharmacokinetic (PBPK) modeling can be quite useful for such an application. Acute toxicity data are necessary for derivation of AEGLs, since they are acute exposure guidelines. Findings from subacute, subchronic, or chronic investigations are usually not applicable, although data from 2- to 3-d exposures might be utilized if necessary for 8-h AEGLs. Information, on acute exposure levels and times at which toxic endpoints pertinent to AEGLs-1, -2 and -3 are affected, is needed but may not be available. Time scaling is required under these circumstances.

Central nervous system (CNS) depression and mucus membrane irritation are two commonly used toxicity endpoints for AEGLs. Lowest-observed-adverse-effect levels (LOAELs) and no-observed-adverse-effect levels (NOAELs) from human studies are preferred, as human subjects can describe subjective complaints and participate in psychophysiological testing (Storm & Rozman, 1998). Animal toxicity data are used if reliable human data are not available. When toxicokinetic data and a PBPK model are available for a chemical, modeling can be utilized for species-to-species extrapolations. Otherwise, the usual approach is to utilize uncertainty factors for potential intraspecies differences, use of a LOAEL rather than a NOAEL, conversion of an LC50 to an LC01, and a sparse database. Uncertainty factors are frequently smaller than default factors that would be used to derive environmental exposure limits, since emergency warnings and evacuation orders can create significant problems of their own. An intraspecies uncertainty factor of 2 or 3, for example, may be deemed adequate to protect against CNS depression, due to the steepness of anesthesia dose-response curves for diverse patient populations (Stevens et al., 1975; de Jong & Eger, 1975).

TIME SCALING BY STANDARD METHODS

The NAC and the NRC subcommittee are constantly faced with the necessity of time scaling. There is often a lack of data that express the quantitative relationship of exposure conditions to toxicity endpoints for the different AEGLs. There may, for example, only be data suitable for 30-min AEGLs. One must extrapolate to shorter and to longer exposure periods to derive 10-min,

as well as 1-, 4-, and 8-h values. Historically, Haber's rule ($C \times t = k$, where C is the vapor concentration, t the time of exposure, and k a constant) has been used for this purpose (Rozman, 1998; Witschi, 1999). ten Berge et al. (1986) report that relationships between inhaled concentration and time for lethality are more often exponential than linear, and can be expressed by the equation $C^n \times t = k$. When exposure-response data are available, the value of n is derived by linear regression analysis of the log–log transformation of a plot of C versus t. A tiered approach employing this equation is recommended in the aforementioned SOP document (NRC, 2001). When exposure-response data are not available, default values for n that yield relatively conservative AEGL values are generally used.

There are problems inherent in Haber's rule and in ten Berge and coworkers' approach to time scaling. The work of ten Berge et al. (1986) is limited to data on lethality, the most common toxicity endpoint for which acute exposure-response information is available. This approach may be scientifically credible for time scaling AEGL-3 values, but its applicability to AEGL-1 and -2 values is open to question. This is of particular concern when different mechanisms exist for different toxic endpoints. Gelzleichter et al. (1992), for example, report that Haber's rule is valid when measuring protein and epithelial cell content of lavage fluid from ozone-exposed rats. This is not the case when cell renewal in the animals' airways is the endpoint (Rajini et al., 1993). In an early effort to use PBPK modeling to extrapolate 8-h occupational exposure limits to shorter and longer workdays, Andersen et al. (1987) avoided extrapolating to periods shorter than 4 h for styrene and methylene chloride, due to uncertainty about mechanisms of action for very short exposures.

The $C^n \times t = k$ relationship often does not accurately define dose-response relationships for brief periods of exposure. Dalbey et al. (1998), for example, observed severe respiratory tract damage in rats that inhaled 8621 ppm of hydrogen fluoride for 2 min (17,242 ppm-min). In contrast, a 10-min exposure to 1764 ppm (17,640 ppm-min) caused only modest respiratory damage. In the absence of data for short exposures, the shapes of dose-response curves during this interval are largely unknown. Vinegar et al. (2000) utilized breath by breath accounting and PBPK modeling to set acute inhalation exposure limits for a series of volatile organic chemicals (VOCs) intended as replacements for halon fire suppressants. Vinegar and his colleagues linked the 5-min LOAEL for cardiac sensitization in dogs to the associated arterial VOC concentration in dogs, and employed a PBPK model to predict human exposures that would result in this blood concentration and negligible risk. Acceptable exposures for periods as brief as 21 s were estimated. Our own use of PBPK modeling with TCE, as described next, also illustrates how scientifically credible 10- and 30-min AEGLs can be derived from data for a longer exposure.

Difficulties are also encountered with some chemicals when using the $C^n \times t = k$ approach to extrapolate to longer durations of exposure. AEGLs considered by the NAC for hydrogen chloride (HCl) can be used to illustrate this (Table 1). Stevens et al. (1992) found 1.8 ppm HCl to be a NOAEL in exercising

TABLE 1. Tentative AEGLs[a] for Hydrochloric Acid

AEGL	30-min	1-h	4-h	8-h	Endpoint	Subjects
1, Non disabling	1.8	1.8	1.8	1.8	1.8 (45-min NOAEL) Pulmonary function	Exercising asthmatics
2, Disabling	43	22	5.4	2.7	1300 (30-min) Severe nasal and lung histopathology	Nose and mouth breathing rats
3, Lethal	210	100	26	13	3000 (1-h) LC50	Rats

[a]All values in ppm of hydrochloric acid vapor.

asthmatics who inhaled the chemical for 45 min. All the AEGL-1s were set at 1.8 ppm, because it is assumed that mild irritation is independent of duration of exposure (NRC, 2001). In a study by Stavert et al. (1991), rats inhaling 1300 ppm HCl for 30 min exhibited severe nasal epithelial damage. The 30-min AEGL-2 of 43 ppm was obtained by dividing 1300 ppm by a total uncertainty factor of 30. Time scaling, using a value of $n = 1$ derived by regression analysis of rat and mouse mortality data by ten Berge et al. (1986), yielded AEGL-2 values for 1, 4, and 8 h of 22, 5.4, and 2.7 ppm, respectively. These 4- and 8-h values are not very different from the NOAEL for the exercising asthmatics, a susceptible subpopulation. A similar problem was encountered when using a value of $n = 1$ when extrapolating from a 1-h AEGL-3 of 100 ppm, derived by dividing a 1-h rat LC50 of 3000 ppm (Vernot et al., 1977) by a total uncertainty factor of 30, to 4 and 8 h. The projected 8-h AEGL-3 of 13 ppm is not very different from the 8-h occupational exposure limit of 5 ppm (ACGIH, 2000). Thus, the validity of standard time-scaling methods under some circumstances is subject to question.

ILLUSTRATION OF TIME SCALING BY PBPK MODELING

We undertook a PBPK modeling exercise with TCE to illustrate modeling's utility in the interspecies extrapolations and time scaling often necessary in AEGL development. The models of Fisher et al. (1998) and Keys et al. (2003) were employed to forecast arterial blood and/or brain TCE time-course profiles in humans and in Sprague-Dawley rats, respectively. Adverse effects and total uncertainty factors (UFs) appropriate for derivation of AEGL-1, -2, and -3 were arbitrarily selected. For AEGL-1, humans inhaling 200 ppm TCE for 7 h experienced mild drowsiness (Stewart et al., 1970). Use of a UF of 2 yielded a 7-h AEGL-1 of 100 ppm. For AEGL-2, humans inhaling 1000 ppm TCE for 2 h exhibited impaired motor coordination (Vernon & Ferguson, 1969). Use of a UF of 2 yielded a 2-h AEGL-2 of 500 ppm. For AEGL-3, the 4-h LC50 for TCE in rats is reported to be 12500 ppm (Siegel et al., 1971). Use of a UF of 10 yielded a 4-h

AEGL-3 of 1250 ppm. The PBPK models were used to (a) predict the peak arterial blood concentrations of TCE associated with these particular exposure conditions and (b) predict the inhaled vapor concentration required to reproduce each peak blood concentration for each exposure duration (i.e., 10 and 30 min and 1, 4, and 8 h). These simulated vapor concentrations (i.e., AEGLs) are included in Table 2. Time scaling, based on the calculated AEGL-1, -2, and -3 values, was also conducted using $C^n \times t = k$, according to Haber's rule where $n = 1$ and with the ten Berge et al. (1986) approach where $n = 2$. These scaled values for each exposure duration are included in Table 2. Implications of using the scaled values versus the model-predicted values are discussed below.

Use of the $C^n \times t$ approach can underestimate longer AEGLs and thereby overestimate risks when extrapolating from shorter to longer periods for VOCs. AEGL-3s that have been discussed for toluene by the NAC can be used to illustrate this tendency. In the key study, Moser and Balster (1985) reported a 1-h LC50 of 19,000 ppm for mice. Deaths resulted from CNS depression. This exposure level was divided by a total uncertainty factor of 30 to yield a 1-h AEGL-3 of 630 ppm. Extrapolation using $C^n \times t = k$, where $n = 2$, provided 4- and 8-h AEGL-3s of 320 and 220 ppm, respectively. These guidelines for protection from death are not very different from current 8-h occupational time-weighted averages (TWAs) of 50–200 ppm for toluene. Blood levels of toluene and a variety of other VOCs increase very rapidly upon initiation of inhalation sessions, typically reaching near steady-state or equilibrium within an hour or two (Lof et al., 1990; Bruckner & Warren, 2001). Likewise, our own PBPK model simulations

TABLE 2. TCE AEGLs[a] Based on PBPK Modeling versus Haber's Rule[b] and ten Berge's Approach[c]

AEGL	10-min	30-min	1-h	4-h	8-h
AEGL-1[d]					
PBPK[e]	269	191	154	108	99
Haber	4200	1400	700	175	88
ten Berge	648	374	265	132	94
AEGL-2[f]					
PBPK[e]	1175	797	628	413	369
Haber	6000	2000	1000	250	125
ten Berge	1732	1000	707	354	250
AEGL-3[g]					
PBPK[h]	3102	1982	1605	1250	1124
Haber	30,000	10,000	5000	1250	605
ten Berge	6123	3536	2500	1250	884

[a] All values expressed in ppm of trichloroethylene (TCE) vapor.
[b] Time scaling using $C \times t = k$, where C is vapor concentration, t time of exposure, k a constant.
[c] Time scaling using $C^n \times t = k$, where $n = 2$, according to ten Berge et al. (1986).
[d] Extrapolated from a 7-h AEGL-1 of 100 ppm.
[e] Human PBPK model of Fisher et al. (1998).
[f] Extrapolated from a 2-h AEGL-2 of 500 ppm.
[g] Extrapolated from a 4-h AEGL-3 of 1250 ppm.
[h] Rat PBPK model of Keys et al. (2003).

reveal that TCE quickly reaches and maintains near steady-state levels in the blood and brain of rats inhaling different concentrations of the VOC for 8 h (Figure 4). As VOC-induced CNS depression is generally attributed to the physical presence of the parent compound in the neuronal membrane, it follows that there will be only modest increases in neuronal dysfunction once near steady-state is attained (Moser & Balster, 1985). Indeed, the decreases in our PBPK-based AEGL-1, -2, and -3 values are modest between 1 and 8 h (Table 2). The 8-h AEGLs, derived using the $C^n \times t$ approach, are consistently lower than the PBPK-based AEGLs (i.e., the risks of CNS depression are overestimated). Boyes et al. (2000, 2003) also concluded from experiments with rats that risks of CNS dysfunction from TCE were overestimated when using Haber's rule to extrapolate from shorter to longer durations.

The $C^n \times t$ approach can overestimate AEGLs and thereby underestimate risks, when extrapolating from longer to shorter VOC exposure periods. As noted earlier, Moser and Balster (1985) reported a 1-h LC50 of 19,000 ppm for the toluene-exposed mice. Time scaling with $C^n \times t = k$, where $n = 2$, yielded an anticipated 10-min LC50 of 60,000 ppm. The experimental 10-min LC50 for
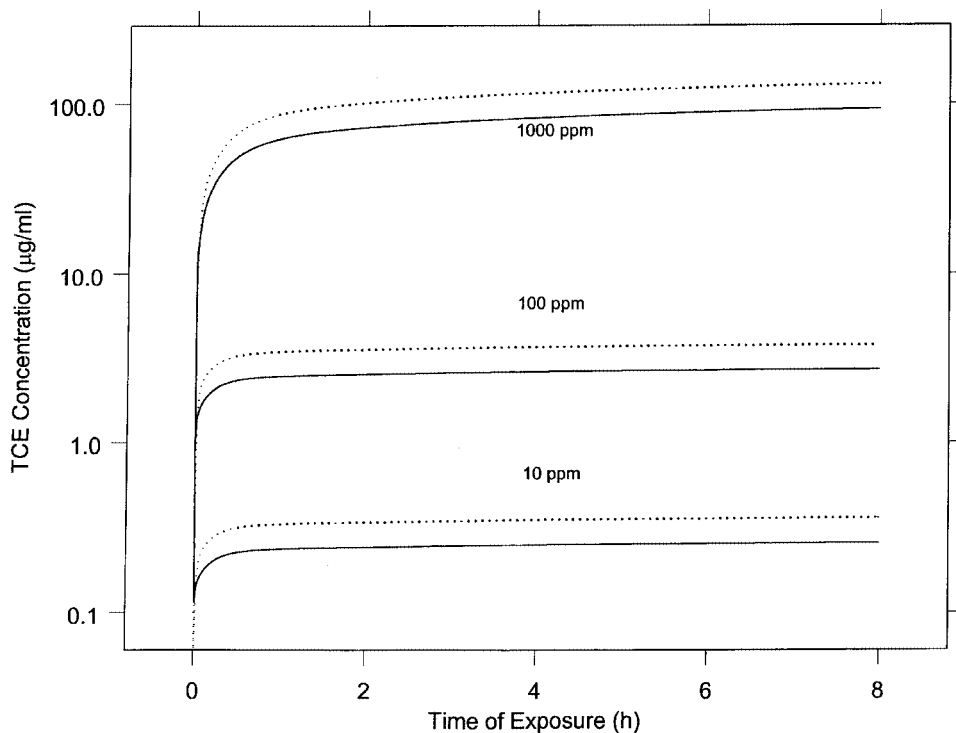

FIGURE 4. PBPK model-predicted time course of trichloroethylene (TCE) in the blood and brain of rats inhaling 10, 100 and 1000 ppm TCE for 8 h. Dotted and solid lines represent brain and blood TCE concentrations, respectively.

mice inhaling toluene was found to be 38,465 ppm (Moser & Balster, 1985). Siegel et al. (1971) reported the 4-h LC50 for TCE in rats to be 12,500 ppm. Application of an uncertainty factor of 10 yielded a 4-h AEGL-3 of 1250 ppm. Time scaling using $C^n \times t = k$, where $n = 1$ and $n = 2$, resulted in 10-min AEGL-3s of 30,000 and 6123 ppm of TCE, respectively (Table 2). In contrast, our PBPK model-based 10-min AEGL-3 was 3102 ppm. The ten Berge et al. method thus resulted in a more accurate AEGL value than did Haber's rule, assuming the PBPK model simulations of TCE dosimetry are reliable. Bushnell (1997) and Boyes et al. (2000) studied effects of inhaled TCE on signal detection behavior, visual evoked potentials, and hearing loss in Long-Evans rats. The researchers found that the degree of CNS dysfunction (i.e., risk) was underestimated by Haber's rule, when extrapolating from longer to shorter duration exposures. Recently Boyes et al. (2003) described use of a PBPK model for Long-Evans rats by Simmons et al. (2002) to predict brain TCE concentrations, which reflected effects of TCE on visual function across exposure levels and durations.

PBPK MODELING AND INTERSPECIES EXTRAPOLATIONS

PBPK models can be quite useful for species-to-species extrapolations when establishing AEGLs. Rodent model parameters can be scaled up, or human physiological and biochemical parameters inputed, if there is no validated human model. A human model and a rat model were used in the current project to predict the inhaled TCE concentrations necessary to produce the same blood TCE level in each species for each time-period. When there was no provision for TCE metabolism, the PBPK models predicted that humans must inhale considerably higher concentrations of TCE for any given time than rats to achieve an equivalent blood level of the chemical (simulations not shown). This is attributable to the rat's larger TCE blood:air partition coefficient (Gargas et al., 1989) and its higher alveolar ventilation and cardiac output/pulmonary perfusion rates (Brown et al., 1997). It is evident in Figure 5 that rats exhibit higher blood levels than humans at high inhaled concentrations (e.g., 1000 ppm) that saturate TCE metabolism. Rats inhaling 10 or 100 ppm also exhibit higher blood levels during the initial 2 h of exposure, but more rapid TCE metabolism by the rodent negates this species difference during the mid and latter parts of the 8-h exposures. Accordingly, AEGLs for humans were higher than those for rats for the shorter-term exposures (Table 3). Use of rodent CNS depression data to calculate AEGLs for TCE and other VOCs should be protective of human health.

As blood TCE levels mirror brain TCE levels during inhalation exposures, empirical or model-simulated blood time-course data can be used to derive AEGLs based on CNS-depressant effects of the parent compound. Inhaled TCE is rapidly absorbed and taken up by the brain (Simmons et al., 2002; Keys et al., 2003), an organ that is well perfused and has a relatively high lipid content (the brain:blood partition coefficient was set to 1.4 for our own modeling). It can be seen in Figure 4 here that the simulated blood and brain TCE profiles of rats
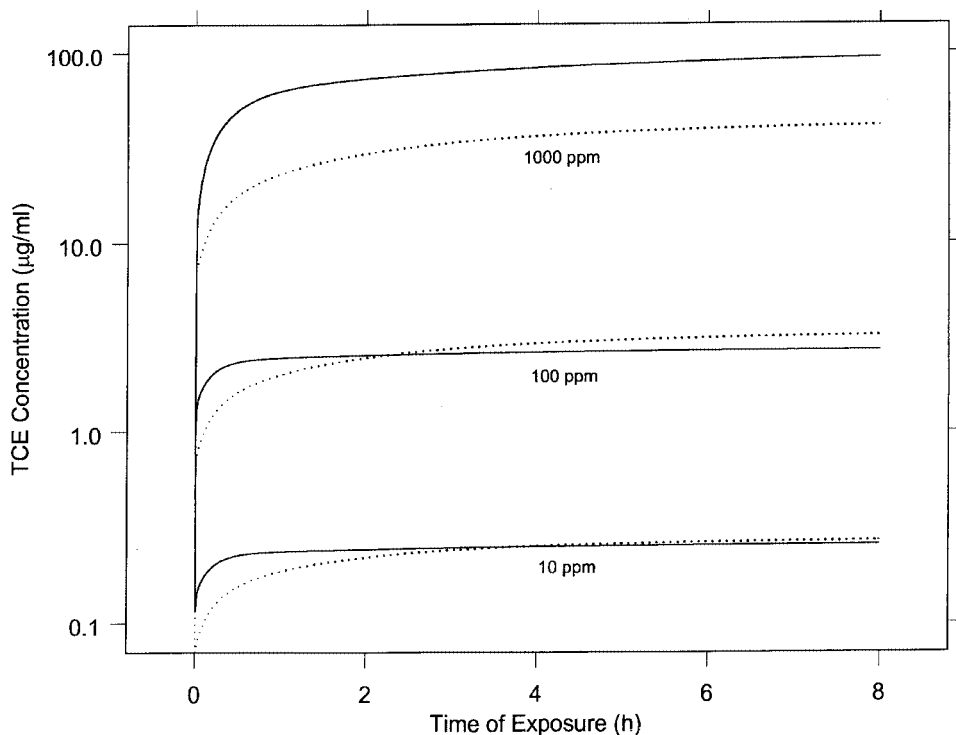
FIGURE 5. PBPK model-predicted time-course of trichloroethylene (TCE) in the blood of rats and humans inhaling 10, 100 and 1000 ppm TCE for 8 h. Dotted and solid lines represent blood TCE concentrations in humans and rats, respectively.

TABLE 3. TCE AEGLs[a] Based on Peak Blood Levels Predicted by PBPK Models[b,c]

AEGL	Species	10-min	30-min	1-h	4-h	8-h
1[d]	Rat	136	114	109	102	100
	Human	269	191	154	108	99
2[e]	Rat	983	664	557	456	420
	Human	1175	797	628	413	369
3[f]	Rat	3102	1982	1605	1250	1124
	Human	3703	2401	1942	1250	1107

[a]All values in ppm of trichloroethylene (TCE) vapor.
[b]Human PBPK model of Fisher et al. (1998).
[c]Rat PBPK model of Keys et al. (2003).
[d]Extrapolated from a 7-h AEGL-1 of 100 ppm.
[e]Extrapolated from a 2-h AEGL-2 of 500 ppm.
[f]Extrapolated from a 4-h AEGL-3 of 1250 ppm.

parallel one another. As would be anticipated, blood- and brain-concentration-based AEGLs were virtually identical with one another for each exposure duration (data not shown). The parent compound is largely responsible for CNS depression, although trichloroethanol, an oxidative metabolite, is also active. Boyes et al. (2000) demonstrated that the acute inhibitory effects of TCE on behavior and visual function of rats correlated well with estimated blood TCE levels at the time of testing. Bruckner and Peterson (1981) found a high degree of correlation between blood and brain toluene concentrations and the depth of CNS depression in mice. Warren and his coworkers reported the same phenomenon for 1,1,1-trichloroethane-exposed rats (1998) and mice (2000). It appears likely that most VOCs will exhibit a similar relationship.

REFERENCES

American Conference of Governmental Industrial Hygienists. 2000. *Guide to occupational exposure values.* Cincinnati, OH: ACGIH.

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

Boyes, W. K., Bushnell, P. J., Crofton, K. M., Evans, M., and Simmons, J. E. 2000. Neurotoxic and pharmacokinetic responses to trichloroethylene as a function of exposure scenario. *Environ. Health Perspect.* 108(suppl. 2):317–322.

Boyes, W. K., Bercegeay, M., Ali, J. S., Krantz, T., McGee, J., Evans, M., Raymer, J. H., Bushnell, P. J., and Simmons, J. E. 2003. Dose-based duration adjustments for the effects of inhaled trichloroethylene on rat visual function. *Toxicol. Sci.* 76:121–130.

Brown, R. P., Delp, M. L., Lindstedt, S. L., Rhomberg, L. R., and Beliles. R. P. 1997. Physiological parameter values for physiologically based pharmacokinetic models. *Toxicol. Ind. Health* 13:407–484.

Bruckner, J. V., and Peterson, R. G. 1981. Evaluation of toluene and acetone inhalant abuse. I. Pharmacology and pharmacodynamics. *Toxicol. Appl. Pharmacol.* 61:27–38.

Bruckner, J. V., and Warren, A. D. 2001. Toxic effects of solvents and vapors. In *Casarett and Doull's toxicology: The basic science of poisons*, 6th ed., ed. C. D. Klaassen, pp. 869–916. New York: McGraw-Hill.

Bushnell, P. J. 1997. Concentration-time relationships for the effects of inhaled trichloroethylene on signal detection behavior in rats. *Fundam. Appl. Toxicol.* 36:30–38.

Dalbey, W., Dunn, B., Bannister, R., Daughtrey, W., Kirwin, C., Reitman, F., Steiner, A., and Bruce, J. 1998. Acute effects of 10-minute exposure to hydrogen fluoride in rats and derivation of a short-term exposure limit for humans. *Regul. Toxicol. Pharmacol.* 27:207–216.

de Jong, R. H., and Eger, E. I. 1975. AD_{50} and AD_{95} values of common inhalation anesthetics in man. *Anesthesiology* 42:384–389.

Gargas, M. L., Burgess, R. J., Voisard, D. E., Cason, G. H., and Andersen, M. E. 1989. Partition coefficients of low-molecular-weight volatile chemicals in various liquids and tissues. *Toxicol. Appl. Pharmacol.* 98:87–99.

Gelzleichter, T. R., Witschi, H., and Last, J. A. 1992. Concentration-response relationships of rat lungs to exposure to oxidant air pollutants: A critical test of Haber's law for ozone and nitrogen dioxide. *Toxicol. Appl. Pharmacol.* 112:73–80.

Keys, D. A., Bruckner, J. V., Muralidhara, S., and Fisher, J. W. 2003. Tissue dosimetry expansion and cross-validation of rat and mouse physiologically based pharmacokinetic models for trichloroethylene. *Toxicol. Sci.* 76:35–50.

Lof, A., Wallen, M., and Hjelm, E. W. 1990. Influence of paracetamol and acetylsalicylic acid on the toxicokinetics of toluene. *Pharmacol. Toxicol.* 66:138–141.

Moser, V. C., and Balster, R. L. 1985. Acute motor and lethal effects of inhaled toluene, 1,1,1-tichloro-ethane, halothane, and ethanol in mice: Effects of exposure duration. *Toxicol. Appl. Pharmacol.* 77:285–291.

National Research Council. 1993. *Guidelines for developing community emergency exposure levels for hazardous substances.* Washington, DC: National Academy Press.

National Research Council. 2001. *Standard operating procedures for developing acute exposure guideline levels for hazardous chemicals.* Washington, DC: National Academy Press.

National Research Council. 2000–2004. *Acute exposure guideline levels for selected airborne chemicals,* vol. 1, 2, 3, and 4. Washington, DC: National Academy Press.

Rajini, P., Gelzleichter, T. R., Last, J. A., and Witschi, H. 1993. Alveolar and airway cell kinetics in the lungs of rats exposed to nitrogen dioxide, ozone, and a combination of the two gases. *Toxicol. Appl. Pharmacol.* 121:186–192.

Rozman. K. 1998. Quantitative definition of toxicity: A mathematical description of life and death with dose and time as variables. *Med. Hypoth.* 51:175–178.

Rusch, G. M., Garrett, R., Tobin, P., Falke, E., and Lu, P.-Y. 2002. The development of acute exposure guideline levels for hazardous substances. *Drug Chem. Toxicol.* 25:339–348.

Siegel, J., Jones. R. A., Coon, R. A., and Lyon, J. P. 1971. Effects on experimental animals of acute, repeated and continuous inhalation exposures to dichloroacetylene mixtures. *Toxicol. Appl. Pharmacol.* 18:168–174.

Simmons, J. E., Boyes, W. K., Bushnell, P. J., Raymer, J. H., Limsakun, T., McDonald, A., Sey, Y. M., and Evans, M. E. 2002. A physiologically based pharmacokinetic model for trichloroethylene in the male Long-Evans rat. *Toxicol. Sci* 69:3–15.

Stavert, D. M., Archuleta, D. C., Behr, M. J., and Lehnert, B. E. 1991. Relative acute toxicities of hydrogen fluoride, hydrogen chloride, and hydrogen bromide in nose- and pseudo-mouth-breathing rats. *Fundam. Appl. Toxicol.* 16:635–655.

Stevens, B., Koenig, J. Q., Rebolledo, V., Hanley, Q. S., and Covert, D. S. 1992. Respiratory effects from inhalation of hydrogen chloride in young adult asthmatics. *J. Occup. Med.* 34:923–929.

Stevens, W. C., Dolan, W. M., Gibbons, R. T., White, A., Eger, E. I., Miller, R. D., de Jong, R. H., and Elashoff, R. M. 1975. Minimum alveolar concentrations (MAC) of isoflurane with and without nitrous oxide in patients of various ages. *Anesthesiology* 42:197–200.

Stewart, R. D., Dodd, H. C., Gay, H. H., and Erley, E. S. 1970. Experimental human exposure to trichloro-ethylene. *Arch. Environ. Health* 20:64–71.

Storm, J. E., and Rozman, K. K. 1998. Derivation of an occupational exposure limit (OEL) for methylene chloride based on acute CNS effects and relative potency analysis. *Regul. Toxicol. Pharmacol.* 27:240–250.

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.

Vernon, R. J., and Ferguson, R. K. 1969. Effects of trichloroethylene on visual-motor performance. *Arch. Environ. Health* 18:894–900.

Vernot, E. H., MacEwen, J. D., Haun, C. C., and Kinkead, E. R. 1977. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. *Toxicol. Appl. Pharmacol.* 42:417–423.

Vinegar, A., Jepson, G. W., Cisneros, M., Rubenstein, R., and Brock, W. J. 2000. Setting safe acute exposure limits for halon replacement chemicals using physiologically based pharmacokinetic modeling. *Inhal. Toxicol.* 12:751–763.

Warren, D. A., Reigle, T. G., Muralidhara, S., and Dallas, C. E. 1998. Schedule-controlled operant behavior of rats during 1,1,1-trichloroethane inhalation: Relationship to blood and brain solvent concentrations. *Neurotoxicol. Teratol.* 20:143–153.

Warren, D. A., Bowen, S. E., Jennings, W. B., Dallas, C. E., and Balster, R. L. 2000. Biphasic effects of 1,1,1-trichloroethane on the locomotor activity of mice: Relationship to blood and brain solvent concentrations. *Toxicol. Sci.* 56:365–373.

Witschi, H. 1999. Some notes on the history of Haber's law. *Toxicol. Sci.* 50:164–168.