24-hour exposures that may reasonably be anticipated to occur. Accordingly, we are denying AF&PA's petition to remove methanol from the list of HAP under section 112(b) of the CAA. Moreover, because we conclude that the information submitted in connection with this petition does not support a determination that methanol emissions will not cause adverse human health effects, we are denying this petition with prejudice, and any future petition for the removal of methanol from the list of HAP will be denied as a matter of law unless such petition is accompanied by substantial new information or analysis.

Dated: April 27, 2001.

Christine T. Whitman,

Administrator.

[FR Doc. 01–10990 Filed 5–1–01; 8:45 am]

BILLING CODE 6560–50–P

ENVIRONMENTAL PROTECTION AGENCY

[OPPTS–00312; FRL–6776–3]

National Advisory Committee for Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances; Proposed AEGL Values

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: The National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) is developing AEGLs on an ongoing basis to provide Federal, State, and local agencies with information on short-term exposures to hazardous chemicals. This notice provides AEGL values and Executive Summaries for 18 chemicals for public review and comment. Comments are welcome on both the AEGL values in this notice and the Technical Support Documents placed in the public version of the official docket for these 18 chemicals.

DATES: Comments, identified by the docket control number OPPTS–00312, must be received by EPA on or before June 1, 2001.

ADDRESSES: Comments may be submitted by mail, electronically, or in person. Please follow the detailed instructions for each method as provided in Unit I. of the **SUPPLEMENTARY INFORMATION.** To ensure proper receipt by EPA, it is imperative that you identify docket control number OPPTS–00312 in the subject line on the first page of your response.

FOR FURTHER INFORMATION CONTACT: *For general information contact*: Barbara Cunningham, Acting Director, Environmental Assistance Division (7401), Office of Pollution Prevention and Toxics, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460; telephone number: (202) 554–1404; e-mail address: TSCA-Hotline@epa.gov.

For technical information contact: Paul S. Tobin, Designated Federal Officer (DFO), Office of Prevention, Pesticides and Toxic Substances (7406), 1200 Pennsylvania Ave., NW., Washington, DC 20460; telephone number: (202) 260–1736; e-mail address: tobin.paul@epa.gov.

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this Action Apply to Me?

This action is directed to the general public to provide an opportunity for review and comment on ''Proposed'' AEGL values and their supporting scientific rationale. This action may be of particular interest to anyone who may be affected if the AEGL values are adopted by government agencies for emergency planning, prevention, or response programs, such as EPA's Risk Management Program under the Clean Air Act and Amendments Section 112r. It is possible that other Federal agencies besides EPA, as well as State and local agencies and private organizations, may adopt the AEGL values for their programs. As such, the Agency has not attempted to describe all the specific entities that may be affected by this action. If you have any questions regarding the applicability of this action to a particular entity, consult the DFO listed under **FOR FURTHER INFORMATION CONTACT.**

B. How Can I Get Additional Information, Including Copies of this Document or Other Related Documents?

1. *Electronically* . You may obtain electronic copies of this document, and certain other related documents that might be available electronically, from the EPA Internet Home Page at http://www.epa.gov/. To access this document, on the Home Page select ''Laws and Regulations,'' ''Proposed Rules and Regulations,'' and then look up the entry for this document under the ''**Federal Register**—Environmental Documents.'' You can also go directly to the **Federal Register** listings at http://www.epa.gov/fedrgstr/.

2. *In person*. The Agency has established an official record for this action under docket control number OPPTS–00312. The official record consists of the documents specifically referenced in this action, any public comments received during an applicable comment period, and other information related to this action, including any information claimed as Confidential Business Information (CBI). This official record includes the documents that are physically located in the docket, as well as the documents that are referenced in those documents. The public version of the official record does not include any information claimed as CBI. The public version of the official record, which includes printed, paper versions of any electronic comments submitted during an applicable comment period, is available for inspection in the TSCA Nonconfidential Information Center, North East Mall Rm. B–607, Waterside Mall, 401 M St., SW., Washington, DC. The Center is open from noon to 4 p.m., Monday through Friday, excluding legal holidays. The telephone number of the Center is (202) 260–7099.

3. *Fax-on-Demand*. You may request to receive a faxed copy of the document(s) by using a faxphone to call (202) 401–0527 and select the item number 4800 for an index of the items available by fax-on-demand in this category, or select the item number for the document related to the chemical(s) identified in this document as listed in the chemical table in Unit III. You may also follow the automated menu.

C. How and to Whom Do I Submit Comments?

You may submit comments through the mail, in person, or electronically. To ensure proper receipt by EPA, it is imperative that you identify docket control number OPPTS–00312 in the subject line on the first page of your response.

1. *By mail*. Submit your comments to: Document Control Office (7407), Office of Pollution Prevention and Toxics (OPPT), Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460. (Note: for express delivery, please see ''In person or by courier'' in Unit I.C.2.).

2. *In person or by courier*. Deliver your comments to: OPPT Document Control Office (DCO) in East Tower Rm. G–099, Waterside Mall, 401 M St., SW., Washington, DC. The DCO is open from 8 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The telephone number for the DCO is (202) 260–7093.

3. *Electronically*. You may submit your comments electronically by e-mail to: oppt.ncic@epa.gov, or mail your computer disk to the address identified above. Do not submit any information electronically that you consider to be CBI. Electronic comments must be submitted as an ASCII file avoiding the

use of special characters and any form of encryption. Comments and data will also be accepted on standard disks in WordPerfect 6.1/8.1 or ASCII file format. All comments in electronic form must be identified by docket control numbers OPPTS–00312. Electronic comments may also be filed online at many Federal Depository Libraries.

D. How Should I Handle CBI that I Want to Submit to the Agency?

Do not submit any information electronically that you consider to be CBI. You may claim information that you submit to EPA in response to this document as CBI by marking any part or all of that information as CBI. Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR part 2. In addition to one complete version of the comment that includes any information claimed as CBI, a copy of the comment that does not contain the information claimed as CBI must be submitted for inclusion in the public version of the official record. Information not marked confidential will be included in the public version of the official record without official notice. If you have any questions about CBI or the procedures for claiming CBI, please consult the DFO listed under **FOR FURTHER INFORMATION CONTACT**.

E. What Should I Consider as I Prepare My Comments for EPA?

You may find the following suggestions helpful for preparing your comments:

1. Explain your views as clearly as possible.

2. Describe any assumptions that you used.

3. Provide copies of any technical information and/or data that you used that support your views.

4. If you estimate potential burden or costs, explain how you arrived at the estimate that you provide.

5. Provide specific examples to illustrate your concerns.

6. Offer alternative ways to improve the notice.

7. Make sure to submit your comments by the deadline in this document.

8. To ensure proper receipt by EPA, be sure to identify the docket control number assigned to this action in the subject line on the first page of your response. You may also provide the name, date, and **Federal Register** citation.

II. Background

A. Introduction

EPA's Office of Prevention, Pesticides and Toxic Substances (OPPTS) provided notice on October 31, 1995 (60 FR 55376) (FRL–4987–3) of the establishment of the NAC/AEGL Committee with the stated charter objective as ''the efficient and effective development of Acute Exposure Guideline Levels (AEGLs) and the preparation of supplementary qualitative information on the hazardous substances for federal, state, and local agencies and organizations in the private sector concerned with [chemical] emergency planning, prevention, and response.'' The NAC/AEGL Committee is a discretionary Federal advisory committee formed with the intent to develop AEGLs for chemicals through the combined efforts of stakeholder members from both the public and private sectors in a cost-effective approach that avoids duplication of efforts and provides uniform values, while employing the most scientifically sound methods available. An initial priority list of 85 chemicals for AEGL development was published in the **Federal Register** of May 21, 1997 (62 FR 27734) (FRL–5718–9). This list is intended for expansion and modification as priorities of the stakeholder member organizations are further developed. While the development of AEGLs for chemicals are currently not statutorily based, at lease one rulemaking references their planned adoption. The Clean Air Act and Amendments Section 112(r) Risk Management Program states, ''EPA recognizes potential limitations associated with the Emergency Response Planning Guidelines and Level of Concern and is working with other agencies to develop AEGLs. When these values have been developed and peer reviewed, EPA intends to adopt them, through rulemaking, as the toxic endpoint for substances under this rule (see 61 FR 31685).'' It is believed that other Federal and State agencies and private organizations will also adopt AEGLs for chemical emergency programs in the future.

B. Characterization of the AEGLs

The AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. AEGL–2 and AEGL–3 levels, and AEGL–1 levels as appropriate, will be developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and will be distinguished by varying degrees of severity of toxic effects. It is believed that the recommended exposure levels are applicable to the general population including infants and children, and other individuals who may be sensitive and susceptible. The AEGLs have been defined as follows:

AEGL–1 is the airborne concentration (expressed as parts per million (ppm) or milligram/meter cubed (mg/m^3)) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL–2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape.

AEGL–3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL–1 represent exposure levels that could produce mild and progressively increasing odor, taste, and sensory irritation, or certain non-symptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL level, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL level. Although the AEGL values represent threshold levels for the general public, including sensitive subpopulations, it is recognized that certain individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL level.

C. Development of the AEGLs

The NAC/AEGL Committee develops the AEGL values on a chemical-by-chemical basis. Relevant data and information are gathered from all known sources including published scientific literature, State and Federal agency publications, private industry, public data bases, and individual experts in both the public and private sectors. All key data and information are summarized for the Committee in draft form by Oak Ridge National Laboratories together with ''draft'' AEGL values prepared in conjunction with NAC/AEGL Committee members. Both

the ''draft'' AEGLs and ''draft'' technical support documents are reviewed and revised as necessary by the NAC/AEGL Committee members prior to formal committee meetings. Following deliberations on the AEGL values and the relevant data and information for each chemical, the NAC/AEGL Committee attempts to reach a consensus. Once the NAC/AEGL Committee reaches a consensus, the values are considered ''Proposed'' AEGLs. The Proposed AEGL values and the accompanying scientific rationale for their development are the subject of this notice.

In this notice the NAC/AEGL Committee publishes proposed AEGL values and the accompanying scientific rationale for their development for 18 hazardous substances. These values represent the fourth set of exposure levels proposed and published by the NAC/AEGL Committee EPA published the first ''Proposed'' AEGLs for 12 chemicals from the initial priority list in the **Federal Register** of October 30, 1997 (62 FR 58840–58851) (FRL–5737–3); for 10 chemicals in the **Federal Register** of March 15, 2000 (65 FR 14186–14196) (FRL–6492–4); for 14 chemicals in the **Federal Register** of June 23, 2000 (65 FR 39263–39277) (FRL–6591–2); and for 7 chemicals in the **Federal Register** of December 13, 2000 (65 FR 77866–77874) (FRL–6752–5) in order to provide an opportunity for public review and comment. In developing the proposed AEGL values, the NAC/AEGL Committee has followed the methodology guidance ''Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances,'' published by the National Research Council of the National Academy of Sciences (NAS) in 1993. The term Community Emergency Exposure Levels (CELLS) is synonymous with AEGLs in every way. The NAC/AEGL Committee has adopted the term Acute Exposure Guideline Levels to better connote the broad application of the values to the population defined by the NAS and addressed by the NAC/AEGL Committee. The NAC/AEGL Committee invites public comment on the proposed AEGL values and the scientific rationale used as the basis for their development.

Following public review and comment, the NAC/AEGL Committee will reconvene to consider relevant comments, data, and information that may have an impact on the NAC/AEGL Committee's position and will again seek consensus for the establishment of Interim AEGL values. Although the Interim AEGL values will be available to Federal, State, and local agencies and to organizations in the private sector as biological reference values, it is intended to have them reviewed by a subcommittee of the NAS. The NAS subcommittee will serve as a peer review of the Interim AEGLs and as the final arbiter in the resolution of issues regarding the AEGL values, and the data and basic methodology used for setting AEGLs. Following concurrence, ''Final'' AEGL values will be published under the auspices of the NAS.

III. List of Chemicals

On behalf of the NAC/AEGL Committee, EPA is providing an opportunity for public comment on the AEGLs for the 18 chemicals identified in the following table. This table also provides the fax-on-demand item number for the chemical specific documents, which may be obtained as described in Unit I.B.3.

A. Fax-On-Demand Table

TABLE 1.—FAX-ON-DEMAND NUMBERS

CAS No.	Chemical name	Fax-on-demand item no.
67–56–1	Methanol	4938
77–81–6, 107–44–8, 96–64–0, 329–99–7	Nerve Agents GA, GB, GD, GF	4940
79–10–7	Acrylic acid	4941
107–18–6	Allyl alcohol	4879
107–30–2	Chloromethyl methyl ether	4880
108–88–3	Toluene	4882
108–95–2	Phenol	4943
110–00–9	Furan	4885
127–18–4	Tetrachloroethylene	4889
509–14–8	Tetranitromethane	4894
594–42–3	Perchloromethyl mercaptan	4897
630–08–0	Carbon monoxide	4944
10294–34–5	Boron trichloride	4928
19287–45–7	Diborane	4931
50782–69–9	Nerve Agent VX	4945

B. Executive Summaries

The following are executive summaries from the chemical specific Technical Support Documents (which may be obtained as described in Unit I.B.) that support the NAC/AEGL Committee's development of AEGL values for each chemical substance. This information provides the following information: A general description of each chemical, including its properties and principle uses; a summary of the rationale supporting the AEGL–1, -2, and -3 concentration levels; a summary table of the AEGL values; and a listing of key references that were used to develop the AEGL values. More extensive toxicological information and additional references for each chemical may be found in the complete Technical Support Documents. Risk managers may be interested to review the complete Technical Support Document for a chemical when deciding issues related to use of the AEGL values within various programs.

1. *Methanol*—i. *Description.* Methanol is a clear, colorless, volatile flammable liquid with a pungent odor. It is used in industrial production as a solvent and raw material for the production of many important organic compounds.

The acute and short-term toxicity of methanol varies greatly between different species: Due to pharmacokinetic differences, at higher exposure concentrations rodents develop higher blood methanol concentrations than humans and monkeys. Primate, but not rodent species, show accumulation of the metabolite formate. At lower concentrations methanol causes symptoms characteristic of effects on the visual system, such as blurred vision, and the central nervous system (CNS), such as nausea, dizziness, and headaches, as well as slight eye and nose irritation. At high concentrations, the accumulation of the toxic metabolite formic acid may lead to blindness and death by metabolic acidosis. In rodents methanol causes developmental toxic effects and fetal death.

The AEGL–1 was based on a pharmacokinetic study in which human volunteers were exposed to 800 ppm methanol for 8 hours (Batterman *et al.*, 1998), because no other experimental human study was available that used an exposure concentration above a level of 200 ppm, which was used in other studies and which was considered below the AEGL–1 threshold. In this pharmacokinetic study no statement was made on the presence or absence of any signs or symptoms of the methanol exposure; in a personal communication, the second author, Dr. Franzblau, stated that none of the subjects reported symptoms. A factor of 3 was applied for intraspecies variation because the exposure level in the Batterman *et al.* (1998) study was considered below the effect threshold and thus the effect level was less severe than defined for the AEGL–1 level. However, interindividual variability with regard to slight neurotoxic effects (*e.g.*, headache) is likely to exist (although it cannot be quantified exactly from the existing experimental and epidemiological studies) and, thus, it cannot be ruled out that a fraction of the general population might experience slight effects under the exposure conditions of the experimental study of Batterman *et al.* (1998), which used healthy individuals. Because exposure repsonse data were unavailable for all of the AGEL-specific exposure durations, temporal extrapolation was used in the development of AEGL values for the specific AEGL–time periods. The concentration exposure-time relationship for many systematically acting vapors and gases may be described by $C^n \times t = k$, where C = concentration, t = time, k is a constant, and the exponent n ranges from 0.8 to 3.5. In this case, the value was scaled to appropriate exposure periods according to the dose-response regression equation $C^n \times t = k$, using the default of n = 3 for shorter exposure periods, due to the lack of suitable experimental data for deriving the concentration exponent.

The AEGL–2 values were based on developmental toxic effects in mice. After a single exposure to different concentration-time combinations on gestational day 7, the most sensitive endpoint was cervical rib induction, which occurred at concentration-time products greater than or equal to 15,000 ppm × h, but not at concentration-time products below 15,000 ppm × h (*i.e.*, no effects were observed after exposure to 2,000 ppm × 5 h, 2,000 ppm × 7 h and 5,000 ppm × 2 h; authors expressed data only as C × t values) (Rogers *et al.* 1995, abstract; Rogers, 1999, personal communication). These results are supported by a repeated exposure teratogenicity study (Rogers *et al.,* 1993), in which a significant increase in cervical vertebrae was observed at 2,000 ppm or higher, and by a single 7-hour exposure study at 10,000 ppm (Rogers *et al.,* 1997). For the no-observed-effect level (NOEL) of 2,000 ppm for 7 hours (Rogers *et al.* 1995, abstract; Rogers, 1999, personal communication), the corresponding end-of-exposure blood concentration was measured as 487 mg/Liter (l) (Rogers *et al.,* 1993). A total uncertainty factor (UF) of 10 was applied. A factor of 1 was applied for interspecies variability because a sensitive species was used for derivation of AEGL–2 values and because toxicokinetic differences between species were accounted for by using a pharmacokinetic model for calculating exposure concentrations. A factor of 10 was used for intraspecies variability because no information on developmental toxic effects of methanol on humans is available and because also for other chemicals the variability in susceptibility of humans for developmental toxic effects is not well characterized. The total UF was applied to the blood methanol concentration resulting in a concentration of 48.7 mg/l. For this blood methanol concentration, inhalation exposure concentrations for appropriate time periods were calculated so that a blood methanol concentration of 48.7 mg/l would be reached at the end of the time period. For these calculations, a pharmacokinetic model based on the model from Perkins *et al.* (1995) was used. The calculated exposure concentrations were set as AEGL–2 values. For 10 minutes, a concentration of 11,000 ppm was calculated using the pharmacokinetic model. Since this value was considered too close to the 10-minute AEGL–3 value of 15,000 ppm, the 10-minute AEGL–2 was set at the 30-minute value.

The AEGL–3 values were based on acute lethal effects on humans after oral methanol uptake (Naraqi *et al.*, 1979; Erlanson *et al.*, 1965; Bennett *et al.*, 1955; Gonda *et al.,* 1978). For lethal cases without relevant concommitant ethanol exposure, the peak blood methanol concentration was calculated from the measured concentration and the time between intoxication and measurement using Michaelis-Menten kinetics. The lowest calculated peak blood concentration was 1,109 mg/l from the study by Naraqi *et al.* (1979). Due to the very steep dose-response curve for lethality in monkeys (Gilger and Potts, 1955), a factor of 2 was applied to derive a peak blood concentration of 555 mg/l as the NOEL for lethality. An factor of 3 was applied for intraspecies variability, because of the very steep dose response-relationship for lethality after oral exposure seen in rhesus monkeys (Gilger and Potts, 1955) and because a factor of 10 would have resulted in blood methanol concentrations of about 70 mg/l which would be far below a level of 130–200 mg/l, at which ethanol therapy is recommended (ATSDR, 1993; Becker, 1983; Meyer *et al.,* 2000) (these

values refer to concentrations measured after hospital admission, which are usually considerably lower than peak concentrations). For the resulting blood methanol concentration of 185 mg/l, inhalation exposure concentrations for appropriate time periods were calculated so that a blood methanol concentration of 185 mg/l would be reached at the end of the time period. For calculations, a pharmacokinetic model based on the model from Perkins *et al.* (1995) was used. These exposure concentrations were set as AEGL–3 values. The 10-minute AEGL–3 was set at the 30-minute value because at the concentration of 44,000 ppm calculated by the model additional immediate toxic effects could not be excluded and because the calculated value is close to the lower explosive limit in air.

The calculated values are listed in Table 2 below:

TABLE 2.—SUMMARY TABLE OF PROPOSED AEGL VALUES FOR METHANOL[A]

Classification	10-Minutes	30-Minutes	1-Hour	4-Hours	8-Hours	Endpoint (Reference)
AEGL–1 (Nondisabling)	670 ppm (880 mg/m^3)	670 ppm (880 mg/m^3)	530 ppm (690 mg/m^3)	340 ppm (450 mg/m^3)	270 ppm (350 mg/m^3)	Pharmacokinetic study (Batterman *et al.,* 1998); according to a personal communication, none of the subjects reported symptoms (Franzblau, 1999; 2000)
AEGL–2 (Disabling)	4,000 ppm (5,200 mg/m^3)	4,000 ppm (5,200 mg/m^3)	2,100 ppm (2,800 mg/m^3)	720 ppm (940 mg/m^3)	510 ppm (670 mg/m^3)	No developmental toxic effects in mice Rogers *et al.* (1993; 1995, abstract; 1997); Rogers (1999, personal communication)
AEGL–3 (Lethal)	15,000 ppm (20,000 mg/m^3)	15,000 ppm (20,000 mg/m^3)	7,900 ppm (10,000 mg/m^3)	2,500 ppm (3,300 mg/m^3)	1,600 ppm (2,100 mg/m^3)	Lethality in humans after oral exposure (Naraqi *et al.,* 1979; Erlanson *et al.,* 1965; Bennett *et al.,* 1955; Gonda *et al.,* 1978; Meyer *et al.,* 2000)

[a] Cutaneous absorption may occur; direct skin contact with the liquid should be avoided.

ii. *References.*

a. ATSDR (Agency for Toxic Substances and Disease Registry). 1993. Methanol toxicity. *American Family Physician*. Vol. 47:163–171.

b. Batterman, S.A., Franzblau, A., D'Arcy, J.B., Sargent, NE., Gross, K.B., and Schreck, R.M. 1998. Breath, urine, and blood measurements as biological exposure indices of short-term inhalation exposure to methanol. *International Archives of Occupational and Environmental Health*. Vol. 71:325–335.

c. Becker, C.E. 1983. Methanol poisoning. *Journal of Emergency Medicine*. Vol. 1:51–58.

d. Bennett, I., Cary, F.H., Mitchell, G.L., and Cooper, M.N. 1953. Acute methyl alcohol poisoning: a review based on experiences in an outbreak of 323 cases. *Medicine*. Vol. 32:431–463.

e. Erlanson, P., Fritz, H., Hagstam, K. E., Liljenberg, B., Tryding, N., and Voigt, G. 1965. Severe methanol intoxication. *Acta Medica Scandinavica*. Vol. 177:393–408.

f. Franzblau, A. 1999. Dr. Alfred Franzblau, University of Michigan School of Public Health, Ann Arbor, MI. Personal communication. E-mail dated June 14, 1999.

g. Franzblau, A. 2000. Dr. Alfred Franzblau, University of Michigan School of Public Health, Ann Arbor, MI. Personal communication. E-mail dated October 3, 2000.

h. Gilger, A.P. and Potts, A.M. 1955. Studies on the visual toxicity of methanol. V. The role of acidosis in experimental methanol poisonings. *American Journal of Ophthalmology*. Vol. 39:63–86.

i. Gonda, A., Gault, H., Churchill, D., and Hollomby, D. 1978. Hemodialysis for methanol intoxication. *The American Journal of Medicine*. Vol. 64:749–758.

j. Meyer, R.J., Beard, M.E.J., Ardagh, M.W., and Henderson, S. 2000. Methanol poisoning. *New Zealand Medical Journal*. Vol. 113:11–13.

k. Naraqi, S., Dethlefs, R.F., Slobodniuk, R.A., and Sairere, J.S. 1979. An outbreak of acute methyl alcohol intoxication. *Australia and New Zealand Journal of Medicine*. Vol. 9:65–68.

l. Perkins, R.A., Ward, K.W., and Pollack, G.M. 1995. A pharmacokinetic model of inhaled methanol in humans and comparison to methanol disposition in mice and rats. *Environmental Health Perspectives*. Vol. 103:726–733.

m. Rogers, J.M., Mole, M.L., Chernoff, N., Barbee, B.D., Turner, C.I., Logsdon, T.R., and Kavlock, R.J. 1993. The developmental toxicity of inhaled methanol in the CD-1 mouse, with quantitative dose-response modeling for estimation of benchmark doses. *Teratology*. Vol. 47:175–188.

n. Rogers, J.M., Barbee, B.D., and M.L. Mole. 1995. Exposure concentration and time (C x T) relationships in the developmental toxicity of methanol in mice. *Toxicologist*. Vol. 15:164 (abstract).

o. Rogers. J.M. and Mole, M.L. 1997. Critical periods of sensitivity to the developmental toxicity of inhaled methanol in the CD-1 mouse. *Teratology*. Vol. 55:364–372.

p. Rogers, J.M. 1999. USEPA. National Health and Environmental Effects Research Laboratory, Research Triangle Park, NC. Personal communication. Letter dated May 27, 1999.

2–5. *Nerve Agents GA, GB, GD, GF*—

i. *Description.* The G-series agents [GA (tabun), GB (sarin), GD (soman), and GF] are all toxic ester derivatives of phosphonic acid containing either a cyanide or fluoride substituent group, and are commonly termed ''nerve'' agents as a consequence of their anticholinesterase properties. These compounds were developed as chemical warfare agents, and one was used by chemical terrorists in the 1995 incident of nerve agent exposure that took place in the Tokyo subway system. The chemical names of these 4 agents are as follows: Agent GA, dimethylamidocyanophosphate; Agent GB, isopropyl methyl phosphonofluoridate; Agent GD, pinacolyl methylphosphonofluoridate; and Agent GF, *O*-cyclohexylmethyl-fluorophosphonate.

The G-agents are all viscous liquids of varying volatility (vapor density relative to air between 4.86 and 6.33) with faint odors (''faintly fruity,'' or ''spicy,'' ''odor of camphor''). Toxic effects may occur at

concentrations below those of odor detection.

The vapor pressures and acute toxicity of the G-series agents are sufficiently high for the vapors to be rapidly lethal. Within the G-series, GB is considered largely a vapor hazard, while GD is considered mainly a vapor hazard. GA represents a smaller vapor hazard and is expected to present a relevant contact hazard. The vapor pressure of agent GF is intermediate between that of agents GA and GD.

Exposure to acutely toxic concentrations of G-agents can result in excessive bronchial, salivary, ocular, and intestinal secretion, sweating, miosis, bronchospasm, intestinal hypermotility, bradycardia, muscle fasciculations, twitching, weakness, paralysis, loss of consciousness, convulsions, depression of the central respiratory drive, and death. Minimal effects observed at low vapor concentrations include miosis (pinpointing of the pupils of the eye, with subsequent decrease in pupil area), tightness of the chest, rhinorrhea, and dyspnea.

The results of agent GB vapor exposure studies conducted with human volunteers indicate that the threshold for miosis and other minimal toxic effects falls in the range of 0.05 to 0.5 mg/m^3 for 10–30 minute exposures. These findings are based on the results of low-concentration nerve agent exposures to informed volunteers who were under clinical supervision during the periods of exposure as well as for post-exposure periods of several months. Inconsistencies between the studies in identifying the toxicity threshold may be due to differences in individual sensitivities or breathing rates of the test subjects, or to differences in experimental protocols or analytical methods.

There is at present no evidence to indicate that asymptomatic exposures to any of the G-agents result in chronic neurological disorders. A major concern associated with symptomatic exposures to anticholinesterase compounds such as the G agents is the possibility of chronic neurological effects. In general, the available epidemiological data indicate that most clinical signs of toxicity resolve within hours to days; severe miosis may require several months after exposure for resolution. However, several studies have shown that subclinical signs may persist for longer periods. Following the chemical terrorist attacks with nerve agent GB that occurred in Japan in 1994 and 1995, clinical signs of agent toxicity were no longer apparent in the surviving victims 3 months after the exposures had occurred. However, several studies conducted on a small number of asymptomatic individuals 6–8 months after the attack revealed subclinical signs of neurophysiological deficits as measured by event-related and visual evoked potentials, psychomotor performance, and increases in postural sway.

Small but measurable changes in single fibre electromyography (SFEMG) of the forearm were detectable between 4 and 15 months following exposure to a concentration of agent GB that produced minimal clinical signs and symptoms in fully informed human subjects who were under clinical supervision in compliance with Helsinki accords (Baker and Sedgwick, 1996). The SFEMG effects were not clinically significant and were not detectable after 15–30 months. In a separate study of workers who had been occupationally exposed to agent GB (sarin), altered electroencephalograms (EEGs) were recorded 1 year or more after the last exposure had occurred. Spectral analysis of the EEGs indicated significant increases in brain beta activity (12–30 Hz) in the exposed group when compared to non-exposed controls, and sleep EEGs revealed significantly increased rapid eye movement in the exposed workers; these observations were not clinically significant. Increases in beta activity were also observed in rhesus monkeys 1 year after being dosed with 5 μg GB/kilogram (kg). Slight, but non-significant increases in beta activity, without deleterious effects on cognitive performance, were reported for marmosets injected with 3.0 μg GB/kg and tested 15 months later. The significance of subclinical neurological effects for the long-term health of exposed individuals has not been determined.

Animal data from vapor and oral exposure studies for agent GB suggest that agent GB does not induce reproductive or developmental effects in mammals. Oral exposure studies of agents GB and GD in lab animals, as well as injection exposure studies of agent GA, likewise suggest the lack of reproductive or development effects for these agents. Agent GB was not found to be genotoxic in a series of microbial and mammalian assays, but agent GA was reported to be weakly mutagenic. There is no evidence that agents GB and GA are carcinogenic.

The data base for toxicological effects in humans is more complete for agent GB than for any of the other G-agents. Furthermore, agent GB is the only G-agent for which sufficient human data are available to directly derive AEGL–1 and AEGL–2 values, and the only G-agent for which sufficient laboratory animal data are available for deriving an AEGL–3 value for all five AEGL time periods. The AEGL–1 values for agent GB were derived from a study on human volunteers in which minimal and reversible effects occurred as a consequence of a 20-minute exposure to a GB vapor concentration of 0.05 mg/m^3 (Harvey, 1952; Johns, 1952).

The AEGL–2 values for agent GB were derived from a study in which miosis, dyspnea, photophobia, inhibition of red blood cell cholinesterase (RBC-ChE), and changes in SFEMG were observed in human volunteers following a 30-minute exposure to 0.5 mg/m^3 (Baker and Sedgwick, 1996). The SFEMG changes noted in the study were not clinically significant, and were not detectable after 15–30 months. Baker and Sedgwick considered SFEMG changes to be a possible early indicator or precursor of the nondepolarising neuromuscular block found associated with Intermediate Syndrome paralysis in severe organophosphorous insecticide poisoning cases. The study concluded that these electromyographic changes were persistent (>15 months), but that they were reversible and subclinical. While not considered debilitating or permanent effects in themselves, SFEMG changes are here considered an early indicator of exposures that could potentially result in more significant effects. Selection of this effect as a protective definition of an AEGL–2 level is considered appropriate given the steep dose-response toxicity curve of nerve agents. This concept of added precaution for steep dose-response is consistent with emergency planning guidance for nerve agents previously developed by the National Center for Environmental Health of the Centers for Disease Control and Protection.

Animals exposed to low concentrations of the G agents exhibit the same signs of toxicity as humans, including miosis, salivation, rhinorrhea, dyspnea, and muscle fasciculations. Studies on dogs and rats indicate that exposures to 0.001 mg GB/m^3 for up to 6 hours per day are unlikely to produce any signs of toxicity.

Because exposure-response data were unavailable for all of the AEGL–specific exposure durations, temporal extrapolation was used in the development of AEGL values for the AEGL–specific time periods. The concentration-exposure time relationship for many systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5.

Ongoing but unpublished analyses of rat exposure data as performed by Mioduszewski and his colleagues is indicating that the n value for agent GB likely varies with exposure duration (t) (Mioduszewski *et al.,* 2000a, b). Future analyses may provide separate n values for different duration periods of concern, and will be used when available. Current analyses are based on a log-log linear regression of the lethality of GB to female Sprague-Dawley rats (Mioduszewski *et al.,* 2000a, b), which yields an n value of 1.93 with a r^2 of 0.9948. This value indicates a good agreement between the data points. Given that all mammalian toxicity endpoints observed in the data set for all nerve agents represent different points on the response continuum for anticholinesterase exposure, and that the mechanism of mammalian toxicity (cholinesterase inhibition) is the same for all nerve agents, the experimentally derived n = 2 from the Mioduszewski *et al.* (2000a, b) rat lethality data set is used as the scaling function for the AEGL–1 and AEGL–2 derivations rather than a default value. An n of 1.16 was calculated for comparison using other data (human volunteer) and other endpoints (e.g., GB-induced miosis in humans; see Appendix B). However, due to a poor r^2 (0.6704) and other uncertainties associated with some of the exposure measurements in these earlier studies, Mioduszewki *et al.,* data were determined to be the best source of an estimate for n. An n value of 2 was also used to derive the 8-hour AEGL–3 value for GB from the experimental rat lethality data set in which animals were exposed to GB vapor for a maximal period of 6 hours (Mioduszewski *et al.,* 2000a, b).

The fact that AEGL–1 and AEGL–2 analyses for agent GB are based on data from human volunteers (Harvey, 1952; Johns 1952; Baker and Sedgwick, 1996) precludes the use of an interspecies UF. To accommodate known variation in human cholinesterase activity that may make some individuals susceptible to the effects of cholinesterase inhibitors such as nerve agents, a factor of 10 was applied for intraspecies variability (protection of susceptible populations). A modifying factor is not applicable. Thus, the total UF for estimating AEGL–1 and AEGL–2 values for agent GB is 10.

In comparison to agent GB, the data sets characterizing toxicity of agents GA, GD, and GF are less complete. Nevertheless, the literature clearly indicates that inhibition of cholinesterase activity is a common mechanism of toxicity shared by all these nerve agents. Thus, it was possible to develop AEGL estimates for agents GA, GD, and GF by a comparative method of relative potency analysis from the more complete data set for agent GB. This approach has been previously applied in the estimation of nerve agent exposure limits, most recently by Mioduszewski *et al* (1998).

The AEGL–1 and AEGL–2 values for agents GA, GD, and GF were derived from the AEGL–1 and AEGL–2 values for GB using a relative potency approach, based on the potency of the agents to induce LOAEL effects of miosis, rhinorrhea, and SFEMG; and agent concentration in units of mg/m^3. Agents GA and GB were considered to have an equivalent potency for causing miosis. Agents GD and GF are each considered approximately twice as potent as agents GB or GA for these endpoints, and equipotent to each other for AEGL–1 and AEGL–2 effects. Thus, the AEGL–1 and AEGL–2 concentration values for agents GD and GF are equal to 0.5 times those values derived for agents GA and GB.

AEGL–3 values for agent GB were derived from recent inhalation studies in which the lethality of GB to female Sprague-Dawley rats was evaluated for the time periods of 10, 30, 60, 90, 240, and 360 minutes (Mioduszewski *et al.,* 2000a, b). Both experimental LC_{01} and LC_{50} values were evaluated. The use of a rat data set resulted in selection of an interspecies UF of 3; the full default value of 10 was not considered appropriate since the mechanism of toxicity in mammals is cholinesterase inhibition. The full default value of 10 for intraspecies uncertainty was considered necessary to protect susceptible populations. Since a modifying factor is not applicable, the total UF for AEGL–3 determination for agent GB is equal to 30.

The AEGL–3 values for agent GA were derived from the AEGL–3 values for GB using a relative potency approach based on lethality of the agents; the potency of agent GA was considered to be only ½ that of agent GB for this endpoint. Thus, the AEGL–3 concentration values for agent GA are equal to 2.0 times the AEGL–3 values for agent GB.

The lethal potencies of agents GD and GF are considered equivalent, and equipotent to that of agent GB. Thus, the AEGL–3 concentration values for agent GB, GD, and GF are equivalent. A secondary and short-term GD inhalation study of rat lethality for exposure times ≤30 minutes (Aas *et al.,* 1985) lends support to the assumption of lethal equipotency for agents GB and GD. Since the principal mode of action (cholinesterase inhibition) for the G-agents is identical, an n = 2 was used for deriving AEGL–3 values from the data of Aas and his colleagues. Due to the sparse data set for this agent, the full default values for interspecies (10) and intraspecies (10) uncertainty were applied. Since a modifying factor is not applicable, a total UF of 100 was used in deriving 10-minute AEGL–3 (0.27 mg/m^3) and 30-minsute AEGL–3 (0.15 mg/m^3) estimates for agent GD from Aas *et al.* (1985).

The calculated values are listed in Table 3 below:

TABLE 3.—SUMMARY OF PROPOSED AEGL VALUES FOR NERVE AGENTS[A] GA, GB, GD, AND GF [PPM (MG/M^3)]

Agent	Classification	10-Minutes	30-Minutes	1-Hour	4-Hours	8-Hours	Endpoint (Reference)
GA	AEGL–1 (Non-disabling)	0.0010 ppm (0.0069 mg/m³)	0.00060 ppm (0.0040 mg/m³)	0.00042 ppm (0.0028 mg/m³)	0.00021 ppm (0.0014 mg/m³)	0.00015 ppm (0.0010 mg/m³)	Based on relative potency from GB[b]
	AEGL–2 (Disabling)	0.013 ppm (0.087 mg/m³)	0.0075 ppm (0.050 mg/m³)	0.0053 ppm (0.035 mg/m³)	0.0026 ppm (0.017 mg/m³)	0.0020 ppm (0.013 mg/m³)	Based on relative potency from GB[b]
	AEGL–3 (Lethal)	0.11 ppm (0.76 mg/m³)	0.057 ppm (0.38 mg/m³)	0.039 ppm (0.26 mg/m³)	0.021 ppm (0.14 mg/m³)	0.015 ppm (0.10 mg/m³)	Based on relative potency from GB[c]

TABLE 3.—SUMMARY OF PROPOSED AEGL VALUES FOR NERVE AGENTS[A] GA, GB, GD, AND GF [PPM (MG/M^3)]—Continued

Agent	Classification	10-Minutes	30-Minutes	1-Hour	4-Hours	8-Hours	Endpoint (Reference)
GB	AEGL–1 (Non-disabling)	0.0012 ppm (0.0069 mg/m^3)	0.00068 ppm (0.0040 mg/m^3)	0.00048 ppm (0.0028 mg/m^3)	0.00024 ppm (0.0014 mg/m^3)	0.00017 ppm (0.0010 mg/m^3)	Headache, eye pain, rhinorrhea, tightness in chest, cramps, nausea, malaise, miosis in human volunteers exposed to 0.05 mg/m^3 for 20 minutes (Harvey, 1952; Johns, 1952)
	AEGL–2 (Disabling)	0.015 ppm (0.087 mg/m^3)	0.0085 ppm (0.050 mg/m^3)	0.0060 ppm (0.035 mg/m^3)	0.0029 ppm (0.017 mg/m^3)	0.0022 ppm (0.013 mg/m^3)	Miosis, dyspnea, RBC-ChE inhibition, SFEMG changes in human volunteers exposed to 0.5 mg/m^3 for 30 minutes (Baker and Sedgwick, 1996)
	AEGL–3 (Lethal)	0.064 ppm (0.38 mg/m^3)	0.032 ppm (0.19 mg/m^3)	0.022 ppm (0.13 mg/m^3)	0.012 ppm (0.070 mg/m^3)	0.0087 ppm (0.051 mg/m^3)	Based on experimental Sprague-Dawley rat lethality data (LC_{01} and LC_{50}); whole-body dynamic exposure to concentrations between 2–56 mg/m^3 for 3, 10, 30, 60, 90, 240, and 360 minutes (Mioduszewski *et al.,* 2000a,b)
GD	AEGL–1 (Non-disabling)	0.00046 ppm (0.0035 mg/m^3)	0.00026 ppm (0.0020 mg/m^3)	0.00018 ppm (0.0014 mg/m^3)	0.000091 ppm (0.00070 mg/m^3)	0.000065 ppm (0.00050 mg/m^3)	Based on relative potency from GB[d]
	AEGL–2 (Disabling)	0.0057 ppm (0.044 mg/m^3)	0.0033 ppm (0.025 mg/m^3)	0.0022 ppm (0.018 mg/m^3)	0.0012 ppm (0.0085 mg/m^3)	0.00085 ppm (0.0065 mg/m^3)	Based on relative potency from GB[d]
	AEGL–3 (Lethal)	0.049 ppm (0.38 mg/m^3)	0.025 ppm (0.19 mg/m^3)	0.017 ppm (0.13 mg/m^3)	0.0091 ppm (0.070 mg/m^3)	0.0066 ppm (0.051 mg/m^3)	Based on relative potency from GB. Supported by Wistar rat LC_{50}; dynamic chamber exposures at 21 mg/m^3 for 3 time periods of <30 minutes duration (Aas *et al.,* 1985)[e]
GF	AEGL–1 (Non-disabling)	0.00049 ppm (0.0035 mg/m^3)	0.00028 ppm (0.0020 mg/m^3)	0.00020 ppm (0.0014 mg/m^3)	0.00010 ppm (0.00070 mg/m^3)	0.000070 ppm (0.00050 mg/m^3)	Based on relative potency from GB[d]
	AEGL–2 (Disabling)	0.0062 ppm (0.044 mg/m^3)	0.0035 ppm (0.025 mg/m^3)	0.0024 ppm (0.018 mg/m^3)	0.0013 ppm (0.0085 mg/m^3)	0.00091 ppm (0.0065 mg/m^3)	Based on relative potency from GB[d]
	AEGL–3 (Lethal)	0.053 ppm (0.38 mg/m^3)	0.027 ppm (0.19 mg/m^3)	0.018 ppm (0.13 mg/m^3)	0.0098 ppm (0.070 mg/m^3)	0.0071 ppm (0.051 mg/m^3)	Based on relative potency from GB[e]

[a] Percutaneous absorption of G-agent vapor is known to be an effective route of exposure; nevertheless, percutaneous vapor concentrations needed to produce similar adverse effects are greater than inhalation vapor concentrations by several orders of magnitude. Thus, the AEGL values presented are considered protective for both routes of exposure.

[b] Based on relative potency equal to that of agent GB (see section 4.3 and Mioduszewski *et al.,* 1998)

[c] Agent GA is considered approximately ½ as potent as GB in causing lethality; thus, AEGL–3 values for GA are estimated by multiplying each time-specific AEGL–3 value for agent GB by a factor of 2 (see section 4.3 and Mioduszewski *et al.,* 1998)

[d] Agents GD and GF are considered approximately twice as potent as agents GA and GB for causing miosis, and equipotent to each other. Thus, AEGL–1 and AEGL–2 values are estimated by multiplying each time-specific AEGL–1 or AEGL–2 value for agent GB by a factor of 0.5 (see section 4.3 and Mioduszewski *et al.,* 1998)

[e] Based on a relative potency for lethality of GD = GF = GB and lethality data of Aas *et al.* (1985) (which provides a 10-minute AEGL–3 estimate of 0.27 mg/m^{3}and a 30-minute AEGL–3 value of 0.15 mg/m^3) (see section 4.3 and Appendix A)

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6. *Acrylic acid*—i. *Description*. Acrylic acid is a clear, colorless, corrosive liquid with a pungent odor. The primary use of acrylic acid, accounting for about two third of its use, is in the production of acrylic esters and resins, which are used primarily in coatings, paint, plastics, and adhesives. Acrylic acid is also used in oil treatment chemicals, detergent intermediates, and water treatment chemicals.

Except for reports on odor threshold and a personal communication about irritative effects in humans no studies reporting effects in humans are available. Irritative effects of acrylic acid in animals have been described in studies using repeated 6-hour exposures of rabbits, rats, and mice. Consistently, histopathological alterations of the nasal mucosa was a more sensitive toxicological endpoint than the appearance of clinical signs of irritation: The lowest concentrations leading to clinical signs of irritation (concentrations without effect given in brackets) were 129 (77) ppm in rabbits (blepharospasm, perinasal and perioral wetness), 218 (114) ppm in rats (eyelid closure, discharge from eyes), and 223 (72) ppm in mice (scratching at the nose). Repeated exposure for 1–2 weeks led to histopatholgical changes of the nasal mucosa at the lowest concentrations tested, which were 34 ppm for rabbits, 74 ppm for rats and 25 ppm for mice. In mice, effects were found after exposure to 5 ppm for 22 hours/day, but not 6 hours/day, for 2 weeks. A number of studies described lethal effects in rats. In a study in which rats were exposed to acrylic acid aerosol (Hagan and Emmons, 1988), LC_{50} values of 5,670; 3,804; and 2,553 ppm for 30 minutes, 1 hour, and 2 hours, respectively, were reported. Studies evaluating the acute toxicity of acrylic acid vapors used very small numbers of animals or were not reported in detail and gave somewhat varying results. In summary, the available studies do not indicate a large difference in the toxicity of acrylic acid vapor and aerosol. No developmental toxic effects of acrylic acid were found in several inhalation studies. Acrylic acid may have a weak clastogenic effect *in vitro*. No carcinogenic effects were found after application of acrylic acid in the drinking water, while after subcutaneous and topical application tumors were found (probably attributable to local irritative effects).

AEGL–1 values were based on the odor recognition threshold of 1 ppm determined by Hellman and Small (1974). Since this odor threshold was determined in a trained odor panel, it was assumed that the olfaction of the general population is less good. For this reason, the reported recognition threshold and not the detection threshold was chosen for derivation of AEGL–1 values. This concentration of acrylic acid is supposed to have warning properties since most people should perceive the odor of acrylic acid at this concentration. Since the odor threshold is considered to depend primarily on exposure concentration and not much on exposure time, a flat line was used for time scaling. An UF of 1 was applied for intraspecies variability because this factor was considered adequate for an odor threshold. The derived values are supported by irritative effects in humans: In a personal communication, Renshaw (1991) reported that eye irritation was noted after exposure to concentrations of 5–23 ppm for 15–30 minutes and that slight eye irritation was experienced after exposure to 0.3–1.6 ppm for 30 minutes to 2.5 hours. Since occurrence of slight eye irritation can be tolerated at the AEGL–1 level these data support AEGL–1 values in the latter concentration range.

The AEGL–2 was based on blepharospasm in rabbits observed during the first and subsequent exposures in a teratogenicity study using repeated exposures (Neeper-Bradley *et al.,* 1997). Blepharospasm was considered a sign of impaired ability to escape. The highest concentration not leading to this effect was 77 ppm (the LOEL was 129 ppm). A total UF of 3 was used. An interspecies factor of 1 was applied because the rabbit was considered a species especially sensitive for blepharospasm/eyelid closure. An intraspecies factor of 3 was used because it was assumed that only toxicodynamic, but not toxicokinetic differences contribute to variability of this local effect. No information was available on the exposure concentration dependence of the time to onset of blepharospasm. Since the increase of this effect with time was assumed to be small and observations from 6-hour exposure periods were available, use of a flat line to derive values for appropriate exposure periods was considered an appropriate approach.The AEGL–3 was based on a mortality study in rats using single exposures against acrylic acid aerosol for 30 minutes, 1 hour, or 2 hours (Hagan and Emmons, 1988). Using Probit analysis, maximum likelihood estimates for LC_{01} values were calculated for appropriate exposure periods between 10 minutes and 8 hours. These values were similar to the lower 95% confidence limit of LC_{05} values calculated by Probit analysis. The same values were obtained when time scaling was done according to the dose-response regression equation $C^n \times t = k$, using an n of 1.7, that was derived by Probit analysis from the data of the AEGL–3 key study (Hagan and Emmons, 1988) or by linear regression of log (LC_{50}) − log (time) data. A total UF of 10 was used. An interspecies factor of 3 was applied because the interspecies variability was assumed to be small due to the facts that acrylic acid is a contact-site, direct-acting toxicant, the mechanism of action is unlikely to differ between species and the influence of metabolism, detoxification, and elimination on lethal effects after inhalation is estimated to be small. An intraspecies factor of 3 was applied because a small interindividual variability can be assumed since acrylic acid is a contact-site, direct-acting toxicant not requiring metabolic conversion.

The calculated values are listed in Table 4 below:

TABLE 4.—SUMMARY TABLE OF PROPOSED AEGL VALUES FOR ACRYLIC ACID

Classification	10-Minutes	30-Minutes	1-Hour	4-Hours	8-Hours	Endpoint (Reference)
AEGL–1 (Nondisabling)	1.0 ppm (3.0 mg/m^3)	1.0 ppm (3.0 mg/m^3)	1.0 ppm (3.0 mg/m^3)	1.0 ppm (3.0 mg/m^3)	1.0 ppm (3.0 mg/m^3)	Odor detection threshold in humans (Hellman and Small, 1974)
AEGL–2 (Disabling)	26 ppm (78 mg/m^3)	26 ppm (78 mg/m^3)	26 ppm (78 mg/m^3)	26 ppm (78 mg/m^3)	26 ppm (78 mg/m^3)	Blepharospasm in rabbits (Neeper-Bradley *et al.,* 1997)
AEGL–3 (Lethal)	470 ppm (1,400 mg/m^3)	250 ppm (750 mg/m^3)	170 ppm (510 mg/m^3)	77 ppm (231 mg/m^3)	51 ppm (153 mg/m^3)	Lethality in rats (Hagan and Emmons, 1988)

ii. *References.*

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7. *Allyl alcohol*—i. *Description.* Allyl alcohol is a colorless liquid that is a potent sensory irritant. Toxic effects following inhalation exposures to allyl alcohol vapor include lacrimation, pulmonary edema and congestion, and inflammation, hemorrhage, and degeneration of the liver and kidney. Human data were limited to voluntary exposures for short durations and general statements about the signs of toxicity following accidental exposures to unknown concentrations of allyl alcohol for unspecified amounts of time in the workplace. Animal data were limited to studies in which lethality was the only endpoint of interest, subchronic exposures, or single-exposure experiments in which the model was questionable.

The AEGL–1 value was based on the mean odor detection threshold concentration of 1.8 ppm (AIHA, 1989). Odor is considered a threshold effect; therefore the values were not scaled across time, but rather the threshold value is applied to all times.

The AEGL–2 values were based on a subchronic exposure study in which rats were repeatedly exposed to 40 ppm for 7 hours/day (Dunlap *et al.,* 1958). Irritation was noted to occur during the first few exposures. An UF of 3 was applied for species to species extrapolation because there did not appear to be much variation between species: A NOEL for lethality was the same for 3 different species (mice, rats, and rabbits). An UF of 3 was also applied for intraspecies extrapolation. Although the traditional approach for UF in a case such as this would argue for an uncertainty factor of 10 because of the lack of data addressing interindividual variability, this would result in a composite uncertainty factor of 30. An UF of 30 would drive the AEGL–2 values (8 hour AEGL–2 of 1.2 ppm) to a level that would be inconsistent with available data: Dunlap, *et al.* (1958) reported that rats exposed for 7 hours/day, 5 days/week for 60 exposures to 1, 2, or 5 ppm had no observable adverse effects, while rats exposed to 20 ppm only exhibited decreased body-weight gain, and Torkelson *et al.* (1959) reported that no adverse effects were noted when rats, guinea pigs, rabbits, and dogs were exposed to 2 ppm for 7 hours/day, 5 days/week for 28 exposures, while exposure of rats, guinea pigs, and rabbits exposed to 7 ppm for 7 hours/day, 5 days/week for 134 exposures exhibited only reversible liver and kidney damage. Therefore, a total UF of 10 was applied to the AEGL–2 value.

The experimentally derived exposure value was then scaled to AEGL time frames using the concentration-time relationship given by the equation $C^n \times t = k$, where the exponent n generally ranges from 1 to 3.5 (ten Berge, 1986). The value of n was not empirically derived due to the unreliability and inconsistencies of the data; therefore, the default value of n = 1 was used for extrapolating from shorter to longer exposure periods and a value of n = 3 was used to extrapolate from longer to shorter exposure periods. The 10-minute value was set equal to the 30-minute value because it was considered too precarious to extrapolate from the exposure duration of 7 hours to 10 minutes.

The AEGL–3 values were based upon a NOEL for lethality in mice, rats, and rabbits of 200 ppm for 1 hour (Union Carbide, 1951). An UF of 3 was applied for species to species extrapolation because there did not appear to be much variation across species for lethality. A NOEL for lethality was the same for 3 different species (mice, rats, and rabbits), and this endpoint was used for the AEGL–3 derivation. Additionally, the use of a NOEL for lethality is inherently conservative. An UF of 3 was also applied for intraspecies extrapolation. As discussed in the AEGL–2 derivation unit, applying the traditional UF of 10 to account for the lack of data addressing interindividual variability would result in a composite UF of 30, which would drive the AEGL–3 values to a level that would be inconsistent with available data (1 hour AEGL–3 of 6.7 ppm; see AEGL–2 derivation in this unit). Therefore, a total UF of 10 was applied to the AEGL–3 value.

The experimentally derived exposure value was then scaled to AEGL time frames using the concentration-time relationship given by the equation $C^n \times t = k$, where the exponent n generally ranges from 1 to 3.5 (ten Berge, 1986). Again, the value of n was not empirically derived due to the unreliability and inconsistencies of the data; therefore a default value of n should be used in the temporal scaling of AEGL values across time. If one applies the default value of n = 1 for extrapolating from shorter to longer exposure periods and a value of n = 3 to extrapolate from longer to shorter exposure periods, one obtains the following values: 10 minutes: 36 ppm; 30 minute: 25 ppm; 1 hour: 20 ppm; 4 hours: 5.0 ppm; 8 hours: 2.5 ppm. Going with a default value results in AEGL values that are inconsistent with the available data. The AEGL–2 data do not support the hypothesis that n = 1 for extrapolation to 4 or 8 hours: When using an n = 1 (which assumes a ''worse case'' scenario) to extrapolate from 1 hour to 4 or 8 hours, one obtains a 4-hour AEGL–3 value of 5.0 ppm, which

is almost identical to the 4-hour AEGL–2 value of 4.8 ppm, and an 8-hour AEGL–3 value of 2.5 ppm, which is lower than the 8-hour AEGL–2 value of 3.5 ppm. The AEGL–2 values help to serve as a baseline: They are based on a multiple exposure scenario in which rats exposed for 40 ppm for 7 hours/days exhibited reversible signs of irritation. It is unreasonable to have AEGL–3 values below the AEGL–2 values. Therefore, in the absence of any further data, an n of 2 was selected as a reasonable compromise between the possible values for n as reported by ten Berge (1986): It is between the most conservative n = 1 (which results in unreasonable values) and an n = 3, a least conservative value. AEGL–3 values are therefore derived using an n = 3 for extrapolation to 10 and 30 minutes and an n = 2 for extrapolation to 4 or 8 hours.

The calculated values are listed in Table 5 below:

TABLE 5.—SUMMARY OF PROPOSED AEGL VALUES FOR ALLYL ALCOHOL [PPM (MG/M^3)]

Classification	10-Minutes	30-Minutes	1-Hour	4-Hours	8-Hours	Endpoint (Reference)
AEGL–1 (Nondisabling)	1.8 (4.4)	1.8 (4.4)	1.8 (4.4)	1.8 (4.4)	1.8 (4.4)	Mean odor detection threshold (AIHA, 1989)
AEGL–2 (Disabling)	9.6 (23)	9.6 (23)	7.7 (19)	4.8 (12)	3.5 (8.5)	Irritation in rats at 40 ppm for 7 hours (Dunlap *et al.,* 1958)
AEGL–3 (Lethality)	36 (87)	25 (61)	20 (48)	10 (24)	7.1 (17)	NOEL for lethality in mice, rats, and rabbits exposed to 200 ppm for 1 hour (Union Carbide, 1951)

ii. *References*.

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b. Dunlap, M.K., Kodama, J.K., Wellington, J.S., Anderson, H.H., and Hine, C.H. 1958. The toxicity of allyl alcohol. *American Medical Association Archives of Industrial Health*. Vol. 18:303–311.

c. ten Berge, W.F. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. *Journal of Hazardous Materials*. Vol. 13:301–309.

d. Torkelson, T.R., Wolf, M.A., Oyen, F., and Rowe, V.K. 1959a. Vapor toxicity of allyl alcohol as determined on laboratory animals. *American Industrial Hygiene Association Journal*. Vol. 20:217–229.

e. Union Carbide and Carbon Corporation. 1951. Initial submission: letter from DuPont Chemical to USEPA regarding a letter about toxicity studies with allyl alcohol with cover letter dated October 15, 1992. Doc. #88–920009857. Union Carbide and Carbon Corp., New York, NY.

8. *Chloromethyl methyl ether*—i. *Description*. Chloromethyl methyl ether (CMME) is a man-made chemical that is highly flammable and a severe respiratory, eye, nose, and skin irritant. Technical grade CMME contains 1–8% bis-chloromethyl ether (BCME) as a contaminant. Since humans are only exposed to technical grade CMME (a great deal of effort is needed to remove ''all'' BCME from CMME), and the human and animal inhalation exposure data all involved technical grade CMME, the AEGL values derived in this document will address the toxicity and carcinogenicity of technical grade CMME.

Acute exposure to technical grade CMME can lead to delayed fatal pulmonary edema in humans and animals, whereas chronic occupational exposure is linked with small-cell lung carcinoma. The carcinoma has a distinct histology from that of cigarette smoking-associated lung cancer and has a shorter latency period. BCME is a much more potent carcinogen than CMME, and is widely believed to account for most or all of the carcinogenicity of technical grade CMME. The EPA places technical grade CMME (and BCME) in classification A (''human carcinogen'') based on sufficient human carcinogenicity data. Technical grade CMME acute inhalation toxicity has been studied in rats, mice, and hamsters. Numerous epidemiological studies describe occupational exposure to technical grade CMME, although CMME concentrations were almost never measured.

No data were available to determine the concentration-time relationship for CMME toxic effects. The concentration-time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge *et al.,* 1986). To obtain protective AEGL–2 and AEGL–3 values for 30–480 minutes, n = 3 and n = 1 were used to extrapolate to durations shorter and longer, respectively, than the exposure duration in the key study (AEGL–1 values were not derived). The 10-minute values were not extrapolated because the NAC determined that extrapolating from ≥4 hours to 10 minutes is associated with unacceptably large inherent uncertainty, and the 30-minute values were adopted for 10 minutes to be protective of human health.

AEGL–1 values were not recommended because there were no inhalation studies that had endpoints consistent with the definition of AEGL–1.

AEGL–2 values for technical grade CMME were based on a study in which rats were exposed 30 times (probably for 6 hours/day, 5 days/week) to 1 ppm technical grade CMME vapor (Drew *et al.,* 1975). Two rats died (exposure days 16 and 22) but their cause of death was not stated. Some of the rats were allowed to live for their lifetime; they had minimal mucosal effects and several had lung hyperplasia or squamous metaplasia, but no tumors were reported. The AEGL–2 values were based on a single 6-hour exposure, which is expected to cause a similar or lower incidence of hyperplasia and/or metaplasia than 30 exposures. An UF of 10 was used: 3 to account for sensitive humans (response to an irritant gas hydrolyzed *in situ* is not likely to vary greatly among humans) and 3 for interspecies extrapolation (little interspecies variability was seen; the key study was repeat-exposure). A modifying factor of 3 was applied to account for potential differences in BCME content of technical grade CMME. The resulting AEGL values were supported by a lifetime CMME rat and hamster study (Laskin *et al.,* 1975) and a 6-month BCME rat and mouse study (Leong *et al.*, 1975, 1981).

CMME AEGL–2 values were also calculated using a BCME inhalation cancer slope factor with extrapolation to ½ to 8 hours, and based on 10^{-4}, 10^{-5}, and

10^{-6} excess cancer risk levels (BCME was assumed to represent 8% of CMME and to account for all CMME carcinogenicity). CMME AEGL–2 values based on the noncarcinogenicity endpoints were lower than those calculated for 10^{-4} excess cancer risk but were similar to or greater than those calculated for 10^{-5} or 10^{-6} excess cancer risk. AEGL–2 values based on the noncarcinogenic endpoints were considered to be more appropriate because only multiple exposures to CMME were shown to result in tumor formation, and AEGL values are applicable to rare events or single, once-in-a-lifetime exposures of small populations in limited geographic areas.

AEGL–3 values were derived from a rat inhalation LC_{50} study where exposure was for 7 hours (Drew *et al.,* 1975). The threshold for lethality, as represented by the LC_{01} (14.8 ppm) calculated using probit analysis, was the AEGL–3 toxicity endpoint. Animals that died, and to a lesser degree, animals surviving to 14 days, had increased relative lung weights, congestion, edema, hemorrhage, and acute necrotizing bronchitis. An UF of 10 was used: 3 for sensitive humans (response to an irritant gas hydrolyzed *in situ* is not likely to vary greatly among humans) and 3 for interspecies extrapolation (little interspecies variability was seen, as expected for an irritant gas hydrolyzed *in situ*). An additional modifying factor of 3 was applied to account for potential differences in BCME content of technical grade CMME. Comparable AEGL–3 values were obtained with CMME in a hamster LC_{50} study and in a BCME single-exposure rat study (Drew *et al.,* 1975).

The calculated values are listed in Table 6 below:

TABLE 6.—SUMMARY OF PROPOSED AEGL VALUES FOR CHLOROMETHYL METHYL ETHER (CMME) [PPM(MG/M^3)]

Level	10-Minutes	30-Minutes	1-Hour	4-Hours	8-Hours	Endpoint (Reference)
AEGL–1 (Nondisabling)	Not Recommended (No studies available consistent with AEGL–1 definition)					
AEGL–2 (Disabling)	0.076 (0.25)	0.076 (0.25)	0.061 (0.20)	0.038 (0.13)	0.025 (0.082)	Tracheal or bronchial squamous metaplasia; regenerative lung hyperplasia (Drew *et al.,* 1975).
AEGL–3 (Lethal)	1.2 (3.9)	1.2 (3.9)	0.94 (3.1)	0.59 (2.0)	0.43 (1.4)	Lethality threshold for rats (Drew *et al.,* 1975).

ii. *References.*

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c. Leong, B.K.J., Kociba, R.J., Jersey, G.C., and Gehring, P.J. 1975. Effects from repeated inhalation of parts per billion of bis(chloromethyl)ether in rats. *Toxicology and Applied Pharmacology*. Vol. 33:175.

d. Leong, B.K.J., Kociba, R.J., and Jersey, G.C. 1981. A lifetime study of rats and mice exposed to vapors of bis(chloromethyl)ether. *Toxicology and Applied Pharmacology*. Vol. 58:269–281.

e. ten Berge, W. F., Zwart, A., and Appelman, L. M. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapors and gases. *Journal of Hazardous Materials*. Vol. 13:302–309.

9. *Toluene*—i. *Description.* Toluene is a ubiquitous substance that is widely used as a raw material in the chemical manufacturing industry, as an additive in gasoline to increase the octane level, and as a solvent in lacquers, paint thinners, glue, and other compounds. The odor threshold for toluene ranges from 0.16 to 37 ppm for detection and 1.9 to 69 ppm for recognition; the odor is not unpleasant. Toluene is readily absorbed from the respiratory tract and distributed throughout the body, accumulating in tissues with high lipid content. Toluene is a CNS depressant and, at high concentrations, is irritating to the eyes. Other toxic effects observed in humans include renal toxicity, cardiac arrhythmias, blood dyscrasias, hepatomegaly, and developmental abnormalities. A considerable amount of human and animal data were available for derivation of AEGLs.

Mouse lethality data were used for the regression analyses of the concentration-exposure durations. Regression analysis of the relationship between time and concentration ($C^n \times t = k$), based on four studies with the mouse, the most sensitive species, showed that n = 2. This relationship was used for all AEGL levels because the primary mechanism of action of toluene is CNS depression, which at high concentrations results in death.

The AEGL–1 was based on observations of mild sensory irritation and headache in humans at a concentration of 100 ppm for up to 6 hours in an atmosphere controlled setting (Andersen *et al.,* 1983; Rahill *et al.,* 1996; Dick *et al.,* 1984; Baelum *et al.,* 1985; 1990). An UF of 3 was chosen to protect sensitive individuals because the mechanism of action for irritation is not expected to vary greatly among individuals and no effects on ventilatory parameters were found at much higher concentrations. Extrapolation was made to the relevant AEGL time points using the relationship $C^n \times t = k$ where n = 2, based on the mouse lethality data. The endpoint and values are supported by the multiple studies with human subjects, some of which reported no effects at the 100 ppm concentration.

The AEGL–2 was based on more serious effects in humans at concentrations of ≥200 ppm for 8 hours including incoordination, dizziness, decreased reaction time, mental confusion, muscular weakness, and nausea (Wilson, 1943; von Oettingen *et al.,* 1942). These effects were considered to represent the threshold for impaired ability to escape. An UF of 3 was applied to account for sensitive individuals because the threshold for CNS impairment does not vary greatly among individuals. Extrapolation was made to the 10-minute, 30-minute, 1-hour and 4-hour time points using the equation $C^n \times t = k$ where n = 2 (based on mouse lethality data). The above values are supported by the behavioral effects observed in monkeys after a 50-minute exposure to 2,000 ppm toluene (Taylor and Evans, 1985). At this concentration-duration, these animals exhibited significantly decreased

reaction time and decreased accuracy on matching to sample tasks. Dividing the 2,000 ppm concentration by intra- and interspecies UF of 3 each (for a total of 10) results in values similar to those based on the human data.

The AEGL–3 values were derived from the exposure concentrations equal to one third of the mouse 1-hour LC_{50} reported by Moser and Balster (1985). The 1-hour mouse LC_{50} of 19,018 ppm was divided by 3 to estimate the threshold for lethality. A total UF of 10 was applied which includes 3 to account for sensitive individuals and 3 for interspecies extrapolation (the mechanism of action for severe CNS depression does not vary greatly among individuals or among species). The estimated 1-hour threshold for lethality of 6,339 ppm was extrapolated to the 10-minute, 30-minute, 4-hour, and 8-hour AEGL–3 time points using the relationship $C^n \times t = k$ where n = 2 (calculated from the mouse lethality data). These values are supported by the accidental exposure of two men to an estimated concentration of >1,842 ppm toluene for an average duration of 2.5 hours which resulted in severe but reversible CNS depression (Meulenbelt *et al.,* 1990). Scaling of this exposure to the 10-minute, 30-minute, 1-, 4-, and 8-hour time points yields slightly higher values (2,400; 1,400; 970; 490; and 340 ppm, respectively) than those based on the threshold for lethality in the mouse. The proposed values are considered adequately protective since the mouse is more sensitive than humans to the CNS effects of toluene.

The calculated values are listed in Table 7 below:

TABLE 7.—SUMMARY OF PROPOSED AEGL VALUES FOR TOLUENE [PPM (MG/M^3)]

Classification	10-Minutes	30-Minutes	1-Hour	4-Hours	8-Hours	Endpoint (Reference)
AEGL–1 (Nondisabling)	260 (980)	120 (450)	82 (300)	41 (150)	29 (112)	Eye irritation, headache in humans (Andersen *et al*., 1983)
AEGL–2 (Disabling)	600 (2,260)	270 (1,020)	190 (710)	94 (340)	67 (260)	Incoordination, mental confusion, neurobehavioral deficits in humans (Wilson, 1943; von Oettingen *et al*., 1942)
AEGL–3 (Lethal)	1,600 (6,000)	900 (3,380)	630 (2,360)	320 (1,200)	220 (830)	Lethality, ⅓ of the mouse 1-hour LC_{50} (Moser and Balster, 1985)

ii. *References.*

a. Andersen, I., Lundqvist, G.R., Molhave, L., Pedersen, O.F., Proctor, D.F., Vaeth, M., and Wyon, D.P. 1983. Human response to controlled levels of toluene in six-hour exposures. *Scandinavian Journal of Work and Environmental Health*. Vol. 9:405–418.

b. Wilson, R.H. 1943. Toluene poisoning. *Journal of American Medical Association*. Vol. 123:1106–1108.

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d. Moser, V.C. and Balster, R.L. 1985. Acute motor and lethal effects of inhaled toluene, 1,1,1-trichloroethane, halothane, and ethanol in mice: Effects of exposure duration. *Toxicology and Applied Pharmacology*. Vol. 77:285–291.

10. *Phenol*—i. *Description.* Phenol is a colorless to pink, hygroscopic solid with a characteristic, sweet, tarry odor. Pure phenol consists of white to clear acicular crystals. In the molten state, it is a clear, colorless liquid with a low viscosity.

Cases of lethal poisoning of humans by phenol have been reported in the literature after oral uptake or skin contact. Only few studies reporting effects on humans after inhalation of phenol are available: One study reported slight effects on liver and blood parameters (increased serum transaminase activity, increased hemoglobin concentration, increased numbers of white blood cells) after repeated occupational exposure to a mean time-weighted average concentration of 5.4 ppm phenol (Shamy *et al.*, 1994). Piotrowski (1971) did not report on effects in a toxicokinetic study, in which subjects were exposed to 6.5 ppm for 8 hours. Likewise, Ogata *et al.* (1974) in a toxicokinetic field study did not mention any effects on workers exposed to mean workshift concentrations of 4.95 ppm. In persons exposed to >1 mg/l phenol in contaminated drinking water for several weeks following an accidental spill of phenol, gastrointestinal symptoms (diarrhea, nausea, burning pain and sores in the mouth) and skin rashes occurred (Baker *et al.*, 1978). A geometric mean odor detection threshold of 0.060 ppm (range of all critiqued odor thresholds 0.0045–1 ppm) has been reported (AIHA, 1989).

No studies reporting LC_{50} values for phenol in animals are available. Oral LD_{50} values were reported as 420 mg/kg for rabbits, 400–650 mg/kg for rats and 282–427 mg/kg for mice. In rats, exposure to a phenol aerosol concentration of 900 mg/m3 resulted in ocular and nasal irritation and slight incoordination after 4 hours and tremors and prostration in 1 of 6 animals after 8 hours (Flickinger, 1976). After 4 hours exposure to 211 and 156 ppm, a decrease of the number of white blood cells, but no signs of toxicity were reported (Brondeau *et al.*, 1990). After exposure of rats to 0.5, 5, and 25 ppm for 6 hours/day, 5 days/week for 2 weeks no clinical, hematological or histopathological effects were found (CMA, 1998; Hoffmann *et al.*, 1999). Continuous exposure to 5 ppm phenol for 90 days caused no hematological or histological effects in rhesus monkeys, rats and mice. A concentration of 166 ppm (for 5 minutes) resulted in a 50% decrease of respiration (RD_{50}) in mice. No teratogenic effects were found in rats and mice. An oral carcinogenicity study in rats and mice, using exposure through drinking water, found an increased tumor incidence in male rats of the low exposure group, but not in male rats of the high exposure group or in female rats and mice. Phenol has tumor promoting activity when applied dermally and can cause clastogenic and possibly very weak mutagenic effects.

The AEGL–1 was based on a repeated inhalation exposure study in rats (CMA, 1998; Hoffmann *et al.*, 1999), which found no clinical, hematological or histopathological effects after exposure to 25 ppm phenol (highest concentration used) for 6 hours/day, 5 days/week for 2 weeks. A total UF of 10 was used. An UF of 3 was applied for interspecies variability because a multiple exposure study was used for the derivation of AEGL. A factor of 3 was applied for intraspecies variability because the study reported no effects and thus was below the AEGL–1 effect

level and because available human data do not point at a large interindividual variability. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using the default of n = 3 for shorter exposure periods and n = 1 for longer exposure periods, due to the lack of suitable experimental data for deriving the concentration exponent. Continuation of the time scaling to the 10-minute period is supported by the reported RD_{50} value of 166 ppm for an exposure period of 5 minutes in mice (De Ceaurriz *et al.*, 1981): The resulting 10-minute AEGL–1 is 20-fold below the RD_{50} value in mice.

The AEGL–2 was based on a repeated inhalation exposure study in rats (CMA, 1998; Hoffmann *et al.*, 1999), which found no clinical, hematological or histopathological effects after exposure to 25 ppm phenol (highest concentration used) for 6 hours/day, 5 days/week for 2 weeks, and on a single exposure study in rats, in which exposure to 900 mg/m^3 phenol aerosol (equivalent to 234 ppm) led to ocular and nasal irritation, muscle spasms and slight loss of coordination within 4 hours of exposure and to tremors and prostration in 1 of 6 animals at the end of the 8-hour exposure period (Flickinger, 1976). A total UF of 3 was used for the study of CMA (1998), because the exposure concentration used was a no-observed-adverse-effect level (NOAEL) in a repeated exposure study and because use of a higher UF would resulted in the same concentrations set as AEGL–1. This factor was formally split up into an interspecies factor of 1 and an intraspecies factor of 3. A total UF of 30 was used for the Flickinger (1976) study. This factor was formally split up into an interspecies factor of 3 and an intraspecies factor of 10. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using the default of n = 3 for shorter exposure periods, due to the lack of suitable experimental data for deriving the concentration exponent. For the 10-minute AEGL–2 the 30-minute value was applied because the derivation of AEGL values was based on a long experimental exposure period and no supporting studies using short exposure periods were available for characterizing the concentration-time-response relationship. Calculations were done on the basis of both studies and resulted in very similar concentrations. Since slightly lower values were obtained on basis of the CMA (1998) study, these values were set as AEGL–2 values.

The AEGL–3 was based on an inhalation study in rats, in which exposure to a phenol aerosol concentration of 900 mg/m^3 phenol (equivalent to 234 ppm phenol vapor) for 8 hours resulted in tremors, incoordination and prostration in 1 of 6 animals, but not in death (Flickinger, 1976). This study is supported by the study of Brondeau *et al.* (1990), which did report only slight effects after exposure of rats to 211 ppm phenol vapor for 4 hours. The comparison of the dose equivalent to the derived AEGL–3 values with human oral lethality data supports use of a total UF of 10. An additional argument for not choosing a total UF higher than 10 is that a factor of 30 would have resulted in corresponding body doses in the dose range described by Baker *et al.* (1978) for an incident of drinking water contamination. In this study mainly mild gastrointestinal (local) effects, but no systemic/severe effects, were observed upon repeated oral exposure. The total UF of 10 was formally split up into an interspecies factor of 3 and an intraspecies factor of 3. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using the default of n = 3 for shorter exposure periods, due to the lack of suitable experimental data for deriving the concentration exponent. For the 10-minute AEGL–3 the 30-minute value was applied because the derivation of AEGL values was based on a long experimental exposure period and no supporting studies using short exposure periods were available for characterizing the concentration-time-response relationship.

The calculated values are listed in Table 8 below:

TABLE 8.—SUMMARY TABLE OF PROPOSED AEGL VALUES FOR PHENOL [A]

Classification	10-Minutes	30-Minutes	1-Hour	4-Hours	8-Hours	Endpoint (Reference)
AEGL–1 (Nondisabling)	8.3 ppm (32 mg/m^3)	5.7 ppm (22 mg/m^3)	4.5 ppm (17 mg/m^3)	2.9 ppm (11 mg/m^3)	1.9 ppm (7.3 mg/m^3)	No effects in rats (CMA, 1998; Hoffmann *et al.*, 1999)
AEGL–2 (Disabling)	19 ppm (73 mg/m^3)	19 ppm (73 mg/m^3)	15 ppm (58 mg/m^3)	9.5 ppm (36 mg/m^3)	6.3 ppm (24 mg/m^3)	No effects in rats (CMA, 1998; Hoffmann *et al.*, 1999); irritation, loss of coordination, tremors, and prostration in rats (Flickinger, 1976)
AEGL–3 (Lethal)	59 ppm (230 mg/m^3)	59 ppm (230 mg/m^3)	47 ppm (180 mg/m^3)	29 ppm (110 mg/m^3)	23 ppm (88 mg/m^3)	No lethality in rats (Flickinger, 1976)

[a] Rapid dermal penetration occurs from phenol vapor, molten phenol and phenol solutions; skin contact with molten phenol or concentrated phenol solutions should be avoided; fatal intoxications have been observed when a small part of the body surface was involved.

ii. *References.*

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b. Brondeau, M.T., Bonnet, P., Guenier, J.P., Simon, P., and De Ceaurriz, J. 1990. Adrenal-dependent leucopenia after short-term exposure to various airborne irritants in rats. *Journal of Applied Toxicology.* Vol. 10:83–86.

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f. Hoffmann, G.M., Dunn, B.J., Morris, C.R., Butala, J.H., Dimond, S.S., Gingell,

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11. *Furan*—i. *Description*. Furan is a colorless, highly flammable liquid with a strong, ethereal odor. It is used primarily as an industrial intermediate. Because of its relatively high vapor pressure, furan is predicted to exist almost entirely in the vapor phase in the atmosphere.

No toxicity data regarding human exposures to furan were available. Animal toxicity data were limited, with much of the literature focused on metabolism and disposition. Metabolism studies indicate that furan is bioactivated to a reactive metabolite, cis-2-butene-1,4-dial, by cytochrome P450 2E1. Quantitative toxicology data for effects following inhalation exposure to furan were limited to one study.

An AEGL–1 was not derived for furan. No human or animal data relevant to the derivation of an AEGL–1 for furan were available in the searched literature.

The AEGL–2 derivation is based on the threshold for adverse effects in male and female rats at a concentration of 1,014 ppm for 1 hour (Terrill *et al.*, 1989). Although the severity of the reported clinical signs (respiratory distress, increased secretory response) was not reported, this lowest-exposure concentration group did not exhibit a decrease in body weights like the rats exposed to 2,851 ppm or 4,049 ppm.

The AEGL–3 derivation is based upon the highest NOEL for mortality in male and female rats of 2,851 ppm for 1 hour (Terrill *et al.*, 1989). Rats exposed to 1,014; 2,851; or 4,049 ppm exhibited clinical signs including respiratory distress and increased secretory response: however, the degree of the signs at each concentration was not provided. Death occurred in the highest exposure group.

An UF of 10 was applied for species to species extrapolation because quantitative toxicology data were available in only one species, rats. Despite the predicted lower absorbed dose and liver dose of the reactive metabolite in humans compared to rodents (following a simulated exposure to 10 ppm for 4 hours, the predicted absorbed dose of furan (mg/kg) in humans, and consequently the liver dose of the reactive metabolite cis-2-butene-1,4-dial, was 10-fold less than in mice and 3.5-fold lower than in rats (Kedderis and Held, 1996), the differences between humans and rodents in sensitivity to the reactive metabolite are not known, and the liver was the only organ investigated. An UF of 3 was applied for sensitive individuals (intraspecies) because interindividual variations in the activating enzyme are not predicted to be a factor in bioactivation (Kedderis and Held, 1996). A modifying factor of 3 was applied because only one data set addressing furan toxicity following inhalation exposure was available: This study was not repeated, and there was no information on furan toxicity in other species or on reproductive/developmental toxicity. Therefore, a total uncertainty factor/modifying factor of 100 was applied to the AEGL–2 and -3 values.

The experimentally derived exposure values were scaled to AEGL time frames using the concentration-time relationship given by the equation $C^n \times t = k$, where the exponent n generally ranges from 1 to 3.5 (ten Berge, 1986). The value of n was not empirically derived because of insufficient data; therefore, the default value of n = 1 was used for extrapolating from shorter to longer exposure periods and a value of n = 3 was used to extrapolate from longer to shorter exposure periods.

The calculated values are listed in Table 9 below:

TABLE 9.—SUMMARY OF PROPOSED AEGL VALUES FOR FURAN [PPM (MG/M^3)]

Classification	10-Minutes	30-Minutes	1-Hour	4-Hours	8-Hours	Endpoint (Reference)
AEGL–1 (Nondisabling)	Insufficient Data (ID)[a]	ID	ID	ID	ID	ID were available to derive an AEGL–1
AEGL–2 (Disabling)	18 (50)	13 (39)	10 (28)	2.5 (7.0)	1.3 (3.6)	1,014 ppm for 1 hour: Threshold for adverse effects in rats (clinical signs: Severity of respiratory distress, increased secretory response not reported; no decrease in body weights) (Terrill *et al.*, 1989)
AEGL–3 (Lethality)	52 (140)	46 (100)	29 (81)	7.1 (20)	3.6 (10)	2,851 ppm for 1 hour: Threshold for lethality in rats (Terrill *et al.*, 1989)

[a] Absence of an AEGL–1 does not imply that exposure below the AEGL–2 is without adverse effects

ii. *References*.

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b. Terrill, J.B., Van Horn, W.E., Robinson, D., and Thomas, D.L. 1989. Acute inhalation toxicity of furan, 2 methylfuran, furfuryl alcohol, and furfural in the rat. *American Industrial Hygiene Association Journal*. Vol. 50:A359–A361.

12. *Tetrachloroethylene*—i. *Description*. Tetrachloroethylene (PCE), also commonly known as perchloroethylene or Perc, is a colorless, nonflammable liquid. It has an ethereal odor, with a reported odor threshold ranging from 2–71 ppm. PCE is commonly used as a dry-cleaning solvent and as a degreaser, and is also used as a chemical intermediate and as a veterinary antithelmintic.

Following exposure to PCE, humans primarily experience CNS effects and irritation, with some cases of reversible

liver effects reported. CNS effects also predominate in animals, although liver effects are noted in mice, and nephrotoxicity is observed in rats. However, the hepatotoxicity and nephrotoxicity is commonly associated with repeated or chronic exposures.

The AEGL–1 derivation is based on the exposure of six volunteers to 106 ppm for 1 hour (Rowe *et al.*, 1952). At this level, an apparent non-objectionable odor and eye irritation were noted, and one subject experienced a light fullness in the head An interspecies UF was not applicable. An intraspecies UF of 3 is applied because the Minimum Alveolar Concentration (MAC; the concentration that produces lack of movement in 50% of persons exposed) for volatile anesthetics does not vary by more than a factor of 2–3-fold. The AEGL–1 values are consistent with values that would be obtained using a study addressing minor central nervous effects (changes in visual evoked potentials and visual contrast sensitivity, significant performance deficits for vigilance and eye-hand coordination) following exposure to 50 ppm for 4 hours (Altmann *et al.*, 1990; 1992). If one bases on AEGL–1 on these exposure parameters and uses the same UFs and value of n, one obtains almost identical values.

The AEGL–2 value is based upon the no-effect level for ataxia in rats following exposure to 1,150 ppm PCE for 4 hours/day, 5 days/week for 2 weeks (4 hour time period was used for the derivation) (Goldberg *et al.*, 1964). Exposure to the next higher concentration of 2,450 ppm resulted in reversible ataxia. An interspecies UF of 3 is applied based on the similarity of effects manifested in rodents compared to humans produced by agents that are CNS depressants. Additionally, a no-effect level for lethality is identical for rats and mice and the 4-hour and 6-hour LC_{50} values in mice compared to rats vary by less than 1.5-fold. An intraspecies UF of 3 is applied because the MAC for volatile anesthetics does not vary by more than a factor of 2–3-fold. The AEGL–2 values are supported by the Carpenter (1937) inhalation study in which volunteers exposed to 475 ppm for 2 hours, 10 minutes reported salivation, slight eye irritation, tightness in the frontal sinuses, increased hand perspiration, and increased nasal irritation. These effects are milder than those defined by AEGL–2. An AEGL derivation based on the exposure parameters, a total UF of 3 (3 to account for intraspecies variability; an interspecies UF not needed because the derivation is based on human data), and an n of 2 results in identical AEGL–2 values.

The AEGL–3 derivation is based on a no-effect-level for lethality in mice of 2,450 ppm for 4 hours and in rats of 2,445 ppm for 4 hours (Friberg *et al.*, 1953; NTP, 1986). An interspecies UF of 3 is applied because a no-effect level for lethality is identical for rats and mice and the 4-hour and 6-hour LC_{50} values in mice compared to rats vary by less than 1.5-fold. The interspecies UF of 3 is further supported by the similarity of effects manifested in rodents compared to humans produced by agents that are CNS depressants. An intraspecies UF of 3 is applied because the MAC for volatile anesthetics should not vary by more than a factor of 2–3-fold. The AEGL–3 values are supported by a human study in which the effects noted were milder than those defined by the AEGL–3 definition (humans exposed to 934 ppm for 95 min experienced tightness of the frontal sinuses, increased hand perspiration, nostril irritation, congestion of eustachian tubes, lassitude, slight mental fogginess, stinging eyes, exhilaration, and/or the tip of nose and lips anesthetized; Carpenter, 1937), and an animal study in which rats exposed to 2,300 ppm for 4 hours/day, 5 days/week for 2 weeks exhibited overt ataxia only following the first 4 hour exposure (Goldberg *et al.*, 1964). Although the Carpenter study (1937) was not used because the effects were below that of the definition of AEGL–3 type endpoints, the study does support the use of a total UF of 10 for the Friberg *et al.* (1953) and NTP (1986) studies as being protective of human health.

The experimentally derived exposure values were then scaled to AEGL time frames using the equation $C^n \times t = k$, where the exponent n generally ranges from 1 to 3.5 (ten Berge, 1986). The value of n used for PCE was the calculated and published value of n = 2 based upon the Rowe *et al.* (1952) rat mortality data for PCE (ten Berge, 1986). The 10-minute AEGL–1, -2, and -3 values were set equal to the 30-minute values. The 10-minute AEGL–1 value was set equal to the 30-minute value of 50 ppm because human data indicated that exposure to 75–80 ppm for 1–4 minutes resulted in slight eye irritation (Stewart *et al.*, 1961). The 10-minute AEGL–2 value was set equal to the 30-minute value of 330 ppm because it was considered too precarious to extrapolate from the exposure duration of 4 hours to 10 minutes, and because a human study demonstrated an exposure to 600 ppm for 10 minutes caused significant effects (eye and nose irritation, dizziness, tightness, and numbing about the mouth, some loss of inhibitions, and motor coordination required great effort; Rowe *et al.*, 1952). The 10-minute AEGL–3 was set equal to the 30-minute value of 690 ppm because it was considered too precarious to extrapolate from the exposure duration of 4 hours to 10 minutes.

The calculated values are listed in Table 10 below:

TABLE 10.—SUMMARY OF PROPOSED AEGL VALUES FOR TETRACHLOROETHYLENE [PPM (MG/M^3)]

Classification	10-Minutes	30-Minutes	1-Hour	4-Hours	8-Hours	Endpoint (Reference)
AEGL–1 (Nondisabling)	50 (340)	50 (340)	35 (240)	18 (120)	12 (81)	Mild eye irritation in six subjects exposed to 106 ppm for 1 hour (Rowe *et al.*, 1952)
AEGL–2 (Disabling)	330 (2,200)	330 (2,200)	230 (1,600)	120 (810)	81 (550)	No-effect level for ataxia in rats following exposure to 1,150 ppm PCE for 4 hours/day, 5 days/week for 2 weeks (4 hour time period used for the derivation) (Goldberg *et al.*, 1964).
AEGL–3 (Lethal)	690 (4,700)	690 (4,700)	490 (3,300)	240 (1,600)	170 (1,200)	No-effect-level for lethality in mice of 2,450 ppm for 4 hours and in rats of 2,445 ppm for 4 hours (Friberg *et al.*, 1953; NTP, 1986)

ii. *References*.

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13. *Tetranitromethane*—i. *Description*. Tetranitromethane (TNM) is a highly explosive chemical that is used as an oxidizer in rocket propellants, to increase the cetane of diesel fuels, and as a reagent to detect double bonds in organic molecules (Budavari *et al.*, 1996; ACGIH, 1996). TNM is also formed as an impurity during the manufacture of trinitrotoluene (TNT). In humans, impure TNM has caused irritation of the eyes, nose, throat, dizziness, chest pain, dyspnea, methemoglobinemia, and cyanosis (Budavari *et al.*, 1996). TNM causes a variety of lung lesions and induced lung tumors in both rats and mice (NTP, 1990).

No data were available to determine the concentration-time relationship for TNM concentration-time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge *et al.*, 1986). To obtain protective AEGL values, scaling across time was performed using n = 3 to extrapolate to <6 hours (exposure duration in key study) and n = 1 to extrapolate to >6 hours. The 10-minute values were not extrapolated from 6 hours because the NAC determined that extrapolating from ≥4 hours to 10 minutes is associated with unacceptably large inherent uncertainty, and the 30-minute values were adopted for 10 minutes to be protective of human health.

AEGL–1, AEGL–2, and AEGL–3 values were derived from an NTP (1990) study in which rats and mice were exposed to 2, 5, 10, 25, or 50 (mice only) ppm TNM for 2 weeks (6 hours/day, 5 days/week). At 2 ppm, no effects were specifically noted in either species. A single 6-hour exposure to 2 ppm was used for AEGL–1 derivation. An UF of 10 was applied: 3 to account for sensitive humans (response to an irritant gas is not likely to vary greatly among humans) and 3 for interspecies extrapolation (toxicity of TNM did not vary greatly between two species; the key study was repeat-exposure).

Exposure to 5 ppm TNM resulted in lowered body weight gains and reddened lungs in mice (rats may have been lethargic), and one 6-hour exposure is the basis for the derived AEGL–2 values. An UF of 10 was used: 3 to account for sensitive humans (response to an irritant gas is not likely to vary greatly among humans) and 3 for interspecies extrapolation (most sensitive species was used; the key study was repeat-exposure). The resulting AEGL–2 values were similar to those derived using a TNM inhalation cancer slope factor (derived from a 103-week NTP, 1990 carcinogenicity study) and based on a 10^{-4} excess cancer risk level. Use of the noncarcinogenicity endpoints was considered to be more appropriate because it appears that the tumorigenic response to inhaled TNM is a function of prolonged nasal and lung tissue irritation resulting from repeated exposures and not the result of a single-low exposure.

Rats and mice exposed to 10 ppm in the NTP (1990) 2-week study were lethargic, lost weight, and the mice had reddened lungs, polypnea, and ataxia, whereas rats exposed to 25 ppm all died on the first day, and most mice exposed to 25 ppm died on day 3 or 4. Therefore, 10 ppm is considered to approximate the lethality threshold for both species, and is supported by an LC_{50} study in which the NOEL for lethality for a 4-hour exposure was 10 and 17 ppm for rats and mice, respectively (Kinkead *et al.*, 1977a; 1977b). AEGL–3 values were developed using one 6-hour exposure and an UF of 10: 3 to account for sensitive humans (response to an irritant gas is not likely to vary greatly among humans) and 3 for interspecies extrapolation (toxicity of TNM did not vary greatly between two species; the key study was repeat-exposure).

The calculated values are listed in Table 11 below:

TABLE 11.—SUMMARY OF PROPOSED AEGL VALUES FOR TETRANITROMETHANE (TNM) [PPM (MG/M^3)]

Classification	10-Minutes	30-Minutes	1-Hour	4-Hours	8-Hours	Endpoint (Reference)
AEGL–1 (Nondisabling)	0.46 (3.7)	0.46 (3.7)	0.36 (2.9)	0.23 (1.8)	0.15 (1.2)	No effects in rats or mice (NTP, 1990).
AEGL–2 (Disabling)	1.1 (9.1)	1.1 (9.1)	0.91 (7.3)	0.57 (4.6)	0.38 (3.5)	Lower weight gain and reddened lungs in mice (NTP, 1990).
AEGL–3 (Lethal)	2.3 (28)	2.3 (28)	1.8 (15)	1.1 (9.2)	0.75 (6.0)	Lethality threshold for rats and mice (NTP, 1990).

ii. *References*.

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14. *Perchloromethyl mercaptan*—i. *Description*. Perchloromethyl mercaptan is an oily, yellow liquid with an unbearable, acrid odor. Although it was used as a chemical warfare gas by the French in the battle of the Champagne in 1915, its wartime use was abandoned shortly thereafter because of its strong warning odor, decomposition in the presence of iron and steel, and because the vapors could easily be removed by charcoal (Prentiss, 1937). Today, perchloromethyl mercaptan is used as an intermediate in the synthesis of dyes and fungicides (Captan, Folpet).

Data addressing human and animal toxicity following exposure to perchloromethyl mercaptan vapors were very limited. Human data were generally limited to case reports describing exposures to an unquantifiable amount of perchloromethyl mercaptan, secondary sources, and/or sources in which the experimental details were not provided. Animal data addressing the lethal and nonlethal effects of perchloromethyl mercaptan were primarily limited to rats.

Exposure to perchloromethyl mercaptan for 6 hours/day, 5 days/week for 2 weeks at a concentration of 0.02 ppm did not result in any measurable changes in rats, while exposure to 0.13 ppm resulted only in mild nasal epithelial changes in rats (Knapp *et al.*, 1987). Likewise, no clear treatment related changes were observed in rats exposed to 0.014 or 0.079 ppm perchloromethyl mercaptan for 6 hours/day, 5 days/week, for a total of 70 to 72 exposure days (Knapp and Thomassen, 1987). Based on these data, a NOAEL of 0.079 ppm in rats exposed for 6 hours/day, 5 days/week, for a total of 70 to 72 exposure days was used for the derivation of an AEGL–1 (Knapp and Thomassen, 1987). An interspecies factor of 3 was applied because although little is known about differences in perchloromethyl mercaptan toxicity between species, the AEGL–1 is based on a NOAEL from a subchronic study and is therefore inherently conservative. An intraspecies UF of 3 was applied to protect for sensitive individuals because the mechanism of action of perchloromethyl mercaptan is likely to be that of an irritant.

A subchronic study in which rats were exposed to 0.58 ppm for 6 hours/day, 5 days/week for 70 days was chosen for the AEGL–2 derivation (Knapp and Thomassen, 1987). Rats exposed to 0.58 ppm for 70 days exhibited only minimal effects: Lung weights were increased, and the only treatment-related pulmonary lesion was mild to minimal focal subacute interstitial pneumonia in 28% of males and 6% of females. An interspecies factor of 10 was applied because little is known about differences in perchloromethyl mercaptan toxicity between species. An intraspecies UF of 3 was applied to protect for sensitive individuals because the mechanism of action of perchloromethyl mercaptan is likely to be that of an irritant.

The no-effect level for lethality of 9 ppm for 1 hour in male and female rats was chosen for use in the AEGL–3 derivation (Stauffer Chemical Company, 1971). An interspecies factor of 10 was applied because little is known about differences in perchloromethyl mercaptan toxicity between species. An intraspecies UF of 3 was applied to protect for sensitive individuals because the mechanism of action of perchloromethyl mercaptan is likely to be that of an irritant.

The experimentally derived exposure values were scaled to AEGL time frames using the concentration-time relationship given by the equation $C^n \times t = k$, where the exponent n generally ranges from 1 to 3.5 (ten Berge, 1986). The value of n was not empirically derived because of insufficient data; therefore, the default value of n = 1 was used for extrapolating from shorter to longer exposure periods and a value of n = 3 was used to extrapolate from longer to shorter exposure periods. The 10-minute values for the AEGL–1 and AEGL–2 levels were flat-lined from the 30-minute values because it was considered too precarious to extrapolate from an exposure duration of 6 hours to an exposure duration of 10 minutes.

The calculated values are listed in Table 12 below:

TABLE 12.—SUMMARY OF PROPOSED AEGL VALUES FOR PERCHLOROMETHYL MERCAPTAN [PPM (MG/M^3)]

Classification	10-Minutes	30-Minutes	1-Hour	4-Hours	8-Hours	Endpoint (Reference)
AEGL–1 (Nondisabling)	0.018 (0.14)	0.018 (0.14)	0.014 (0.11)	0.0090 (0.068)	0.0060 (0.046)	NOAEL of 0.079 ppm for 6 hours/day, 5 days/week for 70–72 exposure days (Knapp and Thomassen, 1987)
AEGL–2 (Disabling)	0.044 (0.33)	0.044 (0.33)	0.035 (0.27)	0.022 (0.17)	0.015 (0.11)	Treatment-related mild to minimal focal subacute interstitial pneumonia and slightly increased lung weights in rats exposed to 0.58 ppm for 6 hours/day, 5 days/week for 70 days (Knapp and Thomassen, 1987)
AEGL–3 (Lethality)	0.54 (4.1)	0.38 (2.9)	0.30 (2.3)	0.075 (0.57)	0.038 (0.29)	No-effect level for lethality in rats (9 ppm for 1 hour) (Stauffer Chemical Co., 1971)

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acting vapours and gases. *Journal of Hazardous Materials*. Vol. 13:301–309.

15. *Carbon monoxide*—i. *Description*. Carbon monoxide (CO) is a tasteless, non-irritating, odorless and colorless gaseous substance. The main source of CO production is the combustion of fuels. Environmental exposure to CO can occur while traveling in motor vehicles (9–25 and up to 35 ppm), working, visiting urban locations with heavily traveled roads (up to 50 ppm), or cooking and heating with domestic gas, kerosene, coal or wood (up to 30 ppm) as well as in fires and by environmental tobacco smoke. Endogenous CO formation during normal metabolism leads to a background carboxyhemoglobin concentration ([COHb]) of about 0.5–0.8%. Smokers are exposed to considerable CO concentrations leading to a [COHb] of about 3–8%.

CO binds to hemoglobin forming [COHb] and thereby renders the hemoglobin molecule less able to bind oxygen. Due to this mechanism, the oxygen transport by the blood and the release of bound oxygen in the tissues are decreased. Tissue damage results from local hypoxia. Organs with a high oxygen requirement, such as the heart and the brain, are especially sensitive for this effect.

CO is a tasteless, non-irritating, odorless and colorless toxic gas which can cause lethal poisonings with very few and late occurring warning signs. Until very severe symptoms occur none or only nonspecific symptoms are noted. For this reason, AEGL–1 values were not recommended.

The AEGL–2 was based on cardiovascular effects in patients with coronary artery disease, which constitute the most susceptible subpopulation. For the derivation of AEGL–2 values a level of 4% [COHb] was chosen. At this exposure level, patients with coronary artery disease may experience a reduced time until onset of angina (chest pain) during physical exertion (Allred *et al.*, 1989; 1991). In the available studies, the CO exposure alone (i.e., with subjects at rest) did not cause angina, while exercise alone did so. However, it should be noted that all studies used patients with stable exertional angina, who did not experience angina while at rest. Thus, it cannot be ruled out that in more susceptible individuals (a part of the patients with unstable angina pectoris might belong to this group) CO exposure alone could increase angina symptoms. The changes in the electrocardiogram (ST-segment depression of 1 mm or greater) associated with angina symptoms were fully reversible. An exposure level of 4% [COHb] is unlikely to cause a significant increase in the frequency of exercise-induced arrhythmias. Ventricular arrhythmias have been observed at [COHb] of 5.3%, but not at 3.7% (Sheps *et al.*, 1990; 1991), while in another study no effect of CO exposure on ventricular arrhythmia was found at 3 and 5% [COHb] (Dahms *et al.*, 1993). An exposure level of 4% [COHb] was considered protective of acute neurotoxic effects in children, such as syncopes, headache, nausea, dizziness, and dyspnea (Crocker and Walker, 1985), and long-lasting neurotoxic effects (defects in the cognitive development and behavioral alterations) in children (Klees *et al.*, 1985). A mathematical model (Coburn *et al.*, 1965; Peterson and Stewart, 1975) was used to calculate exposure concentrations in air resulting in a [COHb] of 4% at the end of exposure periods of 10 and 30 minutes and 1, 4, and 8 hours. A total UF of 1 was used. An intraspecies UF of 1 was considered adequate because the values are based on observations in the most susceptible human subpopulation (patients with coronary artery disease).

The AEGL–3 was based on observations in humans. Several case reports indicate that in patients with coronary artery disease, CO exposure can contribute to myocardial infarction (which was considered an AEGL–3 endpoint). In the published cases of myocardial infarction, the following [COHb] were measured after transport to the hospital: 52.2% (Marius-Nunez, 1990), 30%, 22.8% (Atkins and Baker, 1985), 21% (Ebisuno *et al.*, 1986), 15.6% (Grace and Platt, 1981). Case reports on stillbirths after CO poisoning of pregnant women reported measured maternal [COHb] of about 22–25% or higher (Caravati *et al.*, 1988; Koren *et al.*, 1991). Since in all case studies COHb levels were determined after admission to hospital, the [COHb] at the end of the exposure were probably higher than the measured concentrations. These anecdotal case reports were not considered an adequate basis for the derivation of AEGL–3 values because of uncertainties in the end-of-exposure [COHb] and the insufficient characterization of the exposure conditions (with repeated and/or prolonged exposures in several cases). Therefore, the experimental studies of Chiodi *et al.* (1941) and Haldane (1895), that reported no severe or life-threatening symptoms in healthy subjects exposed to a [COHb] of about 40–56%, were used as the basis for derivation of AEGL–3 values. A mathematical model (Coburn *et al.*, 1965; Peterson and Stewart, 1975) was used to calculate exposure concentrations in air resulting in a [COHb] of 40% at the end of exposure periods of 10 and 30 minutes and 1, 4, and 8 hours. A total UF of 3 was used. An intraspecies UF of 3 was applied to the calculated CO concentrations in air because a factor of 10 would have resulted in exposure concentrations sometimes found in homes and the environment and because the derived values (corresponding to a [COHb] of about 15%) are supported by information on effects, such as myocardial infarction and stillbirths, reported in more susceptible subpopulations.

The calculated values are listed in Table 13 below:

TABLE 13.—SUMMARY TABLE OF PROPOSED AEGL VALUES FOR CARBON MONOXIDE

Classification	10-Minutes	30-Minutes	1-Hour	4-Hours	8-Hours	Endpoint (Reference)
AEGL–1 (Nondisabling)	NR[a]	NR	NR	NR	NR	
AEGL–2 (Disabling)	420 ppm (480 mg/m^3)	150 ppm (170 mg/m^3)	83 ppm (95 mg/m^3)	33 ppm (38 mg/m^3)	27 ppm (31 mg/m^3)	Cardiac effects in humans with coronary artery disease (Allred *et al.*, 1989; 1991)
AEGL–3 (Lethal)	1700 ppm (1,900 mg/m^3)	600 ppm (690 mg/m^3)	330 ppm (380 mg/m^3)	150 ppm (170 mg/m^3)	130 ppm (150 mg/m^3)	No severe or life-threatening effects in humans (Chiodi *et al.*, 1941; Haldane, 1895)

[a] Not recommended since CO is a non-irritating orderless gas which can cause lethal poisonings with very few late occurring warning signs.

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16. *Boron trichloride*—i. *Description.* Boron trichloride is a colorless gas at room temperature that fumes in moist air, or a colorless fuming liquid at low temperatures. It hydrolyzes in water and moist air to produce heat, hydrochloric acid, and boric acid at ordinary temperatures. No data were available regarding human exposures to boron trichloride, and animal inhalation toxicity data were limited to two studies. Vernot *et al.* (1977) reported 1-hour LC_{50} values of 2,541 ppm for male rats and 4,418 ppm for female rats. The other available study by Stokinger and Spiegl (1953) served only as a pilot study, and provided preliminary data on the toxicity of boron trichloride vapor following inhalation exposure in rats, mice, and guinea pigs.

No data relevant to the AEGL–1 defined endpoints were available. Based on the knowledge that one mole of boron trichloride theoretically hydrolyzes to form 3 moles of hydrogen chloride in moist air, the AEGL–1 values were derived by a ⅓ reduction of the accepted hydrogen chloride (HCl) values and are recommended as guidance levels[a]. The hydrogen chloride AEGL–1 was based on a 45 minute NOAEL in exercising adult asthmatics (Stevens *et al.*, 1992). No UFs were applied for inter- or intraspecies variability since the study population consisted of sensitive humans. Additionally, the same value was applied across the 10- and 30-minute, and 1-, 4-, and 8-hour exposure time points since mild irritantcy is a threshold effect and generally does not vary greatly over time. Thus, prolonged exposure will not result in an enhanced effect.

No data relevant to the AEGL–2 defined endpoints were available. Based on the knowledge that one mole of boron trichloride theoretically hydrolyzes to form 3 moles of hydrogen chloride in moist air, the AEGL–2 values were derived by a ⅓ reduction of the accepted HCl values and are recommended as guidance levels[a]. The hydrogen chloride AEGL–2 for the 30-minute, 1-, 4-, and 8-hour time points was based on severe nasal or pulmonary histopathology in rats exposed to 1,300 ppm hydrogen chloride for 30 minutes (Stavert *et al.*,1991). An UF of 3 was applied for interspecies variability because the test species (rodents) is more sensitive to the effects of hydrogen chloride than primates and because direct irritation is not expected to vary greatly between species. An UF of 3 was applied for intraspecies extrapolation since the mechanism of action is direct irritation and the subsequent effect or response is not expected to vary greatly among individuals. An additional modifying factor of 3 was applied to account for the sparse database of effects defined by AEGL–2 and since the effects observed at the concentration used to derive AEGL–2 values were somewhat severe. Thus, the total uncertainty and modifying factor adjustment is 30-fold. It was then time-scaled to the 1-, 4-, and 8-hour AEGL exposure periods using the $C^n \times t = k$ relationship, where n = 1 based on regression analysis of combined rat and mouse LC_{50} data (1 minute to 100 minutes) as reported by ten Berge *et al.*, 1986. The 10-minute AEGL–2 value was derived by dividing the mouse RD_{50} of 309 ppm by a factor of 3 to obtain a concentration causing irritation (Barrow *et al.*, 1977). One-third of the mouse RD_{50} for hydrogen chloride corresponds to an approximate decrease in respiratory rate of 30%, and decreases in the range of 20 to 50% correspond to moderate irritation (ASTM, 1991).

The AEGL–3 was based on ⅓ of the 1-hour boron trichloride LC_{50} of 2,541 ppm in male rats (Vernot *et al.*, 1977). An UF of 3 was applied for intraspecies variability and an additional UF of 10

was applied for interspecies extrapolation to account for a poor data base (total UF = 30). No boron trichloride data were available from which to derive an n value for the scaling of the derived AEGL–3 value across time. Because boron trichloride hydrolyzes in moist air to form hydrogen chloride, the value of n = 1 for hydrogen chloride as calculated by ten Berge (1986) was used for the scaling to the 10- and 30-minute, 1-, 4-, and 8-hour exposures using the relationship $C^n \times t = k$. The derived AEGL–3 values were consistent with the application of the Stokinger and Spiegl (1953) data where exposure to 50 ppm for 2 x 7 hours in rats, mice, and guinea pigs did not result in mortality when clean cages were substituted every 2 hours of the exposure (to reduce contact with the hydrolysis products formed in the cage).

It is recommended that in the event of a boron trichloride release, the concentrations of both boron trichloride and HCl should be monitored. It is conceivable that boron trichloride concentrations could be within the acceptable AEGL range, while the hydrolysis product HCl could exceed permissible AEGL levels. Another likely situation is that the concentration of each will fall below the AEGL criteria but the combination of the two will produce an overall HCl exposure exceeding a given AEGL criteria and thus produce more toxicity than expected by the designated AEGL level.

The calculated values are listed in Table 14 below:

TABLE 14.—SUMMARY OF PROPOSED AEGL VALUES FOR BORON TRICHLORIDE [PPM (MG/M^3)]

Classification	10-Minutes	30-Minutes	1-Hour	4-Hours	8-Hours	Endpoint (Reference)
AEGL–1 (Nondisabling)	0.6 (2.9)	0.6 (2.9)	0.6 (2.9)	0.6 (2.9)	0.6 (2.9)	Recommended as guidance levels: ⅓ the NAC-approved HCl values [NOAEL of HCl in exercising human asthmatics (Stevens *et al.*, 1992)]
AEGL–2 (Disabling)	34 (160)	14 (67)	7.3 (35)	1.8 (8.6)	0.90 (4.3)	Recommended as guidance levels: ⅓ the NAC-approved HCl values [Mouse RD_{50} (Barrow *et al.*, 1977); Histopathology in rats (Stavert *et al.*, 1991)]
AEGL–3 (Lethal)	170 (810)	57 (270)	28 (130)	7.1 (34)	3.5 (17)	⅓ the 1-hour boron trichloride LC_{50} value of 2,541 ppm in male rats (Vernot *et al.*, 1977)

ii. *References.*

a. ASTM. (American Society for Testing and Materials). 1991. Standard Test Method for estimating sensory irritancy of airborne chemicals. Method E981, Vol. 11.04, pp. 610–619. Philadelphia, PA.

b. Barrow, C.S., Alarie, Y., Warrick, M., and Stock, M.F. 1977. Comparison of the sensory irritation response in mice to chlorine and hydrogen chloride. *Archives of Environmental Health*. Vol. 32:68–76.

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f. ten Berge, W.F. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. *Journal of Hazardous Materials*. Vol. 13:301–309.

g. USEPA (Environmental Protection Agency). 2000. Acute exposure guideline levels (AEGLs) for hydrogen chloride (NAC/Proposed Draft 1: 5/2000).

h. 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. *Toxicology and Applied Pharmacology*. Vol. 42:417–423.

17. *Diborane*—i. *Description.* Diborane a highly unstable gas, and is combustible upon exposure to moist air or high heat. It rapidly hydrolyzes in water to produce boric acid, hydrogen, and heat. Because of its strong reducing character, it has many industrial uses such as a rubber vulcanizer, a catalyst for olefin polymerization, an intermediate in the production of other boron hydrides, and as a doping gas in the semiconductor industry. Diborane was also investigated in the 1950's as a potential rocket fuel.

Data on acute exposures of humans to diborane were limited to case reports of accidental work-related exposures. Signs and symptoms of exposure included chest tightness, shortness of breath and dyspnea, wheezing, nonproductive cough, and precordial pain. Workers exposed to diborane generally experienced a complete recovery of symptoms within a short period following exposure. No quantitative information was given regarding the exposure terms of these individuals, and the data were therefore unsuitable for derivation of AEGLs. No reports of death were found in the literature.

Data on lethal and sublethal effects of diborane were available for several animal species, including dogs, rats, mice, hamsters, rabbits, and guinea pigs. Fifteen-minute LC_{50} values in rats ranged from 159–182 ppm, and 4-hour LC_{50} values ranged from 40–80 ppm in rats and 29–31.5 ppm in mice. Animals exposed to lethal and sublethal concentrations developed pulmonary hemorrhages, congestion, and edema, and death was related to these severe pulmonary changes. Recent studies in rats and mice have also uncovered the development of multi-focal and/or diffuse inflammatory epithelial degeneration in the bronchioles following exposure to diborane. These pulmonary changes produced by exposure to sublethal concentrations were completely reversible in rats by two weeks after an acute exposure, and were being repaired in the mouse by 2 weeks post-exposure. The signs of toxicity and repair of pulmonary lesions following acute exposure to sublethal concentrations in animals were similar

to the human case reports. It is likely that the mechanism of toxicity is due to direct interaction of diborane with cellular components, especially since diborane is such a potent reducer. There appears to be a similar mechanism of toxicity between species because the cause of death from diborane exposure has always been from pulmonary damage, including edema, hemorrhage, and congestion. Mice appeared to be the more sensitive species, and the mice data were therefore used for the derivations of AEGLs.

An AEGL–1 value was not derived because it was not appropriate. The AEGL–2 value is below the odor threshold of diborane and no other data pertaining to endpoints relevant to AEGL–1 definition were available.

The AEGL–2 values were based on a LOAEL (lowest-observed-adverse-effect level) for pulmonary changes in male ICR mice following acute inhalation exposure to diborane. No effects were observed in mice exposed to 5 ppm for 1 hour, while exposure to 5 ppm for 2 hours resulted in 4/10 mice developing multi-focal and/or diffuse inflammatory epithelial degeneration in the bronchioles (Nomiyama *et al.*, 1995). There were no other treatment related changes, such as changes in behavior or appearance, body or organ weight, or in hematological or clinical chemistry indices.

The AEGL–3 values were based on the estimate a 4-hour LC_{01} of 9.2 ppm obtained by probit analysis of data from a 4-hour LC_{50} study in male ICR mice (Uemura *et al.*, 1995).

A total UF of 10 was applied to the AEGL–2 and AEGL–3 values. An interspecies UF of 3 was applied because the most sensitive species, the mouse, was used, and the endpoint of toxicity, histological changes in the lungs, was the most sensitive endpoint. Further support of a value of 3 is that signs of toxicity and repair of pulmonary lesions following acute exposure to sublethal concentrations in animals were similar to the human case reports. It is likely that the mechanism of toxicity is due to direct interaction of diborane with cellular components, especially since diborane is such a potent reducer. There appears to be a similar mechanism of toxicity between species because the cause of death from diborane exposure has always been from pulmonary damage, including edema, hemorrhage, and congestion. An intraspecies factor of 3 was applied because the mechanism of action is not expected to differ greatly among individuals. The lung remained the target organ at all concentrations of exposure, and the biological response remained the same, becoming more severe with increasing concentration until death occurred from anoxia as a consequence of severe pulmonary changes.

The derived AEGL values were scaled to 10-minute, 30-minute, 1-hour, 4-hour, and 8-hour exposures using $C^n \times t = k$. To calculate n for diborane, a regression plot of the effective concentration (EC_{50}) values was derived from the studies by Nomiyama *et al.* (1995) and Uemura *et al.* (1995) investigating 1-, 2-, and 4-hour exposures to 1, 5, or 15 ppm diborane, with multi-focal and/or diffuse inflammatory epithelial degeneration in the bronchioles as the endpoint of toxicity. From the regression analysis, the derived value of n = 1 was used in the temporal scaling of all the AEGL values ($C^1 \times t = k$; Haber's Law). For the AEGL–3, the 30-minute value was flat-lined for the 10-minute value because it was considered too precarious to extrapolate from the exposure duration of 4 hours to 10 minutes. Although it is considered appropriate to extrapolate from a 2-hour exposure to a 10-minute exposure duration in the AEGL–2 derivation, the 10-minute value of 6.0 ppm would approach that of the 10-minute AEGL–3 value of 7.3 ppm. Therefore, the 30-minute AEGL–2 value was flat-lined for the 10-minute value.

The calculated values are listed in Table 15 below:

TABLE 15.—SUMMARY OF PROPOSED AEGL VALUES FOR DIBORANE [PPM (MG/M^3)]

Classification	10-Minutes	30-Minutes	1-Hour	4-Hours	8-Hours	Endpoint (Reference)
AEGL–1 (Nondisabling)	Not recommended (NR)[a]	NR	NR	NR	NR	Not recommended because proposed AEGL–2 value is below the odor threshold, and no other data pertaining to endpoints relevant to the AEGL–1 definition were available
AEGL–2 (Disabling)	6.0 (6.6)	2.0 (2.2)	1.0 (1.1)	0.25 (0.28)	0.13 (0.14)	LOAEL for pulmonary changes in male ICR mice; 5 ppm for 2 hour (Nomiyama *et al.*, 1995)
AEGL–3 (Lethality)	7.3 (8.0)	7.3 (8.0)	3.7 (4.1)	0.92 (1.0)	0.46 (0.51)	4-hour LC_{01} of 9.2 ppm estimated from a 4-hour LC_{50} in male ICR mice (Uemura *et al.*, 1995)

[a] Absence of an AEGL–1 does not imply that exposure below the AEGL–2 is without adverse effects.

ii. *References.*

a. Nomiyama, T., Omae, K., Uemura, T., Nakashima, H., Takebayashi, T., Ishizuka, C., Yamazaki, K., and Sakurai, H. 1995. No-observed-effect level of diborane on the respiratory organs of male mice in acute and subacute inhalation experiments. *Journal of Occupational Health.* Vol. 37:157–160.

b. Uemura, T., Omae, K., Nakashima, H., Sakurai, H., Yamazaki, K., Shibata, T., Mori, K., Kudo, M., Kanoh, H., and Tati, M. 1995. Acute and subacute inhalation toxicity of diborane in male ICR mice. *Archives of Toxicology.* Vol. 69:397–404.

18. *Nerve Agent VX*—i. *Description.* Nerve agent VX [*O*-ethyl-*S*-(isopropylaminoethyl) methyl phosphonothiolate] is a toxic ester derivative of phosphonic acid containing a sulfur substituent group, and is commonly termed a ''nerve'' agent as a consequence of its anticholinesterase properties. Agent VX was developed as a chemical warfare agent, and shares many of the same properties as the G-series nerve agents (GA, GB, GD, and GF).

Agent VX is a amber-colored liquid with a molecular weight of 267.38; it has a vapor density of 9.2 (air = 1) and a liquid density of 1.006 gram/milliter (g/ml) at 20° C; its water solubility is 3 g per 100 g at 25° C and 7.5 g per 100 g at 15° C. Agent VX was deliberately formulated to possess a low volatility (10.5 mg/m^3 at 25° C), and is approximately 2,000 times less volatile

than nerve agent GB (DA, 1990). As a consequence, agent VX is a persistent, ''terrain denial'' military compound with the potential to off-gas toxic concentrations for days following surface application.

Toxic effects may occur at concentrations below those of odor detection.

Exposure to acutely toxic concentrations of agent VX can result in excessive bronchial, salivary, ocular, and intestinal secretion, sweating, miosis, bronchospasm, intestinal hypermotility, bradycardia, muscle fasciculations, twitching, weakness, paralysis, loss of consciousness, convulsions, depression of the central respiratory drive, and death (Dunn and Sidell, 1989). Minimal effects observed at low vapor concentrations include miosis (pinpointing of the pupils of the eye, with subsequent decrease in pupil area), tightness of the chest, rhinorrhea, and dyspnea.

There is at present no evidence to indicate that asymptomatic exposures to agent VX result in chronic neurological disorders. However, a major concern associated with symptomatic exposures to anticholinesterase compounds such as agent VX is the possibility of chronic neurological effects. No human data exist for evaluating the potential of agent VX for inducing chronic neurological effects following acute symptomatic exposures.

Animal studies have shown that exposures to agent VX have not caused reproductive or developmental effects. Agent VX was not found to be genotoxic in a series of microbial and mammalian assays, and there is no evidence indicating that VX is carcinogenic.

Animals exposed to acutely toxic concentrations of agent VX exhibit the same signs of toxicity as humans, including miosis, salivation, and tremors. In a short-term inhalation toxicity study, no signs of toxicity, except miosis, were observed in rats, mice, guinea pigs, or rabbits exposed to VX vapor concentrations of 0.0002 mg/m^3 or less (6 hours/day, 5 days/week, for 2 weeks) (Crook *et al.*, 1983).

Insufficient data are available from which to derive AEGL values for VX from human or animal inhalation toxicity studies. The few studies available are historical, and are considered nonverifiable due to flawed study design, poor sampling techniques, or suspect contamination of sampling and detection apparatus. Nevertheless, available literature clearly indicates that inhibition of cholinesterase activity is a common mechanism of toxicity shared by the G-series nerve agents and nerve agent VX. Thus, it was possible to develop AEGL estimates for agent VX by a comparative method of relative potency analysis from the more complete data set for nerve agent GB. This approach has been previously applied in the estimation of nerve agent exposure limits, most recently by Reutter *et al.* (2000). Available literature indicates that Agent VX is considered approximately 12 times more potent than agent GB (Callaway and Dirnhuber, 1971).

All mammalian toxicity endpoints observed in the data set for nerve agent VX as well as the G-series agents represent different points on the response continuum for anticholinesterase effects. Further, the mechanism of mammalian toxicity (cholinesterase inhibition) is the same for all nerve agents. As a consequence, the experimentally derived n = 2 from the Mioduszewski *et al.* (2000a, b) rat lethality data set for agent GB is here used as the scaling function for the agent VX AEGL–1, AEGL–2, and AEGL–3 derivations rather than a default value.

Under comparable conditions of exposure, the current analysis finds that agent VX has a potency to cause miosis and other transient effects approximately 12 times greater than that of agent GB. The AEGL–1 values for agent GB were derived from a study of human subjects in which minimal effects occurred following a 20-minute exposure to a GB vapor concentration of 0.05 mg/m^3 (Harvey, 1952; Johns, 1952). These findings are based on the results of low-concentration nerve agent exposures to informed volunteers who were under clinical supervision during the periods of exposure as well as for post-exposure periods of several months.

The AEGL–2 values for agent GB were derived from a study of human subjects in which miosis, dyspnea, photophobia, inhibition of red blood cell cholinesterase (RBC-ChE) to approximately 60% of individual baseline, and small but measurable changes in SFEMG of the forearm occurred following a 30-minute exposure to 0.5 mg GB/m^3 (Baker and Sedgwick, 1996). This recent study was performed under Helsinki accords and clinical supervision, and was conducted with the cooperation of fully informed human subjects.

The fact that AEGL–1 and AEGL–2 analyses for agent VX are based on data from human volunteers (Harvey, 1952; Johns 1952; Baker and Sedgwick, 1996; GB vapor exposure to clinically supervised human volunteers) precludes the use of an interspecies UF. To accommodate known variation in human cholinesterase activity that may make some individuals more susceptible to the effects of cholinesterase inhibitors such as nerve agents, a factor of 10 was applied for intraspecies variability (protection of susceptible populations). With application of a modifying factor of 3 for the incomplete VX data set, the total UF for estimating AEGL–1 and AEGL–2 values for agent VX is 30.

The SFEMG effects noted in the study chosen for estimation of AEGL–2 values were not clinically significant, and were not detectable after 15–30 months. Baker and Sedgwick (1996) considered SFEMG changes to be a possible early indicator or precursor of the nondepolarising neuromuscular block found associated with Intermediate Syndrome paralysis in severe organophosphorous insecticide poisoning cases. The Baker and Sedgwick (1996) study concluded that these electromyographic changes were persistent (>15 months), but that they were reversible and subclinical. While not considered debilitating or permanent effects in themselves, SFEMG changes are here considered an early indicator of exposures that could potentially result in more significant effects. Selection of this effect as a protective definition of an AEGL–2 level is considered appropriate given the steep dose-response toxicity curve of nerve agents.

Insufficient data are available to directly derive an AEGL–3 for agent VX. The AEGL–3 values for agent VX were indirectly derived from the AEGL–3 values for GB using a relative potency approach in which agent VX is considered 12 times more potent than agent GB for lethality. As a result, AEGL–3 values for agent VX were derived from recent inhalation studies in which the lethality of GB to female Sprague-Dawley rats was evaluated for the time periods of 10, 30, 60, 90, 240, and 360 minutes (Mioduszewski *et al.*, 2000a, b). Both experimental LC_{01} and LC_{50} values were evaluated. The use of a rat data set resulted in selection of an interspecies UF of 3; the full default value of 10 was not considered appropriate for the interspecies UF since the mechanism of toxicity in both laboratory rodents and humans is cholinesterase inhibition. To accommodate known variation in human cholinesterase activity, the full default value of 10 for intraspecies uncertainty was considered necessary to protect susceptible populations. With the additional application of a modifying factor of 3 for the incomplete VX data set, the total UF for AEGL–3 determination for agent VX is equal to 100.

The NAC noted that an earlier report by the National Research Council (NRC) (NRC, 1997) included an evaluation of the same VX toxicity data base, and had recommended at that time that additional research was needed to more fully characterize the toxicity of VX vapor. The NAC further notes that such studies could be limited and should specifically focus on obtaining data that would reduce uncertainties regarding the relative potency between agents GB and VX, or the potency of agent VX, for critical effects such as miosis, rhinorrhea, and lethality. To acknowledge the significant gaps in the data base for this nerve agent, the NAC considers the proposed AEGL values to be temporary in nature and subject to re-evaluation in 3 years.

The calculated values are listed in Table 16 below:

TABLE 16.—SUMMARY OF PROPOSED TEMPORARY AEGL VALUES[A] FOR AGENT VX [PPM (MG/M^3)][B]

Classification	10-Minutes	30-Minutes	1-Hour	4-Hours	8-Hours	Endpoint (Reference)
AEGL–1 (Non-disabling)	0.000018 ppm (0.00020 mg/m^3)	0.000010 ppm (0.00011 mg/m^3)	0.0000073 ppm (0.000080 mg/m^3)	0.0000037 ppm (0.000040 mg/m^3)	0.0000026 ppm (0.000028 mg/m^3)	Derived by relative potency from study of multiple minimal effects in human volunteers exposed to 0.05 mg/m^3 GB vapor for 20 minutes; headache, eye pain, rhinorrhea, tightness in chest, cramps, nausea, malaise, miosis (Harvey, 1952; Johns, 1952)[c]
AEGL–2 (Disabling)	0.00022 ppm (0.0024 mg/m^3)	0.00013 ppm (0.0014 mg/m^3)	0.000090 ppm (0.00098 mg/m^3)	0.000045 ppm (0.00049 mg/m^3)	0.000032 ppm (0.00035 mg/m^3)	Derived by relative potency from study of GB vapor exposure to exercising human volunteers exposed to 0.5 mg/m^3 for 30 minutes; miosis, dyspnea, inhibition of RBC-ChE changes in SFEMG (Baker and Sedgwick, 1996)[d]
AEGL–3 (Lethal)	0.00088 ppm (0.0096 mg/m^3)	0.00045 ppm (0.0049 mg/m^3)	0.00030 ppm (0.0033 mg/m^3)	0.00016 ppm (0.0017 mg/m^3)	0.00012 ppm (0.0013 mg/m^3)	Derived by relative potency from experimental Sprague-Dawley rat lethality data (LC_{01} and LC_{50}); whole-body dynamic exposure to GB vapor concentrations between 2–56 mg/m^3 for 3, 10, 30, 60, 90, 240, and 360 minutes (Mioduszewski *et al.*, 2000a, b)[e]

[a] Percutaneous absorption of VX vapor is known to be an effective route of exposure; nevertheless, percutaneous vapor concentrations needed to produce similar adverse effects are greater than inhalation vapor concentrations by an approximate factor of 10. Thus, the AEGL values presented in this table are considered protective for both routes of exposure.

[b] Agent VX is considered approximately 12 times more potent than agent GB. (see section 4.3, and Callaway and Dirnhuber, 1971).

[c] Derived from multiple minimal effects noted in human volunteers exposed to agent GB vapor at 0.05 mg-min/m^3 for 20 minutes (Harvey, 1952; Johns, 1952). VX concentration to achieve same endpoint estimated by relative potency comparison presented in footnote ''b'' in this table.

[d] Derived from transient effects noted in exercising human volunteers exposed to agent GB vapor at 0.5 mg-min/m^3 for 30 minutes (Baker and Sedgwick, 1996). VX concentration to achieve same endpoint estimated by relative potency comparison presented in footnote ''b'' in this table.

[e] Derived from LC_{01} values for female Sprague-Dawley rats exposed to GB vapor in dynamic exposure chamber (Mioduszewski *et al.*, 2000a, b). VX concentrations to achieve same endpoint estimated by relative potency comparison presented in footnote ''b'' in this table.

ii. *References.*

a. Baker, D.J. and Sedgwick, E.M. 1996. Single fibre electromyographic changes in man after organophosphate exposure. *Human and Experimental Toxicology*. Vol. 15:369–375.

b. Callaway, S. and Dirnhuber, P. 1971. Estimation of the concentration of nerve agent vapour required to produce measured degrees of miosis in rabbit and human eyes. Technical Paper No. 64 Chemical Defence Establishment, Porton Down, Salisbury, Wilts., UK

c. Crook, J.W., Hott, P., and Owens, E.J., *et al.* 1983. The effects of subacute exposures of the mouse, rat, guinea pig, and rabbit, to low-level VX concentrations. U.S. Army Armament Research and Development Command, Chemical Systems Laboratory, Technical Report ARCSL-TR-82038, Aberdeen Proving Ground, MD.

d. DA (U.S. Department of the Army). 1990. Potential military chemical/biological agents and compounds. Field Manual FM 3-9 (NAVFAC P-467, AFR 355-7), Headquarters, Department of the Army, Department of the Navy, Department of the Air Force, Washington, DC (December 12, 1990).

e. Dunn, M.A. and Sidell, F.R. 1989. Progress in the medical defense against nerve agents. *Journal of the American Medical Association*. Vol. 262:649–652.

f. Harvey, J.C. 1952. Clinical observations on volunteers exposed to concentrations of GB. Medical Laboratories Research Report No. 114, Publication Control No. 5030–114 (CMLRE-ML-52), MLCR 114. Army Chemical Center, Aberdeen Proving Ground, MD.

g. Johns, R.J. 1952. The effect of low concentrations of GB on the human eye. Research Report No. 100, Publication Control No. 5030–100 (CMLRE-ML-52). Chemical Corps Medical Laboratories, Army Chemical Center, Aberdeen Proving Ground, MD.

h. Mioduszewski, R.J., Manthei, J., Way, R., Burnett, D., Gaviola, B., Muse, W., Crosier, R., and Sommerville, D. 2000a. Estimating the probability of sarin vapor toxicity in rats as a function of exposure concentration and duration. Presented at the 39th Annual Meeting of the Society of Toxicology, March, 2000. Philadelphia, PA. *Toxicologist*. Vol. 54(1):18 (#84).

i. Mioduszewski, R.J., Manthei, J., Way, R., Burnett, D., Gaviola, B. Muse, W., Thomson, S., Sommerville, D., and Crosier, R. 2000b. Estimating the probability of sarin vapor toxicity in rats as a function of exposure concentration and duration. Proceedings of the International Chemical Weapons Demilitarization Conference (CWD-2000). The Hague, NL (May 21–24, 2000).

j. NRC. 1997. Review of the acute human-toxicity estimates for selected chemical warfare agents. Committee on Toxicology, Subcommittee on Toxicity Values for Selected Nerve Agents and Vesicant Agents. National Academy Press, Washington, DC.

k. Reutter, S.A., Mioduszewski, R.J., and Thomson, S.A. 2000. Evaluation of airborne exposure limits for VX: worker and general population exposure criteria. ECBC-TR-074. Edgewood Chemical Biological Center, U.S. Army Soldier and Biological Chemical Command, Aberdeen Proving Ground, MD.

IV. Next Steps

The NAC/AEGL Committee plans to publish ''Proposed'' AEGL values for five-exposure periods for other chemicals on the priority list of 85 in groups of approximately 10 to 20 chemicals in future **Federal Register** notices during the calendar year 2001.

The NAC/AEGL Committee will review and consider all public comments received on this notice, with revisions to the ''Proposed'' AEGL values as appropriate. The resulting AEGL values will be established as ''Interim'' AEGLs and will be forwarded to the NRC/NAS, for review and comment. The ''Final'' AEGLs will be published under the auspices of the NRC/NAS following concurrence on the values and the scientific rationale used in their development.

List of Subjects

Environmental protection, Hazardous substances.

Dated: April 23, 2001.

Stephen L. Johnson,

Acting Assistant Administrator for Prevention, Pesticides and Toxic Substances.

[FR Doc. 01–11001 Filed 5–1–01; 8:45 am]

BILLING CODE 6560–50–S

ENVIRONMENTAL PROTECTION AGENCY

[OPPTS–140289; FRL–6777–5]

Access to Confidential Business Information by GEOMET Technologies

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: EPA has authorized Versar, Incorporated's (Versar) wholley owned subsidiary GEOMET Technologies, Incorporated (GEOMET) of Germantown, MD access to information which has been submitted to EPA under sections 4, 5, 6, and 8 of the Toxic Substances Control Act (TSCA). Some of the information may be claimed or determined to be confidential business information (CBI).

DATES: Access to the confidential data will occur no sooner than May 7, 2001.

FOR FURTHER INFORMATION CONTACT: Barbara A. Cunningham, Acting Director, Environmental Assistance Division (7408), Office of Pollution Prevention and Toxics, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460; telephone number: (202) 554–1404; e-mail address: TSCA-Hotline@epamail.epa.gov.

SUPPLEMENTARY INFORMATION:

I. Does this Notice Apply to Me?

This action is directed to the public in general. This action may, however, be of interest to ''those persons who are or may be required to conduct testing of chemical substances under the Toxic Substances Control Act (TSCA).'' Since other entities may also be interested, the Agency has not attempted to describe all the specific entities that may be affected by this action. If you have any questions regarding the applicability of this action to a particular entity, consult the technical person listed under **FOR FURTHER INFORMATION CONTACT.**

II. How Can I Get Additional Information, Including Copies of this Document or Other Related Documents?

You may obtain electronic copies of this document, and certain other related documents that might be available electronically, from the EPA Internet Home Page at http://www.epa.gov/. To access this document, on the Home Page select ''Laws and Regulations,'' ''Regulations and Proposed Rules,'' and then look up the entry for this document under the ''**Federal Register**—Environmental Documents.'' You can also go directly to the **Federal Register** listings at http://www.epa.gov/fedrgstr/.

III. What Action is the Agency Taking?

Under contract number 68–W–99–041, Versar's subsidiary, GEOMET of 20251 Century Boulevard, Germantown, MD, will assist the Office of Pollution Prevention and Toxics (OPPTS) providing exposure assessments for new and existing chemicals.

In accordance with 40 CFR 2.306(j), EPA has determined that under EPA contract number 68–W–99–041, GEOMET will require access to CBI submitted to EPA under sections 4, 5, 6, and 8 of TSCA to perform successfully the duties specified under the contract.

GEOMET personnel will be given access to information submitted to EPA under sections 4, 5, 6, and 8 of TSCA. Some of the information may be claimed or determined to be CBI.

EPA is issuing this notice to inform all submitters of information under sections 4, 5, 6, and 8 of TSCA that the Agency may provide GEOMET access to these CBI materials on a need-to-know basis only. All access to TSCA CBI under this contract will take place at EPA Headquarters and at the Versar site located at 6850 Versar Center, Springfield, VA.

GEOMET will be required to adhere to all provisions of EPA's *TSCA Confidential Business Information Security Manual.*

Clearance for access to TSCA CBI under this contract may continue until April 30, 2004.

GEOMET personnel will be required to sign nondisclosure agreements and will be briefed on appropriate security procedures before they are permitted access to TSCA CBI.

List of Subjects

Environmental protection, Confidential business information.

Dated: April 19, 2001.

Deborah A. Williams,

Acting Director, Information Management Division, Office of Pollution Prevention and Toxics.

[FR Doc. 01–10999 Filed 5–1–01; 8:45 am]

BILLING CODE 6560–50–S

ENVIRONMENTAL PROTECTION AGENCY

[OPP–34171B; FRL–6770–9]

Ethyl Parathion; Receipt of Request For Registration Cancellations and Amendments

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: In accordance with section 6(f)(1) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended, EPA is issuing a notice of receipt of request by a number of registrants, including Cheminova, Inc. and Cheminova A/S, for the following actions: to immediately cancel the registrations for their manufacturing use products containing O, O-Diethyl-O-p-nitrophenyl thiophosphate (ethyl parathion), to immediately cancel the use on corn grown for seed by amending their ethyl parathion end-use product registrations; and to cancel all of their ethyl parathion end-use products effective as of December 31, 2002. EPA will decide whether to approve the requests after consideration of public comment.

DATE: Comments on the requested cancellation of product and use registrations must be submitted to the address provided below by June 1, 2001.