ENVIRONMENTAL PROTECTION AGENCY

[OPPTS–00289; FRL–6492–4]

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

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice and request for comments.

SUMMARY: The National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) is developing AEGL values on an ongoing basis to provide Federal, State, and local agencies with information on short-term exposures to hazardous chemicals. This notice provides ''Proposed'' AEGL values and Executive Summaries for 10 chemicals for public review and comment. Comments are welcome on both the ''Proposed'' AEGL values in this notice and the Technical Support Documents placed in the public version of the official record in the TSCA Docket for these 10 chemicals.

DATES: Comments, identified by the docket control number OPPTS–00289, must be received by EPA on or before April 14, 2000.

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–00289 in the subject line on the first page of your response.

FOR FURTHER INFORMATION CONTACT: *For general information contact:* Joseph S. Carra, Deputy Director, Office of Pollution Prevention and Toxics (7401), Environmental Protection Agency, Ariel Rios Bldg., 1200 Pennsylvania Ave., NW., Washington, DC 20460; telephone numbers: (202) 554–1404 and TDD: (202) 554–055; e-mail address: TSCA-Hotline@epa.gov.

For technical information contact: Paul S. Tobin, Designated Federal Officer (DFO), Office of Pollution Prevention and Toxics (7406), Environmental Protection Agency, Ariel Rios Bldg., 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'' 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–00289. 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*. Using a faxphone call (202) 401–0527 and select item 4800 for an index of items in this category. For a more specific item number, see the table in Unit III.

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–00289 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, Ariel Rios Bldg., 1200 Pennsylvania Ave., NW., Washington, DC 20460.

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 number OPPTS-00289. 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 prior notice. If you have any questions about CBI or the procedures for claiming CBI, please consult the technical person identified 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 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 proposed rule or collection activity.

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

Since its first meeting on June 19–21, 1996, the NAC/AEGL Committee has been evaluating scientific data and developing ''Proposed'' AEGLs for 76 of the first 85 priority chemicals initially scheduled for development of AEGL values. This first list of 85 chemicals was published in the **Federal Register** of May 21, 1997 (62 FR 27733–27734) (FRL–5718–9). EPA published the first ''Proposed'' AEGL values for 12 chemicals from the initial priority list in the **Federal Register** of October 30, 1997 (62 FR 58839–58851) (FRL–5737–3) in order to provide an opportunity for public review and comment. That **Federal Register** notice also provides the AEGL Program's history and development process. Since then, the NAC/AEGL Committee continues to develop AEGL values for other chemicals from the initial priority list and continues to establish greater consistency in the procedures and methodologies used in their development. Additionally, the NAC/AEGL Committee has expanded the number of exposure periods to include AEGL values for 10 minute exposure periods to cover a wider range of potential exposures to hazarous chemicals. The NAC/AEGL Committee plans to publish ''Proposed'' AEGL values for 10 minute exposure periods for other chemicals on the priority list of 85 in groups of approximately 10 to 20 chemicals in future **Federal Register** notices.

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'' AEGL values and will be forwarded to the National Research Council, National Academy of Sciences (NRC/NAS), for review and comment. The ''Final'' AEGL values will be published under the auspices of the NRC/NAS following concurrence on the values and the scientific rationale used in their development.

III. 10 Chemicals for Public Notice and Comment

A. Fax-On-Demand Table

CAS No.	Chemical name	Fax-On-Demand item no.
71–55–6	1,1,1-Trichloroethane	4937
74–90–8	Hydrogen cyanide	4858
156–59–2	*Cis-1,2-Dichloroethylene*	4895
156–60–5	*Trans-1,2-Dichloroethylene*	4895
505–60–2	Agent HD (sulfur mustard)	4936
811–97–2	HFC–134a (1,1,1,2-tetrafluoroethane)	4899
1717–00–6	HCFC–141b (1,1-dichloro-1-fluoroethane)	4902
7664–39–3	Hydrogen fluoride	4909
7783–06–4	Hydrogen sulfide	4917
106602–80–6	Otto Fuel II (main component propylene glycol dinitrate; CAS No. 6423–43–4)	4935

B. Executive Summaries

1. *Cis-1,2-Dichloroethylene* and 2. *Trans-1,2-Dichloroethylene*—i. *Description.* 1,2-Dichloroethylene is a flammable, colorless liquid existing in both *cis*- and *trans*-forms and as a mixture of these two isomers. It has been used as an intermediate in the production of chlorinated solvents and as a low-temperature extraction solvent for decaffeinated coffee, dyes, perfumes, lacquers, and thermoplastics. The compound is a narcotic. Data on narcosis in humans, cats, rats, and mice, and systemic effects in cats, rats, and mice were available for development of AEGLs. The data were considered adequate for derivation of the three AEGL classifications.

The AEGL-1 was based on a human exposure concentration of 825 parts per million (ppm) *trans*-1,2-dichloroethene for 5 minutes (Lehmann and Schmidt-Kehl 1936). This concentration is a no-effect-level for eye irritation. Because the mechanism of irritation is not expected to differ greatly among individuals (including sensitive individuals), this value was divided by an uncertainty factor (UF) of 3 to protect sensitive individuals. This UF of 3 was applied for AEGL-1 values for both the *cis*- and *trans*-isomers. Since animal data suggest that the *cis*-isomer is approximately twice as toxic as the *trans*-isomer, a modifying factor of 2 was applied in the derivation of the *cis*-isomer values only. The same value was applied across the 10- and 30-minute and 1-, 4-, and 8-hour exposure time points since mild irritantancy is a threshold effect and generally does not vary greatly over time. Thus, prolonged exposure will not result in an enhanced effect.

The AEGL-2 for the 4- and 8-hour time points was based on narcosis observed in pregnant rats exposed to 6,000 ppm of the *trans*-isomer for 6 hours (Hurtt et al., 1993). Uncertainty factors of 3 each (total UF = 10) were applied for both inter- and intraspecies differences because the endpoint,

narcosis, is unlikely to vary greatly among individuals or species. This total UF of 10 was applied for AEGL-2 values for both the *cis*- and *trans*-isomers. The concentration-exposure 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 in the absence of an empirically derived chemical-specific scaling exponent, a conservative approach to temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation. The AEGL-2 for the 10- and 30-minute and 1-hour time points was set as a ceiling based on a plateau for anesthetic effects in humans (Lehman and Schmidt-Kehl, 1936). Since data suggest that the *cis*-isomer is approximately twice as toxic as the *trans*-isomer, a modifying factor of 2 was applied in the derivation of the *cis*-isomer values only.

The AEGL-3 for the 4- and 8-hour time points was based on a 4-hour no-effect-level for death in rats of 12,300 ppm *trans*-1,2-dichloroethene (Kelly, 1999). Uncertainty factors of 3 each (total UF = 10) were applied for both inter- and intraspecies differences. Rat and mouse lethality data indicate little species variability with regard to death. This total UF of 10 was applied for AEGL-3 values for both the *cis*- and *trans*-isomers. The concentration-exposure 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 in the absence of an empirically derived chemical-specific scaling exponent, a conservative approach to temporal scaling was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation. The AEGL-3 for the 10- and 30-minute and 1-hour time points was set as a ceiling based on a plateau for intracranial pressure, nausea, and severe dizziness in humans (Lehman and Schmidt-Kehl, 1936). Since data suggest that the *cis*-isomer is approximately twice as toxic as the *trans*-isomer, a modifying factor of 2 was applied in the derivation of the *cis*-isomer values only.

The calculated values are listed in the tables below.

SUMMARY OF PROPOSED AEGL VALUES FOR TRANS-1,2-DICHLOROETHENE [PPM (MG/M^3 (MILLIGRAM/METER^3)]

Classification	10-min.	30-min.	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	280 (1,109)	280 (1,109]	280 (1,109)	280 (1,109)	280 (1,109)	Ocular irritation in humans (Lehman and Schmidt-Kehl, 1936)
AEGL-2 (Disabling)	1,000 (3,960)	1,000 (3,960)	1,000 (3,960)	690 (2,724)	450 (1,782)	Narcosis in rats: 4- and 8-hour (Hurtt et al., 1993); Anesthetic effects in humans (Lehman and Schmidt-Kehl, 1936)
AEG L-3 (Lethality)	1,700 (6,732)	1,700 (6,732)	1,700 (6,732)	1,200 (4,752)	620 (2,455)	No-effect-level for death in rats: 4- and 8-hour (Kelly, 1999); Nausea, intracranial pressure, and dizziness in humans (Lehman and Schmidt-Kehl, 1936)

SUMMARY OF PROPOSED AEGL VALUES FOR CIS-1,2-DICHLOROETHENE [PPM (MG/M^3)]

Classification	10-min.	30-min.	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	140 (554)	140 (554)	140 (554)	140 (554)	140 (554)	Ocular irritation in humans (Lehman and Schmidt-Kehl, 1936)
AEGL-2 (Disabling)	500 (1,980)	500 (1,980)	500 (1,980)	340 (1,346)	230 (911)	Narcosis in rats: 4- and 8-hour (Hurtt et al., 1993); Anesthetic effects in humans (Lehman and Schmidt-Kehl, 1936)
AEGL-3 (Lethality)	850 (3,366)	850 (3,366)	850 (3,366)	620 (2,455)	310 (1,228)	No-effect-level for death in rats: 4- and 8-hour (Kelly, 1999); Nausea, intracranial pressure, and dizziness in humans (Lehman and Schmidt-Kehl, 1936)

ii. *References.*

Hurtt, M.E., Valentine, R., and Alvarez, L. 1993. Developmental toxicity of inhaled *trans*-1,2-dichloroethylene in the rat. *Fundamental and Applied Toxicology*. 20:225–230.

Kelly, D. P. 1999. *Trans*-1,2-dichloroethylene and *cis*-1,2-dichloroethylene: Inhalation median lethal concentration (LC_{50}) study in rats. E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE. Laboratory Project ID: DuPont–2806.

Lehman, K.B. and Schmidt-Kehl, L. 1936. The thirteen most important chlorinated aliphatic hydrocarbons from the standpoint of industrial hygiene. *Archiv Fuer Hygiene und Bakteriologie*. 116:9–268.

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

3. *Agent HD (sulfur mustard)*—i. *Description.* Sulfur mustard (Agent HD) is an alkylating chemical vesicant developed as a warfare agent that affects any epithelial surface it contacts. The active component is *bis*(2-chloroethyl)sulfide (CAS No. 505–60–2). Although the chemical is a liquid at ordinary ambient temperatures, its volatility results in rapid generation of vapors with a garlic-like odor. Due to its low aqueous solubility, it is persistent in the environment. Odor thresholds of 1 mg-min/m^3 (milligram-minute/meter) and 0.6 mg/m^3 have been reported.

Exposure to sulfur mustard vapor may result in irritation and damage to the eyes, respiratory tract, and skin. The toxic effects of sulfur mustard are temperature and humidity dependent; for a given exposure, the effects may be greater with increasing temperature and humidity. An exposure-dependent latency period of hours to days is documented for the toxic effects of sulfur mustard and is relevant for all routes of exposure but may be less for

ocular and upper respiratory tract effects than for dermal and systemic responses. Both human and animal data indicate that the eyes are the most sensitive organ/tissue although deaths resulting from sulfur mustard exposure are likely the result of respiratory tract involvement. Because the toxic effects of sulfur mustard (at least for short-time periods) appear to be a linear function of exposure duration and exposure concentration, most of the available exposure-response data are expressed as cumulative exposures (Ct).

Minor ocular irritation (conjunctival injection in the absence of irritation) is reported to occur in humans following exposures to 12–30 mg-min/m^3 and more severe effects at 60–75 mg-min/m^3 (conjunctivitis, irritation, photophobia) and 100 mg-min/m^3 (severe ocular irritation). Exposure estimates for human lethality range from 900–1,500 mg-min/m^3.

Animal lethality following acute exposure to sulfur mustard occurs at cumulative exposures ranging from approximately 600–1,500 mg-min/m^3. Nonlethal effects were similar to those observed in humans and included effects on the eyes, respiratory tract, and skin. Long-term exposure of dogs, rats, and guinea pigs to concentrations of 0.03 mg/m^3 produced only minor signs of ocular and respiratory tract irritation. 1-hour exposure of mice to concentrations up to 16.9 mg/m^3 resulted in notable but not serious effects on respiratory parameters and acute exposures of rabbits (20 minutes to 12 hours) to concentrations ranging from 58–389 mg/m^3 (Ct ≥2,300 mg-min/m^3) resulted in severe respiratory tract damage.

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 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, 1986). Analysis of available data regarding AEGL-1 type effects reported by Reed (1918), Reed et al. (1918), Guild et al. (1941), and Anderson (1942) indicate that, for exposure periods up to several hours, the concentration-exposure time relationship is a near-linear function (i.e., Haber's Law where n = 1 for $C^n \times t = k$) as shown by n values of 1.11 and 0.96 for various data sets analyzed that were consistent with AEGL-1 effects. Therefore, an empirically derived, chemical-specific estimate of n = 1 was used for derivation of most of the AEGL values rather than a default value based upon the ten Berge (1986) analysis. Due to uncertainty regarding linear extrapolation to a time duration notably shorter than that for which empirically derived lethality data were available, the 10-minute AEGL-3 values utilized exponential time scaling where n was 3.

The AEGL-1 values were based upon data from Anderson (1942) who found that an exposure concentration-time product of 12 mg-min/m^3 represented a threshold for ocular effects (conjunctival injection and minor discomfort with no functional decrement) in human volunteers acutely exposed to sulfur mustard. An UF adjustment was limited to a factor of 3 for protection of sensitive individuals. This adjustment was considered appropriate for acute exposures to chemicals whose mechanism of action primarily involves surface contact irritation of ocular and/or respiratory tract tissue rather than systemic activity that involves absorption and distribution of the parent chemical or a biotransformation product to a target tissue. Anderson (1942) noted that there was little variability in the ocular responses among the subjects in his study, thereby providing additional justification for the intraspecies UF of 3.

The AEGL-2 values for sulfur mustard were also developed using the data from Anderson (1942). Anderson reported that a Ct value of approximately 60 mg-min/m^3 represented the lowest concentration-time product for which ocular effects could be characterized as military casualties. The 60 mg-min/m^3 exposure was used as the basis for developing the AEGL-2 values because it represented an acute exposure causing an effect severe enough to impair escape and, although not irreversible, would certainly result in potential for additional injury. Anderson (1942) characterized the 60 mg-min/m^3 Ct as representing the lower margin of the concentration-effect zone that would result in ineffective military performance (necessary to complete a mission), and that may require treatment for up to 1 week. The ocular irritation and damage were also considered appropriate as a threshold estimate for AEGL-2 effects because the eyes are generally considered the most sensitive indicator of sulfur mustard exposure and would likely occur in the absence of vesication effects and severe pulmonary effects. The fact that the AEGL-2 is based upon human data precludes the use of an interspecies UF. A factor of 3 was applied for intraspecies variability (protection of sensitive populations). This factor was limited to three under the assumption that the primary mechanism of action of sulfur mustard involves a direct effect on the ocular surface and that this response will not vary greatly among individuals. Anderson also noted little variability in the ocular responses among the subjects in his study. A modifying factor of 3 was applied to accommodate potential onset of long-term ocular or respiratory effects. This was justified by the fact that there was no long-term follow-up reported by Anderson with which to confirm or deny the development of permanent ocular or respiratory tract damage. The total uncertainty/modifying factor adjustment was 10 [The total adjustment is 10 because the factors of 3 each represent a logarithmic mean (3.16) of 10, therefore 3.16 x 3.16 = 10].

For development of the AEGL-3, a 1-hour exposure of mice to 21.2 mg/m^3 was used as an estimated lethality threshold (Kumar and Vijayaraghavan, 1998). This value is also near the lower bound of the 95% confidence interval for the 1-hour mouse LC_{50} of 42.5 mg/m^3 reported by Vijayaraghavan (1997). An UF for intraspecies variability of 3 was used because the lethality resulting from acute inhalation exposure to sulfur mustard appears to be a function of pulmonary damage resulting from direct contact of the agent with epithelial surfaces and would not likely exhibit an order-of-magnitude variability among individuals. An UF of 3 was also applied to account for possible interspecies variability in the lethal response to sulfur mustard. The resulting total UF adjustment was 10. The modifying factor of 3 utilized for AEGL-2 development to account for uncertainties regarding the latency and persistence of the irritant effects of low-level exposure to sulfur mustard was not applied for AEGL-3 because lethality of the mice was assessed at 14 days post exposure in a study by Vijayaraghavan (1997). Application of any additional UFs or modifying factors was not warranted because the proposed AEGL-3 values are equivalent to exposures in humans that are known to produce only ocular and respiratory tract irritation.

The AEGL values for sulfur mustard are based upon noncancer endpoints. Sulfur mustard is genotoxic and has induced carcinogenic responses in humans following single high exposures and following multiple exposures that were sufficient to produce adverse effects. Carcinogenic responses, however, are not known to occur with asymptomatic exposures. Limitations on the currently available data do not allow for a definitive quantitative cancer risk

assessment, especially for an acute, once-in-a-lifetime, exposure.

The AEGL-1 and AEGL-2 values are based upon human exposure data and are considered to be defensible estimates for exposures representing thresholds for the respective AEGL effect levels. The ocular irritation upon which the AEGL-1 and AEGL-2 values are based is the most sensitive response to sulfur mustard vapor. The AEGL-3 values provide Ct products (approximately 60–130 mg-min/m^3) that are known to cause only moderate to severe ocular irritation and possible respiratory tract irritation in human subjects but not life- threatening health effects or death. Although, the overall database for acute inhalation exposure to sulfur mustard is not extensive, the AEGL values appear to be supported by the available data and in some cases, similar values obtained using somewhat differing approaches.

SUMMARY OF PROPOSED AEGL VALUES FOR SULFUR MUSTARD [PPM (MG/M^3)]

Classification	10-min.	30-min.	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	0.06 (0.40)	0.02 (0.13)	0.01 (0.067)	0.003 (0.017)	0.001 (0.008)	Conjunctival injection and minor discomfort with no functional decrement in human volunteers (Anderson, 1942)
AEGL-2 (Disabling)	0.09 (0.60)	0.03 (0.20)	0.02 (0.10)	0.004 (0.025)	0.002 (0.013)	Well marked, generalized conjunctivitis, edema, photophobia, and eye irritation in human volunteers (Anderson, 1942)
AEGL-3 (Lethality)	0.91 (6.1)	0.63 (4.2)	0.32 (2.1)	0.08 (0.53)	0.04 (0.27)	Lethality estimate in mice (Kumar and Vijayaraghavan, 1998)

ii. *References.*

Anderson, J.S. 1942. The effect of mustard gas vapour on eyes under Indian hot weather conditions. CDRE Report No. 241. Chemical Defense Research Establishment (India).

Guild, W.J., Harrison, K.P., Fairly, A., and Childs, A.E. 1941. The effect of mustard gas vapour on the eyes. Porton Report No. 2297, Serial No. 12. November 8, 1941.

Kumar, O. and Vjayaraghavan, R. 1998. Effect of sulphur mustard inhalation exposure on some urinary variables in mice. *Journal of Applied Toxicology*. 18:257–259.

Reed, C.I. 1918. The minimum concentration of mustard gas effective for man. Preliminary Report. Report 318. War Department, Medical Division, Chemical Warfare Section, Pharmacological Research Section, American University Experiment Station. October 26, 1918.

Reed, C.I., Hopkins, E.F., and Weyand, C.F. 1918. The minimum concentration of mustard gas effective for man. Final Report. Report 329. War Department, Medical Division, Chemical Warfare Section, Pharmacological Research Section, American University Experiment Station. December 2, 1918.

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

Vijayaraghavan, R. 1997. Modifications of breathing pattern induced by inhaled sulphur mustard in mice. *Archives of Toxicology*. 71:157–164.

4. *HCFC-141b (1,1-dichloro-1-fluoroethane) or hydrochlorofluorocarbon-141b*—i. *Description.* 1,1-Dichloro-1-fluoroethane has been developed as a replacement for fully halogenated chlorofluorocarbons as its residence time in the atmosphere is shorter and its ozone depleting potential is lower than that of presently used chlorofluorocarbons. HCFC-141b may be used in the production of rigid polyurethane and polyisocyanurate or phenolic insulation foams for residential and commercial buildings. It may also be used as a solvent in electronic and other precision cleaning applications.

HCFC-141b is of low inhalation toxicity. Its effects have been studied with human subjects and several animal species including the monkey, dog, rat, mouse, and rabbit. In addition, studies addressing repeated and chronic exposures, genotoxicity, carcinogenicity, neurotoxicity, and cardiac sensitization were also available. At high concentrations, halogenated hydrocarbons may produce cardiac arrhythmias; this sensitive endpoint was considered in development of AEGL values.

Adequate data were available for development of the three AEGL classifications. Inadequate data were available for determination of the relationship between concentration and exposure duration for a fixed effect. However, based on the rapidity with which blood concentrations in humans approached equilibrium, the similarity in lethality values in rats exposed for 4 or 6 hours, and the fact that the cardiac sensitization effect is based on a concentration threshold rather than exposure duration, all AEGL values were flat-lined across time. The fact that some experimental exposure durations in both human and animal studies were generally long, 4 to 6 hours, lends confidence to flat-lining the values for the shorter exposure durations.

The AEGL-1 value was based on the observation that exercising human subjects could tolerate exposure to concentrations of 500 or 1,000 ppm for 4 hours with no effects on lung functions, respiratory symptoms, irritation of the eyes, or cardiac symptoms (Utell et al., 1997). Results of exposures of two subjects for an additional 2 hours to the 500 ppm concentration and one of the subjects to the 1,000 ppm concentration for an additional 2 hours did not indicate a clear effect on neurobehavioral parameters. Because the 4- or 6-hour 1,000 ppm concentration is a no-observed-effect-level (NOEL), there were no indications of response differences among tested subjects, and animal studies indicate that adverse effects occur only at considerably higher concentrations, the value was not adjusted by an UF to protect sensitive individuals. Because blood concentrations of HCFC-141b rapidly approached equilibrium and did not greatly increase after 55 minutes of exposure, the value of 1,000 ppm was used for all time periods.

The AEGL-2 value was based on the lowest concentration that caused cardiac sensitization in dogs exposed to HCFC-141b for 10 minutes (Mullin, 1977). This value of 5,200 ppm is far below the lowest concentrations that caused death from cardiac fibrillation (10,000 ppm in this study and 20,000 ppm in a similar study [Hardy et al., 1989a]). Because the cardiac sensitization test is supersensitive as the response to epinephrine is optimized (the epinephrine dose is greater than the physiological level in stressed animals by up to a factor of 10), a single

intraspecies UF of 3 was applied to protect sensitive individuals. Cardiac sensitization is concentration dependent; duration of exposure did not influence the concentration at which this effect occurred. Using the reasoning that the concentration is the determining factor in cardiac sensitization and exposure duration is of lesser importance, the resulting value of 1,700 ppm is proposed for all time periods.

The AEGL-3 values were based on the concentration of 9,000 ppm, the highest value that resulted in mild to marked cardiac responses but did not cause death in a cardiac sensitization study with the dog (Hardy et al., 1989a). Because the cardiac sensitization test is supersensitive as the response to epinephrine is optimized, a single intraspecies UF of 3 was applied to protect sensitive individuals. Using the reasoning that the concentration is the determining factor in cardiac sensitization and exposure duration is of lesser importance, the resulting value of 3,000 ppm is proposed for all time periods.

Based on the extensive database involving both human and animal exposures and use of the most sensitive endpoint in the studies, confidence in the AEGL values is high. Values are summarized in the table below.

SUMMARY TABLE OF PROPOSED AEGL VALUES FOR HCFC-141b (1,1-DICHLORO-1-FLUOROETHANE) [PPM (MG/M3)]

Classification	10-min.	30-min.	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	1,000 (4,850)	1,000 (4,850)	1,000 (4,850)	1,000 (4,850)	1,000 (4,850)	No effect-humans (Utell et al., 1997)
AEGL-2 (Disabling)	1,700 (8,245)	1,700 (8,245)	1,700 (8,245)	1,700 (8,245)	1,700 (8,245)	Threshold for cardiac arrhythmia—dog[1] (Mullin, 1977)
AEGL-3 (Lethality)	3,000 (14,550)	3,000 (14,550)	3,000 (14,550)	3,000 (14,550)	3,000 (14,550)	Threshold for severe cardiac response—dog[1] (Hardy et al., 1989a)

[1] Response to challenge dose of epinephrine (cardiac sensitization test).

ii. *References.*

Hardy, J.C., Sharman, I.J., and Chanter, D.O. 1989a. Assessment of cardiac sensitization potential in dogs and monkeys. Comparison of I–141b and F11. PWT 86/89437, Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England.

Mullin, L.S. 1977. Cardiac sensitisation. Haskell Laboratory Report 957–77, E.I. du Pont de Nemours and Co., Newark, DE.

Utell, M.J., Anders, M.W., and Morrow, P.E. 1997. Clinical inhalation studies with HCFC-141b. Final Report: December 4, 1997. MA–RR–97–2406, Departments of Medicine, Environmental Medicine, and Pharmacology and Physiology, University of Rochester Medical Center, Rochester, NY.

5. *HFC-134a (1,1,1,2-tetrafluoroethane) or hydrofluorocarbon-134a*—i. *Description.* 1,1,1,2-Tetrafluoroethane has been developed as a replacement for fully halogenated chlorofluorocarbons because its residence time in the atmosphere is shorter and its ozone depleting potential is insignificant. HFC-134a may be used in refrigeration and air conditioning systems, as a blowing agent for polyurethane foams, and as a propellant for medical aerosols. Yearly production is estimated at 175,000 tons.

HFC-134a has a very low acute inhalation toxicity. Its acute inhalation effects have been studied with human subjects and several animal species including the monkey, dog, rat, and mouse. In addition, studies addressing repeated and chronic exposures, genotoxicity, carcinogenicity, neurotoxicity, and cardiac sensitization were also available. At high concentrations, halogenated hydrocarbons may produce cardiac arrhythmias; this sensitive endpoint was considered in development of AEGL values.

Adequate data were available for development of the three AEGL classifications. Inadequate data were available for determination of the relationship between concentration and time for a fixed effect. Based on the observations that:

a. Blood concentrations in humans rapidly approach equilibrium with negligible metabolism and tissue uptake.

b. The endpoint of cardiac sensitization is a blood concentration-related threshold phenomenon, derived values for each AEGL classification were flat-lined across time.

The AEGL-1 concentration was based on a 1-hour no-effect concentration of 8,000 ppm in human subjects (Emmen and Hoogendijk, 1998). This concentration was without effects on lung functions, respiratory parameters, the eyes (irritation), or the heart (cardiac symptoms). Because this concentration is considerably below that causing any effect in animal studies, no intraspecies UF was applied. Based on the fact that blood concentrations in this study appeared to be approaching equilibrium following 55 minutes of exposure and effects are determined by blood concentrations, the value of 8,000 ppm was used across all time periods.

The AEGL-2 concentration was based on the no-effect concentration of 40,000 ppm for cardiac sensitization in dogs (Hardy et al., 1991). Because the cardiac sensitization test is supersensitive as the response to epinephrine is optimized (the epinephrine dose is greater than the physiological level in stressed animals by up to a factor of 10), a single intraspecies UF of 3 was applied to protect sensitive individuals. Cardiac sensitization is concentration dependent; duration of exposure does not influence the concentration at which this effect occurs. Using the reasoning that the concentration is the determining factor in cardiac sensitization and exposure duration is of lesser importance, the resulting value of 13,000 ppm is proposed for all time periods.

The AEGL-3 concentration was based on the concentration of 80,000 which caused marked cardiac effects but no deaths in dogs (Hardy et al., 1991). Because the cardiac sensitization test is supersensitive as the response to epinephrine is optimized (the epinephrine dose is greater than the physiological level in stressed animals by up to a factor of 10), a single intraspecies UF of 3 was applied to protect sensitive individuals. Cardiac sensitization is concentration dependent; duration of exposure does not influence the concentration at which this effect occurs. Using the reasoning that the concentration is the determining factor in cardiac sensitization and exposure duration is of lesser importance, the resulting value of 27,000 ppm is proposed for all time periods.

Based on the extensive database involving both human and animal

exposures and use of the most sensitive endpoint in the studies, confidence in the AEGL values is high. Values are summarized in the table below.

SUMMARY TABLE OF PROPOSED AEGL VALUES FOR HFC-134[a] (1,1,1,2-TETRAFLUOROETHANE) [PPM (MG/M^3)]

Classification	10-min.	30-min.	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	8,000 (34,000)	8,000 (34,000)	8,000 (34,000)	8,000 (34,000)	8,000 (34,000)	No effects—humans (Emmen and Hoogendijk, 1998)
AEGL-2 (Disabling)	13,000 (55,250)	13,000 (55,250)	13,000 (55,250)	13,000 (55,250)	13,000 (55,250)	No effect, cardiac sensitization—dogs (Hardy et al., 1991)
AEGL-3 (Lethality)	27,000 (114,750)	27,000 (114,750)	27,000 (114,750)	27,000 (114,750)	27,000 (114,750)	Marked effect, cardiac sensitization—dogs (Hardy et al., 1991)

ii. *References*.

Emmen, H.H. and Hoogendijk, E.M.G. 1998. Report on an ascending dose safety study comparing HFA-134a with CFC-12 and air, administered by whole-body exposure to healthy volunteers. MA–250B–82–306, TNO Report V98.754, The Netherlands Organization Nutrition and Food Research Institute, Zeist, The Netherlands.

Hardy, C.J., Sharman, I.J., and Clark, G.C. 1991. Assessment of cardiac sensitisation potential in dogs: Comparison of HFA 134a and A12. Report No. CTL/C/2521. Huntingdon Research Centre, Huntingdon, Cambridgeshire, U.K.

6. *Hydrogen cyanide (HCN)*—i. *Description*. Hydrogen cyanide is a colorless, rapidly acting, highly poisonous gas or liquid having an odor of bitter almonds. Most HCN is used as an intermediate at the site of production. Major uses include the manufacture of nylons, plastics, and fumigants; it is also used in electroplating and mining. Exposures to HCN may occur in industrial situations as well as from cigarette smoke, combustion products, and naturally occurring cyanide compounds in foods.

HCN is a systemic poison; toxicity is due to inhibition of cytochrome oxidase which prevents cellular utilization of oxygen. Lack of oxygen supply to the brain results in loss of consciousness, respiratory arrest, and, ultimately, death. Stimulation of the chemoreceptors of the carotid and aortic bodies produces a brief period of hyperpnea; cardiac irregularities may also occur. These mechanisms of action are the same for all species.

Inhalation studies resulting in sublethal effects such as incapacitation and changes in respiratory and cardiac parameters were described for the monkey, rat, and mouse; lethality studies were available for the rat, mouse, and rabbit. Exposure durations ranged from a few seconds to 24 hours. Regression analyses of the exposure duration-concentration relationships for both incapacitation and lethality for the monkey determined that the relationship is $C^2 \times t = k$ and that the relationship for lethality (based on rat data) is $C^{2.6} \times t = k$. Although human exposures have occurred, no reliable data on exposure concentrations were available.

The AEGL-1 was not determined because serious effects may occur at concentrations below those causing irritation or notable discomfort. In addition, the onset of serious effects is very rapid.

The AEGL-2 was based on a concentration of 60 ppm for 30 minutes which resulted in a slight depressive effect on the central nervous system of monkeys as evidenced by changes in electroencephalograms; there was no physiological response (Purser, 1984; Purser et al., 1984). The mechanism of action of HCN is the same for all mammalian species, but the rapidity of the toxic effect may be related to relative respiration rates as well as pharmacokinetic considerations. The monkey is an appropriate model for extrapolation to humans as the respiratory systems of monkeys and humans are similar. Because the monkey is an appropriate model and the mechanism of action of HCN is the same for all species, an interspecies UF of 2 was applied. Humans may differ in their sensitivity to HCN but no data regarding specific differences were located in the available literature. Therefore, an intraspecies UF of 3 was applied. The 30-minute concentration of 60 ppm was divided by a combined interspecies and intraspecies UF of 6 and scaled across time for the AEGL specified exposure periods using the relationship $C^2 \times t = k$. The safety of the 10- and 30-minute values are supported by monitoring studies in which concentrations of 10–15 ppm produced central nervous system effects in some workers.

The rat provided the only data set for calculation of LC_{01} values for different time periods (E.I. du Pont de Nemours and Company, 1981). The LC_{01} values were considered the threshold for lethality and were used as the basis for deriving AEGL-3 values. The mouse, rat, and rabbit were equally sensitive to the lethal effects of HCN as determined by similar LC_{50} values for the same time periods. In an earlier study, times to death for several animal species showed that mice and rats may be slightly more sensitive to HCN than monkeys (and presumably humans). The differences in sensitivity were attributed, at least partially, to the more rapid respiratory rate of the rodent species. Because LC_{50} values for several species were within a factor of 1.5 of each other, an interspecies UF of 2 was applied. Humans may differ in their sensitivity to HCN but no data regarding specific differences were located in the available literature. Therefore, an intraspecies UF of 3 was applied to protect sensitive individuals. The 15- and 30-minute and 1-hour LC_{01} values, 138, 127, and 88 ppm, respectively, were divided by a total UF of 6. The 15-minute value was time scaled to 10 minutes to derive the 10-minute AEGL-3, the 30-minute LC_{01} was used for the 30-minute AEGL-3 value, and the 60-minute LC_{01} was used to calculate the 1-, 4-, and 8-hour AEGL-3 concentrations. For the AEGL-3 values, scaling across time utilized the lethal concentration-exposure duration relationship for the rat, $C^{2.6} \times t = k$.

The proposed values appear in the table below.

SUMMARY OF PROPOSED AEGL VALUES FOR HYDROGEN CYANIDE [PPM (MG/M^3)]

Classification	10-min.	30-min.	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NA[1]	NA	NA	NA	NA	Serious effects may occur below detectable concentrations or concentrations causing discomfort
AEGL-2 (Disabling)	17 (19)	10 (11)	7.1 (7.8)	3.5 (3.9)	2.5 (2.8)	Slight central nervous system depression—monkey (Purser, 1984)
AEGL-3 (Lethality)	27 (30)	21 (23)	15 (17)	8.6 (9.7)	6.6 (7.3)	Lethality (LC_{01})—rat (E.I. du Pont de Nemours, 1981)

[1] Not appropriate.

ii. *References.*

E.I. du Pont de Nemours and Company. 1981. Inhalation Toxicity of Common Combustion Gases. Haskell Laboratory Report No. 238–81. Haskell Laboratory, Newark, DE.

Purser, D.A. 1984. A bioassay model for testing the incapacitating effects of exposure to combustion product atmospheres using cynomolgus monkeys. *Journal of Fire Sciences.* 2:20–36.

Purser, D.A., Grimshaw, P., and Berrill, K.R. 1984. Intoxication by cyanide in fires: A study in monkeys using polyacrylonitrile. *Archives of Environmental Health.* 39:394–400.

7. *Hydrogen fluoride (HF)*—i. *Description.* Hydrogen fluoride is a colorless, highly irritating and corrosive gas. Reaction with water is rapid, producing heat and hydrofluoric acid. Hydrogen fluoride is used in the manufacture of artificial cryolite; in the production of aluminum, fluorocarbons, and uranium hexafluoride; as a catalyst in alkylation processes in petroleum refining; in the manufacture of fluoride salts; and in stainless steel pickling operations. It is also used to etch glass and as a cleaner in metal finishing processes.

Hydrogen fluoride is a severe irritant to the eyes, skin, and nasal passages; high concentrations may penetrate to the lungs resulting in edema and hemorrhage. Data on irritant effects in humans and lethal and sublethal effects in six species of mammals (monkey, dog, rat, mouse, guinea pig, and rabbit) were available for development of AEGLs. The data were considered adequate for derivation of the three AEGL classifications for five exposure periods. Regression analyses of the reported concentration-exposure durations for lethality for the animal species determined that the relationship between concentration and time is $C^2 \times t = k$.

The AEGL-1 values were based on the observation that human volunteers could tolerate exposure to a concentration of 2 ppm for 6 hours with only mild irritation of the eyes, skin, and upper respiratory tract (Largent, 1960, 1961). This concentration was adjusted by an UF of 3 to protect sensitive individuals and scaled to the 30-minute and 1-, 4-, and 8-hour exposure durations using $C^2 \times t = k$. The factor of 3 was selected because hydrogen fluoride reacts chemically with the tissues of the respiratory tract; the adverse effects are unlikely to differ among individuals. The resulting derived values, 2.3, 1.6, 0.82, and 0.58 ppm, were rounded to the nearest whole integers of 2.0, 2.0, 1.0, and 1.0, respectively, by the NAC/AEGL Committee. Because irritant properties would not change greatly between the 10-minute and 30-minute time frames, the 10-minute AEGL-1 was set at the same value of 2.0 ppm as the 30-minute AEGL-1.

The 10-minute AEGL-2 value was based on an absence of serious pulmonary or other adverse effects in rats during direct delivery of HF to the trachea for an exposure period of 10 minutes (Dalbey, 1996; Dalbey et al., 1998). This reported concentration-exposure value of 950 ppm for 10 minutes was adjusted by a combined UF of 10: 3 for interspecies variation since the rat was not the most sensitive species in other studies (but direct delivery to the trachea is a sensitive model) and an intraspecies UF of 3 since HF reacts chemically and indiscriminately with the tissues of the respiratory tract and adverse effects are unlikely to differ among individuals.

The 30-minute and the 1-, 4- and 8-hour AEGL-2 values were based on a study in which dogs exposed to 243 ppm for 1 hour showed signs of more than mild irritation, including blinking, sneezing, and coughing (Rosenholtz et al., 1963). The 1-hour value of 243 ppm was adjusted by a total UF of 10: 3 for intraspecies variation since the dog is a sensitive species for sensory irritation and 3 for intraspecies variation since HF reacts chemically and indiscriminately with the tissues of the respiratory tract and effects are unlikely to differ among individuals. The values were scaled across time using $C^2 \times t = k$ where the value of n = 2 was derived from concentration: Exposure duration relationships based on lethality.

The 10-minute AEGL-3 value was based on the reported 10-minute lethal threshold in orally cannulated rats of 1,764 ppm (Dalbey, 1996; Dalbey et al., 1998). This value was rounded down to 1,700 ppm and adjusted by UFs of 3 for interspecies differences (LC_{50} values differ by a factor of approximately 2–4 between the mouse and rat) and 3 for intraspecies differences since HF reacts chemically and indiscriminately with tissues of the respiratory tract and effects are unlikely to differ among individuals. The total adjustment for UFs for the 10-minute AEGL-3 value was 10.

The 30-minute and the 1-, 4-, and 8-hour AEGL-3 values were derived from a reported 1-hour exposure resulting in no deaths in mice (Wohlslagel et al., 1976). The data indicated that the value of 263 ppm was the threshold for lethality. A comparison of LC_{50} values among species in several studies determined that the mouse was the most sensitive species in lethality studies. The 1-hour value of 263 ppm was adjusted by an interspecies UF of 1 since the mouse was the most sensitive species and intraspecies UF of 3 since HF reacts chemically and indiscriminately with tissues of the respiratory tract and effects are unlikely to differ among individuals. A modifying factor of 2 was applied to account for the steepness of the lethal dose-response curve and the value was scaled to the other AEGL-specified exposure periods using a value of n = 2.

Based on the extensive database involving both human and animal exposures (six species of mammals) for various exposure durations, confidence in the AEGL values is high. Values are summarized in the table below.

SUMMARY OF PROPOSED AEGL VALUES FOR HYDROGEN FLUORIDE (HF) [PPM (MG/M^3)]

Classification	10-min.	30-min.	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	2 (1.6)	2 (1.6)	2 (1.6)	1 (0.8)	1 (0.8)	Irritation in humans (Largent, 1960; 1961)
AEGL-2 (Disabling)	95 (78)	34 (28)	24 (20)	12 (9.8)	8.6 (7.0)	NOAEL for lung effects in cannulated rats (Dalbey, 1996; Dalbey et al., 1998);[1] sensory irritation in dogs (Rosenholtz et al., 1963)[2]
AEGL-3 (Lethality)	170 (139)	62 (51)	44 (36)	22 (18)	15 (12)	Lethality threshold in cannulated rats (Dalbey, 1996; Dalbey et al., 1998);[3] Lethality threshold in mice (Wohlslagel et al., 1976)[4]

[1] 10-minute AEGL-2 value.
[2] 30-minute and 1-, 4-, and 8-hour AEGL-2 values.
[3] 10-minute AEGL-3 value.
[4] 30-minute and 1-, 4-, and 8-hour AEGL-3 values.

ii. *References.*

Dalbey, W. 1996. Evaluation of the toxicity of hydrogen fluoride at short exposure times. Petroleum Environmental Research Forum Project 92–09, performed at Stonybrook Laboratories Inc., Pennington, NJ.

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

Largent, E.J. 1960. The metabolism of fluorides in man. *American Medical Association Archives of Industrial Health*. 21:318–323.

Largent, E.J. 1961. Fluorosis: The Health Aspects of Fluorine Compounds. Ohio State University Press, Columbus, OH.

Rosenholtz, M.J., Carson, T.R., Weeks, M.H., Wilinski, F., Ford, D.F., and Oberst, F.W. 1963. A toxicopathologic study in animals after brief single exposures to hydrogen fluoride. *American Industrial Hygiene Association Journal*. 24:253–261.

Wohlslagel, J., DiPasquale, L.C., and Vernot, E.H. 1976. Toxicity of solid rocket motor exhaust: Effects of HCl, HF, and alumina on rodents. *Journal of Combustion Toxicology*. 3:61–69.

8. *Hydrogen sulfide (*H_2S)—i. *Description.* The AEGL-1 was based on persistent odors, eye and throat irritation, headache, and nausea in six workers exposed to a mean concentration of 0.09 ppm H_2S for approximately 5 hours in a monitoring van downwind from an oil refinery (TNRCC, 1998). An UF of 3 was applied to account for intraspecies variability since minor irritation is not likely to vary greatly between individuals. The value was flat-lined across the 10- and 30-minute and 1-, 4-, and 8-hour exposure time points. The flat-lining approach was considered appropriate since mild irritant effects generally do not vary greatly over time.

The AEGL-2 was based on focal areas of perivascular edema and an increase in protein and lactic acid dehydrogenase (LDH) in bronchioalveolar lavage fluid in rats exposed to 200 ppm hydrogen sulfide for 4 hours (Green et al., 1991; Khan et al., 1991). An UF of 3 was used to extrapolate from animals to humans since rat and mouse data suggest little interspecies variability. An UF of 3 was also applied to account for sensitive individuals since data suggest little strain variability of hydrogen sulfide toxicity among rats (total UF = 10). The 4-hour experimental value was then scaled to the 10- and 30-minutes and 1- and 8-hour time points, using $C^{4.36} \times t = k$. The exponent of 4.36 was derived from rat lethality data ranging from 10-minutes to 6-hour exposure duration.

The AEGL-3 was based on a 1-hour no-effect-level for death in rats (504 ppm) (MacEwen and Vernot, 1972). An UF of 3 was used to extrapolate from animals to humans since rat and mouse data suggest little interspecies variability. An UF of 3 was also applied to account for sensitive individuals since data suggest little strain variability of hydrogen sulfide toxicity among rats (total UF = 10). The value was then scaled to the 10- and 30-minutes and 1-, 4-, and 8-hour time points, using $C^{4.36} \times t = k$. The exponent of 4.36 was derived from rat lethality data ranging from 10 minutes to 6 hours exposure duration.

The calculated values are listed in the table below.

SUMMARY OF PROPOSED AEGL VALUES FOR HYDROGEN SULFIDE [PPM (MG/M^3)]

Classification	10-min.	30-min.	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	0.03 (0.04)	0.03 (0.04)	0.03 (0.04)	0.03 (0.04)	0.03 (0.04)	Persistent odor, eye, and throat irritation, headache, nausea (TNRCC, 1998)
AEGL-2 (Disabling)	42 (59)	32 (45)	28 (39)	20 (28)	17 (24)	Perivascular edema, increased protein, and LDH in lavage fluid in rats (Green et al., 1991; Khan et al., 1991)
AEGL-3 (Lethality)	76 (106)	60 (85)	50 (71)	37 (52)	31 (44)	1 hour no-effect-level for death in rats (MacEwen and Vernot, 1972)

ii. *References.*

Green, F. H. Y., Schurch, S., and DeSanctis, G. T., et al. 1991. Effects of hydrogen sulfide exposure on surface properties of lung surfactant. *Journal of Applied Physiology*. 70:1943–1949.

Khan, A. A., Yong, S., and Prior, M. G., et al. 1991. Cytotoxic effects of hydrogen sulfide on pulmonary alveolar macrophages in rats. *Journal of Toxicology and Environmental Health*. 33:57–64.

MacEwen, J. D. and Vernot, E. H. 1972. Toxic Hazards Research Unit Annual Report. Aerospace Medical Research Laboratory, Air Force Systems Command, Wright-Patterson Air Force Base, Ohio. Report No. ARML–TR–72–62. pp. 66–69.

TNRCC (Texas Natural Resources Conservation Commission). 1998. Memo from Tim Doty to JoAnn Wiersma. Corpus Christi Mobile Laboratory Trip, January 31–February 6, 1998; Real-Time Gas Chromatography and Composite Sampling, Sulfur Dioxide, Hydrogen Sulfide, and Impinger Sampling. April 20, 1998.

9. *Otto Fuel II (main component propylene glycol dinitrate; CAS No. 6423–43–4)*—i. *Description.* Otto Fuel II, a liquid propellant used exclusively by the U.S. Navy in torpedoes and other weapon systems, is a mixture of three synthetic compounds: 1,2-Propylene glycol dinitrate (PGDN), which is a nitrate ester explosive, dibutyl sebacate (a desensitizer), and 2-nitrodiphenylamine (a stabilizer). The primary component and the one responsible for the toxicity of Otto Fuel II is PGDN, a volatile liquid with a disagreeable odor. Because PGDN is the primary and most toxic component of Otto Fuel II and because only PGDN is relatively volatile compared with the other components, AEGLs have been derived in terms of PGDN with the notation that the values are appropriate for Otto Fuel II.

PGDN is a systemic toxicant with effects on the cardiovascular and central nervous systems. Its vasodilatory action results in headaches during human exposures. Symptoms of dizziness, loss of balance, nasal congestion, eye irritation, palpitations, and chest pains have also been reported. Methemoglobinemia has been reported at the high concentrations used in studies with animals.

Few data were available that met the definitions of AEGL endpoints. One inhalation study with 20 human subjects described effects of headaches and slight loss of balance at exposure concentrations of 0.1 to 1.5 ppm for exposure durations up to 8 hours (Stewart et al., 1974). Acute exposure of monkeys to concentrations of 70–100 ppm for 6 hours resulted in severe signs of toxicity including convulsions but no deaths (Jones et al., 1972). In the same study, exposure of rats to a higher concentration (#199 ppm for 4 hours) resulted in no toxic signs. Examination of the relationship between exposure duration and concentration for both mild and severe headaches in humans over periods of time of 1 to 8 hours determined that the relationship is $C^1 \times t = k$.

The AEGL-1 values were based on concentrations of 0.5 ppm and 0.1 ppm which were the thresholds for mild headaches at exposure durations of 1 and 6 hours, respectively (Stewart et al., 1974). This effect can be considered the threshold for mild discomfort (only one subject was affected at each exposure) which falls within the definition of an AEGL-1. The 0.5 ppm concentration was used to derive the 30-minutes and 1-hour AEGL-1 values and the 0.1 ppm concentration was used for the 4- and 8-hour values. Because the time and concentration values were based on the most sensitive subject, these concentrations were adjusted by an UF of 3 to account for additional differences in human sensitivity and scaled to the appropriate time periods using the $C^1 \times t = k$ relationship. An UF of 3 was considered sufficient as no susceptible populations were identified (the headache effect is the same as that experienced by heart patients medicated with nitroglycerin for angina and these concentrations are far below those inducing methemoglobinemia in infants); the vasodilatory effects of PGDN, responsible for the headaches, are not expected to vary greatly among individuals. The 10-minute AEGL-1 value was made equal to the 30-minute value.

The AEGL-2 values were based on a concentration of 0.5 ppm which caused severe headaches accompanied by dizziness in one subject and slight loss of equilibrium in two subjects in one of several sensitive equilibrium tests after 6 hours of exposure (Stewart et al., 1974). This concentration-exposure duration was considered the threshold for impaired inability to escape as defined by the AEGL-2. The 0.5 ppm concentration was adjusted by an intraspecies UF of 3 to protect sensitive individuals and scaled across time using the $C^1 \times t = k$ relationship as for the AEGL-1 in Unit III.B.9.

The AEGL-3 values were based on the exposure of squirrel monkeys to concentrations of 70–100 ppm for 6 hours which resulted in vomiting, pallor, cold extremities, semiconscousness, and clonic convulsions; these signs disappeared upon removal from the exposure chamber (Jones et al., 1972). The lower concentration, 70 ppm, was adjusted by a total UF of 10. An interspecies UF of 3 was chosen because both the monkey and human subjects showed changes in electrical activity of the brain at similar PGDN concentrations, the threshold for central nervous system depressants does not vary widely among mammalian species, and the monkey is an appropriate model for extrapolation to humans. An intraspecies UF of 3 was chosen because the threshold for central nervous system depression also does not vary greatly among individuals. Because the endpoint for the AEGL-3 values is different than the endpoint for the AEGLs-1 and -2 and no data on the relationship between concentration and exposure duration is available for the endpoint of central nervous system depression, the more conservative values of $n = 3$ and $n = 1$ were used to scale from 6 hours to the shorter- and longer-time periods, respectively.

The proposed values appear in the table below.

SUMMARY OF PROPOSED AEGL VALUES FOR OTTO FUEL II [PPM (MG/M^3)]

Classification	10-min.	30-min.	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1[a] (Nondisabling)	0.33 (2.3)	0.33 (2.3)	0.17 (1.1)	0.05 (0.34)	0.03 (0.17)	Mild headaches in humans (Stewart et al., 1974)
AEGL-2 (Disabling)	6.0 (43)	2.0 (14)	1.0 (6.8)	0.25 (1.7)	0.13 (0.8)	Severe headaches and slight imbalance in humans (Stewart et al., 1974)
AEGL-3 (Lethality)	23 (165)	16 (114)	13 (93)	8.0 (57)	5.3 (38)	Convulsions in monkeys (Jones et al., 1972)

[a] The distinctive odor of PGDN will be noticeable to most individuals at the 0.33 and 0.17 ppm concentrations.

ii. *References.*

Jones, R.A., Strickland, J.A., and Siegel, J. 1972. Toxicity of propylene glycol 1,2-dinitrate in experimental animals. *Toxicology and Applied Pharmacology*. 22:128–137.

Stewart, R.D., Peterson, J.E., Newton, P.E., Hake, C.L., Hosko, M.J., Lebrun, A. J., and Lawton, G.M. 1974. Experimental human exposure to propylene glycol dinitrate. *Toxicology and Applied Pharmacology*. 30:377–395.

10. *1,1,1-Trichloroethane*—i. *Description.* 1,1,1-Trichloroethane is a colorless, nonflammable liquid used primarily as an industrial metal degreasing agent. It is also used as a solvent for adhesives, inks, and coatings

and as an aerosol propellant (Nolan et al., 1984). Solvent vapor is readily absorbed from the respiratory tract and distributed throughout the body, accumulating in tissues with high lipid content. In both humans and animals, the primary response to acute inhalation exposures involve effects on the central nervous system (CNS). This chemical is arrhythmogenic and there is some evidence that it produces transient hepatotoxicity (Mcleod et al., 1987; Stahl et al., 1969; Hodgson et al., 1989). It has little effect on other organs and does not seem to be a developmental toxin although reliable epidemiological data for humans are unavailable. 1,1,1-Trichloroethane does not seem to have carcinogenic activity based on the available animal studies. A considerable amount of human and animal data are available for derivation of AEGLs. Rat ataxia and lethality data were used for the regression analyses of the concentration-exposure durations. The relationship between time and concentration was $C^n \times t = k$, where n = 3.3 or 3.

The AEGL-1 was based on consistent complaints of eye irritation and slight dizziness experienced by humans in an atmosphere controlled setting with exposures of 450 ppm for two 4-hour sessions separated by a 1.5-hour interval (Salvini et al., 1971). Stewart et al., 1969, exposed human subjects to time-weighted average (TWA) concentration of 500 ppm for 7 hour repeatedly for 5 days, the only consistent complaint was mild sleepiness and failure of the Romberg test by two of the subjects which had trouble with this test initially. Torkelson et al. (1958) reported a NOAEL for the Romberg test in humans after exposure to a TWA of 506 ppm for 7.5 hour. For derivation of the AEGL-1, the observations of Salvini et al. (1971) were used as the starting point for the threshold of eye irritation and very subtle CNS effects in humans at a concentration of 450 ppm for 4 hour . An UF of 2 was chosen based on the observation that the severity of the eye irritation did not increase with time and the threshold for mild CNS effects does not vary by more than two-three fold which should be protective of sensitive individuals. The resulting figure of 230 ppm was used at all time points based on the information reported by Salvini et al. (1971) indicating that this exposure represented a threshold for these effects and the severity did not increase with duration of exposure.

The AEGL-2 was based on more serious CNS effects which might impede escape. Mullin and Krivanek (1982) calculated EC_{50} values for ataxia in rats at 30-minute and 1-, 2-, and 4-hour exposures to be 6,740; 6,000; 4,240; and 3,780 ppm. These values were used as the basis for AEGL-2 derivation using an UF of 10 and extrapolations were made to the 10-minute and 8-hour time points using the equation $C^n \times t = k$, where n = 3.3 based on the data presented by Mullin and Krivanek (1982). An UF of 10 was applied which includes a factor of 3 to account for sensitive individuals and a factor of 3 for interspecies extrapolation. These UFs were based on the two-three fold variation of minimum alveolar concentration for anesthesia (MAC) values among humans and the similarities in toxicity, metabolism, and excretion of 1,1,1-trichloroethane in rats compared to humans. The resulting concentrations are similar to the concentration exposure durations applied in experimental human studies which resulting in effects that could impede escape, i.e., CNS intoxication.

The AEGL-3 values were derived from a lethality concentration-effect curve in the rat for a 6-hour exposure duration (Bonnet et al., 1980). The LC_0 was conservatively estimated from this curve as a concentration of about 7,000 ppm for a 6-hour exposure duration. An extrapolation was made to the 30-minute and 1-, 4-, and 8-hour time points using the equation $C^n \times t = k$, where n = 3 based on the rat lethality data. An UF of 10 was applied. An intraspecies factor of 3 was used to account for sensitive individuals based on the two-three fold variation of MAC values observed among humans and an interspecies factor of 3 was used because of the similarities in toxicity, metabolism, and excretion of 1,1,1-trichloroethane in rats compared to humans. The resulting concentrations were multiplied by a modifying factor of 3 in order to achieve a reasonable concentration at which humans might experience life-threatening toxic effects. This factor is justified by the existence of a higher blood: Air partition coefficient for rats compared to humans. This principle determines the relative blood concentration for a vapor and because it is higher for rats, a higher blood concentration is achieved.

The proposed values appear in the table below.

SUMMARY OF PROPOSED AEGL VALUES FOR 1,1,1-TRICHLOROETHANE [PPM (MG/M^3)]

Classification	10-min.	30-min.	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	230 (1,252)	230 (1,252)	230 (1,252)	230 (1,252)	230 (1,252)	Eye irritation and slight dizziness in humans observed (Salvini et al., 1971)
AEGL-2 (Disabling)	930 (5,064)	670 (3,650)	600 (3,270)	380 (2,070)	310 (1,688)	EC_{50} for ataxia in rats (Mullin and Krivanek, 1982)
AEGL-3 (Lethality)	4,800[1] (26,135)	4,800 (26,135)	3,800 (20,690)	2,400 (13,067)	1,900 (10,345)	LC_0 extrapolated (Bonnet et al., 1980)

[1]The 30-minute value was used as the 10-minute value so as not to exceed the threshold for cardiac sensitization observed in dogs (Reinhardt et al., 1973).

ii. References.

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List of Subjects

Environmental protection, Hazardous substances.

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Susan H. Wayland,

Deputy Assistant Administrator for Prevention, Pesticides and Toxic Substances.

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