ENVIRONMENTAL PROTECTION AGENCY

[OPPTS–00218; FRL–5737–3]

National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

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 Acute Exposure Guideline Levels (AEGLs) on an on going basis to assist Federal and State agencies and private sector organizations with their needs for short-term hazardous chemical exposure information (one time only exposures during chemical emergency situations). The NAC/AEGL Committee has completed work on ''Proposed AEGLs'' for 12 chemicals. The purpose of today's notice is to solicit comments on proposed values and the accompanying scientific rationale for their development. More specifically, this notice solicits comments on the proposed AEGL values, the methodologies used to determine no-observed-adverse-effect-levels (NOAELs) or lowest-observed-adverse-effect-levels (LOAELs) for specific effects, the uncertainty factors selected for intraspecies and interspecies extrapolation, the uncertainity factors used to accommodate for sensitive or susceptible individuals in the human population, the use of modifying factors and the values applied, and other aspects related to the development of the AEGL values.

DATES: Submit written comments on or before December 1, 1997.

ADDRESSES: Submit three copies of written comments on the Proposed AEGLs, identified by docket control number (OPPTS–00218; FRL– 5737–3) to: Environmental Protection Agency, Office of Pollution Prevention and Toxics (OPPT), Document Control Office (7407), Rm. G–009, 401 M St., SW., Washington, DC 20460.

Comments and data may also be submitted electronically to: oppt.ncic@epamail.epa.gov. Follow the instructions under Unit V. of this document. No Confidential Business Information (CBI) should be submitted through e-mail.

All comments which contain information claimed as CBI must be clearly marked as such. Three sanitized copies of any comments containing information claimed as CBI must also be submitted and will be placed in the public record for this notice. Persons submitting information on any portion of which they believe is entitled to treatment as CBI by EPA must assert a business confidentiality claim in accordance with 40 CFR 2.203(b) for each such portion. This claim must be made at the time that the information is submitted to EPA. If a submitter does not assert a confidentiality claim at the time of submission, EPA will consider this as a waiver of any confidentiality claim and the information may be made available to the public by EPA without further notice to the submitter.

FOR FURTHER INFORMATION CONTACT: Susan B. Hazen, Director, Environmental Assistance Division (7408), Rm. ET–543B, Office of Pollution Prevention and Toxics, Environmental Protection Agency, 401 M St., SW., Washington, DC 20460; telephone: (202) 554–1404; TDD: (202) 554–0551; e-mail: TSCA-Hotline@epamail.epa.gov.

SUPPLEMENTARY INFORMATION:

Electronic Availability

Internet

Electronic copies of this notice and various support documents are available from the EPA Home Page at the **Federal Register**—Environmental Documents entry for this document under ''Laws and Regulations'' (http://www.epa.gov/fedrgstr/).

Fax-On-Demand

Using a faxphone call (202) 401–0527 and select item 3800 for an index of items in this category. For a more specific item number, see the table in Unit IV. of this document.

I. 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 objective stated in the charter 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 using 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 May 21, 1997 (62 FR 27734 (FRL–5718–9)). This list is intended to be expanded and also may be modified as priorities of the stakeholder member organizations are further developed.

While the development of AEGLs for chemicals is not statutorily based; at least one EPA rulemaking references their planned adoption. In the final Clean Air Act and Amendment section 112 Risk Management rulemaking (June 20, 1996, 61 FR 31685, (FRL–5516–5)), ''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 toxicity reference for substances under this rule.'' Federal and State agencies and private organizations may also adopt AEGLs for chemical emergency programs in the future.

The NAC/AEGL Committee meets four times per year and plans to develop AEGL values for 30–40 chemicals per year during the next 8 to 10 years. Since its first meeting on June 19–21, 1996, the NAC/AEGL Committee has completed work on ''Proposed AEGLs'' for 12 chemicals. The basic approach and guidance used to derive AEGLs has been the National Academy of Sciences (NAS) publication, ''Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances'' (National Academy Press, Washington, DC, 1993; copies are available in the Docket). The NAC/AEGL Committee meetings have been public and numerous public comments and presentations have been made. At this time, the NAC/AEGL Committee is providing further opportunity for public input through this notice. Comments are welcome on both the AEGL values and their related Technical Support Documents (filed in the public Docket).

The NAC/AEGL Committee will review comments received and revise the Proposed AEGLs as deemed appropriate. The resulting values will be established as ''Interim AEGLs'' and will be available for use in various public and private sector programs on human health effects related to short-term exposures to hazardous chemicals. It is planned that Interim AEGLs will be forwarded to the National Research Council, National Academy of Sciences (NRC/NAS) for further review, collaboration with the NAC/AEGL Committee, and possible revision of the

AEGL values and the methodologies used to derive them. It is anticipated that ''Final AEGLs'' will be published under the auspices of the NAS following concurrence on the values and the scientific rationale used for their development. Until Final AEGLs are published by the NAS, the Interim AEGLs are intended for use as needed by individuals or organizations in both the public and private sectors.

II. Characterization of the AEGLs

The AEGLs represent short-term threshold or ceiling exposure values intended for the protection of the general public, including susceptible or sensitive individuals, but not hypersusceptible or hypersensitive individuals. The AEGLs represent biological reference values for this defined human population and consist of three biological endpoints for each of four different exposure periods of 30 minutes (mins), l hour (hr), 4 hours (hrs), and 8 hrs. In certain instances, AEGL values have been and will be developed for additional exposure periods of 5 or 10 mins. The biological endpoints include AEGL–1, AEGL–2, and AEGL–3 and are defined as follows:

AEGL–1 is the airborne concentration (expressed as parts per millions (ppm) or milligrams (mg)/meters (m)^3) of a substance at or above which it is predicted that the general population, including ''susceptible'' but excluding ''hypersusceptible'' individuals, could experience notable discomfort. Airborne concentrations below AEGL–1 represent exposure levels that could produce mild odor, taste, or other sensory irritations.

AEGL–2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance at or above which it is predicted that the general population, including ''susceptible'' but excluding ''hypersusceptible'' individuals, could experience irreversible or other serious, long-lasting effects or impaired ability to escape. Airborne concentrations below the AEGL–2 but at or above AEGL–1 represent exposure levels that may cause notable discomfort.

AEGL–3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance at or above which it is predicted that the general population, including ''susceptible'' but excluding ''hypersusceptible'' individuals, could experience life-threatening effects or death. Airborne concentrations below AEGL–3 but at or above AEGL–2 represent exposure levels that may cause irreversible or other serious, long-lasting effects or impaired ability to escape.

III. 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 NAC/AEGL Committee in draft form by Oak Ridge National Laboratories and ''Draft AEGL'' values are prepared in conjunction with designated 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 NAC/AEGL Committee meetings. Following deliberations on the Draft AEGL values and the relevant data and information for each chemical presented at the meeting, the NAC/AEGL Committee attempts to reach a consensus on acceptable values. 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 12 hazardous substances. These values represent the first exposure levels proposed and published by the NAC/AEGL Committee. 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 (copies of this guidance document are available for review in the Docket). The term Community Emergency Exposure Levels (CEELs) used by the NAS is synonymous with AEGLs in every way. The NAC/AEGL Committee has adopted the term Acute Exposure Guideline Levels or AEGLs to better connote the broad application of the values to the population defined by the NAS in its guidance document and addressed by the NAC/AEGL Committee in its development of the AEGLs. 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 proposed values 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. It has been planned to have the NAS subcommittee participate in the peer review of the Interim AEGLs and in the resolution of issues regarding the AEGL values and the data and basic methodology used for setting AEGLs. It is anticipated that ''Final AEGL'' values will be published under the auspices of the NAS.

IV. List of Twelve Chemicals With Proposed AEGL Values

CAS No.	Chemical name	Fax-On-Demand item no.
57–14–7 ...	1,1–Dimethylhydrazine	3852
60–34–4 ...	Methylhydrazine	3853
62–53–3 ...	Aniline	3854
75–21–8 ...	Ethylene oxide	3861
302–01–2	Hydrazine	3891
540–59–0	1,2–Dichloroethene	3895
540–73–8	1,2–Dimethylhydrazine	3852
7697–37–2	Nitric acid	3912
7782–41–4	Fluorine	3915
7782–50–5	Chlorine	3916
7784–42–1	Arsine	3921
7803–51–2	Phosphine	3923

Chemicals With Proposed AEGLs (Alphabetical Order)

Aniline

Aniline is an aromatic amine used chiefly in the chemical industry in the manufacture of dyes, dye intermediates, rubber accelerators, antioxidants, drugs, photographic chemicals, isocyanates, herbicides, and fungicides. The primary effect of an acute exposure to aniline is on the hemoglobin of the red blood cell, resulting in the formation of methemoglobin. The effect may occur following inhalation, ingestion, or cutaneous absorption. In addition to methemoglobinemia, chronic exposures or exposures to high concentrations may produce signs and symptoms of headache, paresthesia, tremor, pain,

narcosis/coma, cardiac arrhythmia, and possibly death.

All AEGL values are based on a study in which rats were exposed to concentrations of 0, 10, 30, 50, 100, or 150 ppm for 8 hrs (Kim and Carlson, 1986). The only reported effect was formation of methemoglobin. At a constant concentration (100 ppm), the formation of methemoglobin over time was basically linear, reaching an asymptote at 8 hrs.

The AEGL–1 was based on a concentration of 100 ppm for 8 hrs which resulted in elevation of methemoglobin from a control value of 1.1% (range, 0.4–2.1%) to 22%. This level of methemoglobin results in clinical cyanosis but no hypoxic symptoms. Additional studies on oral ingestion showed that humans are much more sensitive than rats to aniline exposure as indicated by formation of methemoglobin. Thus, an uncertainty factor of 10 was used for interspecies extrapolation. Several sources also indicate that newborns are more sensitive to methemoglobin-forming chemicals than adults; thus, an intraspecies uncertainty factor of 10 was applied. The data were scaled across time using $C^1 \times t = k$ (the relationship between concentration of aniline and methemoglobin formation at a fixed time [8 hrs] is linear as is the relationship between time and severity of effect when concentration is held constant; in addition, data from several lethality [LC_{50}] studies show that the relationship between C and t is linear).

The AEGL–2 was based on the same study with rats in which a concentration of 150 ppm for 8 hrs resulted in elevation of methemoglobin from a control value of 1.1% to 41%. This level of methemoglobin is associated with fatigue, lethargy, exertional dyspnea, and headache in humans and was considered the threshold for disabling effects. The 150 ppm concentration was divided by a combined uncertainty factor of 100 and scaled across time using the same reasons and relationships as for the AEGL–1 above. Because of the small data base and the lack of recent, reliable human inhalation studies, uncertainty factors of 10 were applied for each of the interspecies and intraspecies variabilities.

Data on concentrations of aniline inducing methemoglobin levels at the threshold for lethality were not available. Based on the fact that the relationship between concentration of aniline and methemoglobin formation is linear, the dose-response curve from the study on which the AEGL–1 and AEGL–2 were based was extrapolated to a concentration resulting in >70% formation of methemoglobin, the threshold for lethality. The concentration of 250 ppm for 8 hrs was chosen as the threshold for lethality. The AEGL–3 was based on dividing the 250 ppm value by a combined uncertainty factor of 100 and scaled across time using the same reasons and relationships as for the AEGL–1 above. The uncertainty factors of 10 for each of the interspecies and intraspecies variabilities are supported by the small data base of information and the lack of recent, reliable human inhalation studies.

Studies with repeated exposures at approximately the same concentrations in the rat resulted in additional effects on the blood and spleen, but concentrations up to 87 ppm, 6 hrs/day, 5 days/week, for 2 weeks were not disabling or life-threatening. The calculated values are listed in the table below. Because aniline is absorbed through the skin, a skin notation was added to the summary table.

SUMMARY TABLE OF PROPOSED AEGL VALUES FOR ANILINE [a]

Classification	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	16 ppm (61 mg/m^3)	8.0 ppm (30 mg/m^3)	2.0 ppm (7.6 mg/m^3)	1.0 ppm (3.8 mg/m^3)	22% methemoglobin—cyanosis (Kim and Carlson, 1986)
AEGL–2	24 ppm (91 mg/m^3)	12 ppm (46 mg/m^3)	3.0 ppm (11 mg/m^3)	1.5 ppm (5.7 mg/m^3)	41% methemoglobin—lethargy (Kim and Carlson, 1986)
AEGL–3	40 ppm (152 mg/m^3)	20 ppm (76 mg/m^3)	5.0 ppm (19 mg/m^3)	2.5 ppm (9.5 mg/m^3)	>70% methemoglobin—lethality (extrapolated from data of Kim and Carlson, 1986)

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

References

1. Kim, Y.C. and G.P. Carlson. 1986. The effect of an unusual workshift on chemical toxicity. Part II. Studies on the exposure of rats to aniline. *Fundamental and Applied Toxicology* 7:144–152.

Arsine

Arsine is an extremely toxic, colorless gas used in the semiconductor industry. Exposure to arsine may also result from mining and manufacturing processes involving arsenicals, and from paints and herbicides containing arsenicals.

Arsine is a potent hemolytic agent, ultimately causing death via renal failure. Numerous human case reports are available documenting the extreme toxicity of arsine exposure but these reports lack definitive quantitative exposure data.

Exposure-response data from animal studies were used to derive AEGL values for arsine. AEGL values derived with animal data were more conservative than AEGLs estimated from limited anecdotal human data. The greater conservatism afforded by the animal data may be justified by the incomplete and often equivocal data for human exposures, the documented extreme toxicity of arsine, and the known latency involved in arsine-induced lethality. The AEGL values for the various exposure periods of concern (0.5, 1, 4, and 8 hrs) were scaled from the experimental exposure duration using exponential scaling ($C^2 \times t = k$), where n = 2 represented an estimate of the concentration-time relationship. 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 1 to 3.5 (ten Berge et al 1986). The mid-point value of 2 was used as the exponent n for scaling the AEGL values for arsine across time, because no exposure versus time data were available.

Based upon the available data, derivation of AEGL–1 values was considered to be inappropriate. The available human and animal data affirm that there is little margin between exposures that result in little or no signs of toxicity and those that result in lethality. The mechanism of arsine toxicity (induction of hemolysis that may rapidly result in renal failure and death), and the fact that toxicity in animals and humans has been demonstrated at concentrations at or below the odor threshold also support

such a conclusion by the NAC/AEGL Committee.

The AEGL–2 values were based upon exposure levels that did not result in significant alterations in hematologic parameters in mice exposed to arsine for 1 hr (Peterson and Bhattacharyya, 1985). AEGL–2 derivations based upon several data sets were similar, thereby providing validation to the proposed AEGLs. Derivation of AEGLs based upon limited data for humans resulted in values indicative of potentially hazardous exposures. Uncertainty factor application included a factor of 10 for interspecies variability because of uncertainties regarding species-specific sensitivity to arsine-induced hemolysis. Uncertainty regarding intraspecies variability was limited to 3 because the hemolytic response to arsine is not expected to vary greatly among individuals.

The AEGL–3 values were based upon data assessing the lethality in mice exposed to arsine for 1 hr (Peterson and Bhattacharyya, 1985). A total uncertainty factor application of 30 was applied as for AEGL–2 values and for the same reasons. Derivation of AEGL–3 values using limited data in monkeys affirmed the values derived based upon the mouse data. AEGL–3 values derived from limited human exposure data resulted in levels considered potentially hazardous.

The three AEGL exposure levels reflect the narrow range between exposures resulting in minor effects and those producing lethality. A conservative approach in the development of AEGLs for arsine was justified by the known steep dose-response curve, the induction of hemolysis by arsine at extremely low concentrations, and the potential of hemolysis to progress to life-threatening renal failure.

SUMMARY OF PROPOSED AEGL VALUES FOR ARSINE

Classification	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	NA[a]	NA[a]	NA[a]	NA[a]	Inappropriate based upon steep dose-response relationship, mechanism of toxicity, and because toxicity occurs at or below the odor threshold
AEGL–2	0.24 ppm (0.8 mg/m^3).	0.17 ppm (0.5 mg/m^3).	0.08 ppm (0.3 mg/m^3).	0.06 ppm (0.3 mg/m^3).	Absence of significant hematological alterations in mice consistent with the known continuum of arsine toxicity (Peterson and Bhattacharyya, 1985)
AEGL–3	0.7 ppm (2.2 mg/m^3).	0.5 ppm (1.6 mg/m^3).	0.25 ppm (0.8 mg/m^3).	0.18 ppm (0.6 mg/m^3).	Estimated threshold for nonlethality in mice (Peterson and Bhattacharyya, 1985)

[a] NA Not appropriate

References

1. Peterson, D.P. and Bhattacharyya, M.H. 1985. Hematological responses to arsine exposure: quantitation of exposure response in mice. *Fundamental and Applied Toxicology* 5:499–505.

Chlorine

Chlorine is a greenish-yellow, highly reactive halogen gas with a pungent, suffocating odor. Like other halogens, chlorine does not occur in the elemental state in nature; it rapidly combines with both inorganic and organic substances. Chlorine is used in the manufacture of a wide variety of chemicals, as a bleaching agent in industry and household products, and as a biocide in water and waste treatment plants.

Chlorine is an irritant to the eyes and respiratory tract; reaction with moist surfaces produces hydrochloric and hypochlorous acids. Its irritant properties have been studied in human volunteers and its acute inhalation toxicity has been studied in several laboratory animal species. The data from the human and laboratory animal studies were sufficient for development of three AEGLs for four time periods (i.e., 30 mins and 1, 4, and 8 hrs). Probit and regression analyses of the animal exposure time-concentration-mortality data determined that the relationship between concentration and time is approximately $C^2 \times t = k$.

The AEGL–1 was based on the observation that exposure to human volunteers, including a sensitive individual, of 0.5 ppm for 4 hrs produced no sensory irritation but did result in transient changes in some pulmonary function parameters for the sensitive individual (Rotman et al., 1983). Because both sexes were tested and all subjects were undergoing light exercise, making them more vulnerable to sensory irritation, and because a sensitive individual was included in the test, no uncertainty factor to account for differences in human sensitivity was applied. The 0.5 ppm exposure for 4 hrs was scaled to the other time periods using the relationship $C^2 \times t = k$. The scaling factor n = 2 was based on probit and regression analyses of animal lethality data.

The AEGL–2 values were derived based on the same study (Rotman et al., 1983) in which healthy human subjects experienced transient changes in pulmonary function measurements and a sensitive individual experienced an asthmatic attack (shortness of breath and wheezing) at a concentration of 1 ppm for 4 hrs. The sensitive individual remained in the exposure chamber for the full 4 hrs. Because both sexes were tested and all subjects were undergoing light exercise, making them more vulnerable to sensory irritation, and because a sensitive individual was included in the test, no uncertainty factor to account for differences in human sensitivity was applied. The 4-hr 1 ppm concentration was scaled to the other time periods using the $C^2 \times t = k$ relationship. The scaling factor or exponent of n = 2 is based on probit and regression analyses of animal lethality data.

In the absence of human data, the AEGL–3 values were based on animal lethality data. Because the mouse was shown to be more sensitive than other mammals to irritant gases including chlorine and does not provide an appropriate basis for quantitatively predicting mortality in humans, a value below that resulting in no deaths in the rat, 213 and 322 ppm in two studies (MacEwen and Vernot, 1972; Zwart and Woutersen, 1988) and above that resulting in no deaths in the mouse (150 ppm) for exposure periods of 1 hr was chosen. Mice exposed to chlorine experienced delayed deaths attributable to bronchopneumonia. The AEGL–3 values were derived from a 1-hr concentration of 200 ppm. This value was divided by a combined uncertainty factor of 10. An uncertainty factor of 3

was used to extrapolate from rats to humans, since interspecies values for the same endpoint differed by a factor of approximately 2 within each of several studies. An uncertainty factor of 3 was used to account for differences in human sensitivity, since the toxic effect is due to a chemical reaction with biological tissue of the respiratory tract which is unlikely to be different among individuals. The AEGL–3 values were scaled to the other exposure periods based on the $C^2 \times t = k$ relationship. The scaling factor or exponent of n = 2 is based on probit and regression analyses of animal lethality data.

Based on the large data base and the extensive, well-conducted studies, confidence in the AEGL values is high. The calculated values are listed in the table below.

SUMMARY OF PROPOSED AEGL VALUES FOR CHLORINE

Classi-fication	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	1.4 ppm (4.1 mg/m^3).	1.0 ppm (2.9 mg/m^3).	0.5 ppm (1.5 mg/m^3).	0.5 ppm (1.5 mg/m^3).	Pulmonary function—human (Rotman et al., 1983)
AEGL–2	2.8 ppm (8.1 mg/m^3).	2.0 ppm (5.8 mg/m^3).	1.0 ppm (2.9 mg/m^3).	0.7 ppm (2.0 mg/m^3).	Asthmatic attack—human (Rotman et al., 1983)
AEGL–3	28 ppm (81 mg/m^3).	20 ppm (58 mg/m^3).	10 ppm (29 mg/m^3).	7.1 ppm (21 mg/m^3).	Lethality—rat (MacEwen and Vernot, 1972; Zwart and Woutersen, 1988)

References

1. MacEwen, J.D. and E.H. Vernot. 1972. Toxic Hazards Research Unit Annual Technical Report: 1972. AMRL-TR-72–62, Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, OH; National Technical Information Service, Springfield, VA.

2. Rotman, H.H., M.J. Fliegelman, T. Moore, R.G. Smith, D.M. Anglen, C.J. Kowalski, and J.G. Weg. 1983. Effects of low concentration of chlorine on pulmonary function in humans. *Journal of Applied Physiology* 54:1120–1124.

3. Zwart, A. and R.A. Woutersen. 1988. Acute inhalation toxicity of chlorine in rats and mice: time-concentration-mortality relationships and effects on respiration. *Journal of Hazardous Material* 19:195–208.

1,2-Dichloroethene

1,2-dichloroethene 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 for four time periods.

The AEGL–1 was based on a human exposure concentration of 1,100 ppm *trans*-1,2-dichloroethene for 5 mins (Lehmann and Schmidt-Kehl 1936). Although this is a no-effect-level for narcotic effects it represents a concentration that is above the odor threshold. Because of the mode of action and similarity in response to this chemical as an irritant, this value was divided by an uncertainty factor of 3 to protect sensitive individuals and by a modifying factor of 2 to account for the probable difference in toxicity between the *cis*- and *trans*- isomers. It was then scaled to the 30-min, 1-, 4-, and 8-hr exposures using the $c^n \times t = k$ relationship, where n = 2. 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 1 to 3.5 (ten Berge et al 1986). Because no exposure versus time data were available, the mid-point value of 2 was used as the exponent n for scaling the AEGL values for dichloroethene across time.

The AEGL–2 was based on slight dizziness in humans exposed to 3300 ppm *trans*-1,2-dichloroethene for 5 mins (Lehmann and Schmidt-Kehl 1936). Because of the mode of action and similarity in response to this chemical, this value was divided by an uncertainty factor of 3 to protect sensitive individuals and by a modifying factor of 2 to account for the probable difference in toxicity between the *cis*- and *trans*- isomers. It was then scaled up to the 30-minute (min), 1-, 4-, and 8-hr exposure periods using the $c^n \times t = k$ relationship, where the mid-point of the exponential range n = 2 was used.

The AEGL–3 was based on fibrous swelling and hyperemia of cardiac muscle with little striation in rats exposed to 3000 ppm *trans*-1,2-dichloroethene for 8 hrs. Because the lethality data are limited and quite variable across species for the data that do exist this value was divided by an uncertainty factor of 10 to account for interspecies variation. An additional uncertainty factor of 3 was applied to protect sensitive individuals and a modifying factor of 2 was also applied to account for the probable difference in toxicity between the *cis*- and *trans*- isomers. The 8-hr AEGL value was then scaled to the 30-min, 1-, and 4-hr exposures using the $c^n \times t = k$ relationship, where the midpoint of the experimental range n = 2 was used. The calculated values are listed in the table below.

SUMMARY OF PROPOSED AEGL VALUES FOR 1,2-DICHLOROETHENE

Classification	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1 (Nondisabling)	19 ppm (75 mg/m^3)	13 ppm (53 mg/m^3)	6.6 ppm (26 mg/m^3)	4.7 ppm (19 mg/m^3)	No effect in humans (Lehmann and Schmidt-Kehl, 1936)
AEGL–2 (Disabling)	56 ppm (224 mg/m^3)	40 ppm (160 mg/m^3)	20 ppm (80 mg/m^3)	14 ppm (56 mg/m^3)	Slight dizziness in humans (Lehmann and Schmidt-Kehl, 1936)

SUMMARY OF PROPOSED AEGL VALUES FOR 1,2-DICHLOROETHENE—Continued

Classification	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–3 (Lethality)	200 ppm (800 mg/m^3)	141 ppm (564 mg/m^3)	71 ppm (284 mg/m^3)	50 ppm (200 mg/m^3)	Fibrous swelling and hyperemia of cardiac muscle with poorly maintained striation in rats (Freundt et al., 1977)

References

1. Freundt, K.J., Liebalt, G.P., and Lieberwirth, E. 1977. Toxicity studies on trans-1,2-dichloroethylene. *Toxicology* 7:141–153.

2. Lehmann, K.B. and Schmidt-Kehl, L. 1936. The thirteen most important chlorinated aliphatic hydrocarbons from the standpoint of industrial hygiene. *Archive Fur Hygiene* 116:9–268.

3. 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.

1,1- and 1,2-Dimethylhydrazine

Dimethylhydrazine occurs as a symmetrical (1,2-dimethylhydrazine) and asymmetrical (1,1-dimethylhydrazine) isomer. Both compounds are clear, colorless liquids. Asymmetrical dimethylhydrazine (1,1-dimethylhydrazine) is a component of jet and rocket fuels and is also used as an absorbent for acid gas, as a plant growth control agent, and in chemical synthesis. Although it has been evaluated as a high-energy rocket fuel, commercial use of the symmetrical isomer (1,2-dimethylhydrazine) is limited to small quantities and it is usually considered to be a research chemical. Because data are limited for 1,2-dimethylhydrazine (symmetrical dimethylhydrazine), the AEGL values are based upon 1,1-dimethylhydrazine (asymmetrical). Limited data suggest that1,1-dimethylhydrazine may be somewhat more toxic than 1,2-dimethylhydrazine.

Data on acute exposures of humans to both isomers of dimethylhydrazine are limited to case reports of accidental exposures. Signs and symptoms of exposure include respiratory irritation, pulmonary edema, nausea, vomiting, and neurological effects. However, definitive exposure data (concentration and duration) were unavailable for these exposures.

Toxicity data of varying degrees of completeness are available for several laboratory species, including, rhesus monkeys, dogs, rats, mice, and hamsters (Weeks et al., 1963). Most of the animal studies were conducted using 1,1-dimethylhydrazine, although limited data suggest that 1,2-dimethylhydrazine exerts similar toxic effects. Minor nonlethal effects such as respiratory tract irritation appear to occur at cumulative exposures of <100 (ppm)(hrs). At cumulative exposures at or only slightly greater than 100 (ppm)(hrs), more notable effects have been reported, including, muscle fasciculation, behavioral changes, tremors, and convulsions. At only slightly higher exposure levels, lethality has been demonstrated. The available data suggest that there is very little margin between exposure levels resulting in no significant toxicity and those causing substantial lethality (LC_{50} ≈900–2,000 ppm hrs).

Developmental toxicity of dimethylhydrazines has been demonstrated in rats following parenteral administration of maternally toxic doses. Both isomers of dimethylhydrazine have been shown to be carcinogenic in rodents following oral exposure and 6-month inhalation to 1,1-dimethylhydrazine resulted in an increased tumor response in mice, although these findings are compromised by the contaminant dimethylnitrosamine. Inhalation slope factors are currently unavailable. It was the consensus of the NAC/AEGL Committee that AEGL–1 values for dimethylhydrazine are inappropriate. This conclusion was based upon the onset of toxic effects at or below the odor threshold, and a concentration-response relationship for dimethylhydrazine that indicated little margin between exposures producing no toxic response and those resulting in significant toxicity.

Behavioral changes and muscle fasciculations in dogs exposed for 15 mins to 360 ppm 1,1-dimethylhydrazine (Weeks et al., 1963) served as the basis for deriving AEGL–2 values. Following temporal scaling ($C^1 \times t = k$) to AEGL-specific exposure durations, the values were adjusted by an uncertainty factor of 30. An uncertainty factor of 3 for interspecies variability was applied because the toxic response to dimethylhydrazine was similar across the species tested. An uncertainty factor of 10 for intraspecies variability was applied because of the uncertainties regarding the mechanism of action of dimethylhydrazine toxicity and its impact on susceptible individuals.

The AEGL–3 was derived from the 1-hr LC_{50} (981 ppm) for 1,1-dimethylhydrazine in dogs (Weeks et al., 1963). Because of the steep slope of the dose-response curve of 1,1-dimethyl hydrazine, a modifying factor of 3 was applied to the 1-hr LC_{50} of 981 ppm. Hence, the modified lethality threshold used to determine the AEGL–3 was 327 ppm. The downward adjustment of the LC_{50} using a modification factor of 3 was considered a conservative approach and, in part, justified the total uncertainty factor of 30 (3 for interspecies variability and 10 for intraspecies variability). An uncertainty factor of 3 for interspecies variability was applied because the toxic response to dimethylhydrazine was similar across the species tested. An uncertainty factor of 10 for intraspecies variability was applied because of the uncertainties regarding the mechanism of action of dimethylhydrazine toxicity and its potential impact on susceptible individuals. Temporal scaling as previously described was applied to obtain exposure values for AEGL-specific exposure periods.

An estimation of AEGLs based upon carcinogenic potential resulting from a one time, short term exposure was conducted and the assessment revealed that AEGLs derived from carcinogenic toxicity for a 10^{-4} carcinogenic risk exceeded AEGL–3 values based on non cancer endpoints. The relationship of the various AEGL values reflects the exposure-response relationship shown by available animal data.

SUMMARY OF PROPOSED AEGL VALUES FOR 1,1- AND 1,2-DIMETHYLHYDRAZINES

Classification	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	NA[b]	NA[b]	NA[b]	NA[b]	Inappropriate because notable toxicity may occur at concentrations below the odor threshold; concentration-response relationships suggest little margin between exposures causing minor effects and those resulting in serious toxicity.[a]
AEGL–2	6 ppm (14.7 mg/m^3)	3 ppm (7.4 mg/m^3)	0.8 ppm (2 mg/m^3)	0.4 ppm (1 mg/m^3)	Behavioral changes and muscle fasciculations in dogs exposed to 360 ppm for 15 mins (Weeks et al., 1963)
AEGL–3	22 ppm (54 mg/m^3)	11 ppm (27 mg/m^3)	3 ppm (7.4 mg/m^3)	1.5 ppm (3.7 mg/m^3).	Lethality threshold of 327 ppm for 1-hr estimated from 1-hr LC_{50} in dogs (Weeks et al., 1963)

[a]Refer to AEGL–1 for hydrazine if hydrazine is also present.
[b]NA Not appropriate

References

1. Weeks, M.H., Maxey, G.C., Sicks, and Greene, E.A. 1963. Vapor toxicity of UDMH in rats and dogs from short exposures. *American Industrial Hygiene Association Journal* 24:137–143.

Ethylene Oxide

Ethylene oxide is a highly flammable gas produced in very large quantities in the United States (5.3–6.3 billion pounds). It is very reactive with nucleophiles, such as water, alcohols, halides, amines, and sulfhydryl compounds. Ethylene oxide is used as an intermediate in the production of ethylene glycol and nonionic surfactants; a small amount is used as a fumigant for sterilizing foods and heat-sensitive medical equipment. The odor detection level for ethylene oxide is 260 ppm (468 mg/m^3) to 700 ppm (1,260 mg/m^3).

The database of toxicity to ethylene oxide vapor in humans and experimental animals is very extensive including data on all aspects of toxicity except lethality in humans. Pharmacokinetics data show that ethylene oxide is readily absorbed from the respiratory tract of both humans and animals. It alkylates proteins and DNA, and it is metabolized by hydrolysis and glutathione conjugation.

In humans, inhaled ethylene oxide vapor affects the eyes, respiratory tract, central and peripheral nervous systems, gastrointestinal tract (probably secondary effects to nervous system toxicity), hematopoietic system, and possibly the reproductive system, and fetus. Acute exposure to ethylene oxide at the odor detection level (≥260 ppm) causes eye and upper respiratory tract irritation and signs and symptoms of effects on the central and peripheral nervous system. Acute exposure to a calculated concentration of 500 ppm for 2 to 3 minutes caused hematologic effects and more severe effects on the central nervous system than those noted at the odor detection level. Effects observed after acute exposure are reversible, including severe nervous system effects. Peripheral nervous damage is exacerbated by repeated exposures. Human studies have provided suggestive evidence of reproductive toxicity, some evidence of an association between exposure to ethylene oxide and genetic damage to somatic cells and limited evidence of carcinogenicity.

Acute lethality studies in experimental animals showed that mice are the most sensitive species (4-hrs LC^{50} = 660–835 ppm) (Jacobson et al., 1956), followed by the dog (4-hrs LC^{50} = 960 ppm) (Jacobson et al., 1956) and rat (4-hrs LC^{50} = 1537–1972 ppm; 1-hr LC^{50} = 4439–5748 ppm) (Jacobson et al., 1956). Immediate deaths were due to respiratory failure and delayed deaths were due to secondary respiratory infections. Experimental animals exposed to lethal and nonlethal concentrations of ethylene oxide showed evidence of eye and respiratory irritation and effects on the central and peripheral nervous system (Embree et al., 1977). Additional studies in animals exposed to ethylene oxide for various durations up to 6 hrs/day provided evidence of reproductive toxicity at ≥50 ppm, developmental toxicity at ≥50 ppm, genetic toxicity in germ cells at ≥75 ppm, and carcinogenicity at 100 ppm.

Data were available for deriving AEGL–2 and –3 values. Values for AEGL–1 were not derived because the odor threshold and concentrations causing mild sensory irritation would be above the AEGL–2 levels.

The AEGL–2 values were based on a rat study showing central nervous system depression, diarrhea, and eye and respiratory tract irritation after exposure to 1,000 ppm of ethylene oxide for 4 hrs (Embree et al., 1977); genetic toxicity (dominant lethality) was also seen at this concentration in this same study. An uncertainty factor of 10 was applied for intraspecies variability, because of the steep slope of the dose response relationship from severe irritation and central nervous system depression to the lethality threshold. An uncertainty factor of 3 was applied for interspecies sensitivity, because modes of action are likely to be similar between rodents and humans and systemic uptake of ethylene oxide is similar across species. The time-scaling approach used ten Berge's equation in which $C^n t = k$, and n = 1.2 based on analysis of rat lethality data.

AEGL–3 values were derived from lethality data in the rat. An LC^{01} value (628 ppm), which is considered an approximation of the lethality threshold, was estimated from data in a 4-hr acute inhalation study with rats reported by Jacobson et al. (1956). An uncertainty factor of 10 for intraspecies sensitivity was applied to the LC_{01} estimated value and this was followed by scaling to the different AEGL exposure periods based on ten Berge's equation ($C^n t = k$, where n = 1.2 was used based on reported lethality data for 1- and 4-hr exposures). An interspecies uncertainty factor of 3 was applied because systemic uptake, distribution, and modes of action are likely to be similar between rodents and humans. There are differences in metabolism kinetics, but they are unlikely to affect responses to high acute exposures. Assessment of carcinogenicity data (lung adenomas/carcinomas in female mouse) (NTP, 1987) showed that extrapolating the total cumulative exposure over a 2-year period to single exposures and estimating a 10^{-4} risk resulted in AEGL–3 values of 2,764, 1,382, 346, and 173 ppm for 0.5-, 1-, 4-, and 8-hr exposures. These values exceed those derived from lethality data.

AEGL values derived for ethylene oxide are summarized below:

SUMMARY OF PROPOSED AEGL VALUES FOR ETHYLENE OXIDE

Classification	Exposure Periods				Endpoint (Reference)
	30-minute	1-hour	4-hour	8-hour	
AEGL–1	No values derived	No values derived	No values derived	No values derived	
AEGL–2	190 ppm (342 mg/m^3)	110 ppm (198 mg/m^3)	33 ppm (59 mg/m^3)	19 ppm (34 mg/m^3)	Central nervous system effects Embree et al., 1977
AEGL–3	360 ppm (648 mg/m^3)	200 ppm (360 mg/m^3)	63 ppm (113 mg/m^3)	35 ppm (63 mg/m^3)	Lethality threshold Jacobson et al., 1956

References

1. Embree, J.W., Lyon, J.P., and Hine, C.H. 1977. The mutagenic potential of ethylene oxide using the dominant-lethal assay in rats. *Toxicology and Applied Pharmacology* 40:261–267.

2. Jacobson, K.H., Hackley, E.B., and Feinsliver, L. 1956. The toxicity of inhaled ethylene oxide and propylene oxide vapors. *Archive for Industrial Health* 13:237–244.

Fluorine

Fluorine is a reactive, highly irritant gas used in the nuclear energy industry, as an oxidizer of liquid rocket fuels, and in the manufacture of various fluorides and fluorocarbons. Fluorine is a severe irritant to the eyes, mucous membranes, lungs, and skin; the eyes and the respiratory tract are the target organ/tissues of an acute exposure. Data on irritant effects in humans and lethal and sublethal effects in five species of mammals (dog, rat, mouse, guinea pig, and rabbit) were available for development of AEGLs (Keplinger and Suissa, 1968). Regression analyses of the concentration-exposure durations (for the fixed endpoint of mortality) for all of the animal species reported determined that the relationship between concentration and time is $C^n \times t = k$, where n = approximately 2 (actual value for n for the most sensitive species, the mouse = 1.77). The data were considered adequate for derivation of the three AEGL classifications for four time periods.

The AEGL–1 was based on the observation that human volunteers could tolerate exposure to 10 ppm for 15 mins without irritant effects (Keplinger and Suissa, 1968). An uncertainty factor of 3 was applied to this NOAEL value to protect sensitive individuals, since fluorine reacts corrosively with the tissues of the respiratory tract and effects are not likely to differ greatly among individuals, including sensitive individuals. The value was then scaled to the 30-min and 1-, 4-, and 8-hr exposure durations using the $C^{1.77} \times t = k$ concentration-exposure duration relationship. It was the consensus of the NAC/AEGL Committee that at mildly irritating concentrations there is a tolerance to irritating gases. Therefore, the calculated 30-min and 1-hr values of 2.3 and 1.5 ppm, respectively, were rounded to 2 ppm and the calculated 4- and 8-hr values of 0.7 and 0.5 ppm, respectively, were rounded to 1 ppm.

The AEGL–2 was based on an animal study in which mild lung congestion was observed in mice at 67 ppm for 30 mins and 30 ppm for 60 mins (Keplinger and Suissa, 1968). Although concentrations causing irritant effects for each species for the same time periods suggested similar species sensitivity, the mouse data, because of slightly lower values, were chosen as the basis for developing the AEGL–2 and AEGL–3. Because the action of irritant and corrosive gases is directly on the tissues, with no pharmacokinetic component involved in the toxicity, there is likely to be little difference among species in response to fluorine exposure. Because similar sensitivity was observed among all species in the key study, no uncertainty factor for interspecies variability was applied. The values were divided by an intraspecies uncertainty factor of 3 to protect sensitive individuals, since effects are not likely to differ greatly among individuals. The values also were adjusted by a modifying factor of 2, based on a limited data base. AEGL–2 values for the other exposure periods were scaled based on the $C^{1.77} \times t = k$ relationship.

The AEGL–3 values were derived from exposure concentrations equal to one half of the LC_{50} values reported (Keplinger and Suissa, 1968). The experimental ½ LC_{50} concentrations tested resulted in no deaths in any species for up to 45 days post exposure, but did produce severe lung congestion in the mouse (Keplinger and Suissa, 1968). For the mouse, the 60-min value was 75 ppm. Because of the similar species sensitivity in the key study, no uncertainty factor for interspecies variability was applied. The values were divided by an uncertainty factor of 3 to protect sensitive individuals and by a modifying factor of 2, based on a limited data base. AEGL–3 values for the other exposure times were calculated based on the $C^{1.77} \times t = k$ relationship.

The calculated values are listed in the table below.

SUMMARY OF PROPOSED AEGL VALUES FOR FLUORINE[a]

Classification	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	2ppm (3.1 mg/m^3)	2 ppm (3.1 mg/m^3)	1 ppm (1.6 mg/m^3)	1 ppm (1.6 mg/m^3)	No irritant effect-humans (Keplinger and Suissa, 1968)
AEGL–2[b]	11 ppm (17 mg/m^3).	5.0 ppm (7.8 mg/m^3).	2.3 ppm (3.6 mg/m^3).	1.5 ppm (2.3 mg/m^3).	Mild lung congestion—mice (Keplinger and Suissa, 1968)
AEGL–3	19 ppm (29 mg/m^3).	13 ppm (20 mg/m^3).	5.7 ppm (8.8 mg/m^3).	3.9 ppm (6.0 mg/m^3).	Severe lung congestion—mice (Keplinger and Suissa, 1968)

[a] AEGL–1 values were rounded off because of tolerance to low concentrations of irritant gases. AEGL–2 and AEGL–3 values were rounded to two significant figures.

[b] 30-min and 1-hr AEGL–2 values are based on separate data points.

References

1. Keplinger, M.L. and L.W. Suissa. 1968. Toxicity of fluorine short-term inhalation. *American Industrial Hygiene Association Journal 29:10–18.*

Hydrazine

Hydrazine is a highly reactive reducing agent used in various chemical manufacturing processes. Hydrazine is used by the military as a missile and rocket propellant, and in power sources.

Human data on the toxicity of hydrazine following acute inhalation exposure are limited to anecdotal accounts that lack definitive exposure data. The utility of this information is compromised by concurrent exposure to other chemicals and involvement of simultaneous multiple exposure routes.

Studies have shown that the toxicity of methylated derivatives of hydrazine is qualitatively similar to that of hydrazine except in dogs wherein methylhydrazine has been observed to cause intravascular hemolysis. Based upon limited acute toxicity data, methylhydrazine and symmetrical dimethylhydrazine appear to be somewhat more toxic in rats and mice than is hydrazine while asymmetrical hydrazine appears to be slightly less toxic.

Data from animal studies indicate that hydrazine may be metabolized to acetylhydrazine, diacetylhydrazine, ammonia, and urea, and may form hydrazones with pyruvate and 2-oxoglutarate. The biotransformation of hydrazine is mediated, at least in part, by hepatic monooxygenases. The role of metabolism and absorption/excretion kinetics is uncertain regarding immediate port-of-entry toxic effects from acute inhalation exposures. The highly reactive nature of hydrazine per se is a plausible determinant of acute port-of-entry toxic effects.

AEGLs were based upon data sets defining toxicity endpoints that were specific for the AEGL level. Values for the specific exposure durations were derived based upon exponential scaling ($C^n \times t = k$, where n = 2) from the experimental exposure period. This method was more appropriate for concentration-dependent effects than linear (Haber's Law) scaling. 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 1 to 3.5 (ten Berge et al 1986). Because no exposure versus time data were available, the mid-point value of 2 was used as the exponent n for scaling the AEGL values for hydrazine across time.

AEGL–1 values were based upon a study by House (1964) in which male monkeys exhibited skin flushing and eye irritation after a 24-hr continuous exposure to 0.4 ppm hydrazine. A total uncertainty factor of 10 was applied to derive the AEGL–1 values.[1] An uncertainty factor of 3 was applied for interspecies variability because the contact irritation response to the highly reactive hydrazine is not likely to vary greatly among species, and because a nonhuman primate was the test species. An uncertainty factor of 3 was applied for intraspecies variability because the contact irritation from the highly reactive hydrazine is not expected to vary greatly among individuals. The 24-hr experimental value was scaled to 8 hrs using $C^n \times t = k$, where n = 2 as described above. Because hydrazine is extremely reactive and the effects are considered to be concentration dependent rather than time dependent, the 0.1 ppm AEGL–1 value derived for the 8-hr duration was also applied to the 30-min, 1-hr, and 4-hr durations.

The AEGL–2 was derived based upon data from a study by Latendresse et al. (1995) in which rats exposed to hydrazine (750 ppm) for 1 hr exhibited nasal lesions. Following a dosimetric adjustment based upon regional gas dose (U.S. EPA 1994), the values were scaled to AEGL-specific durations as for AEGL–1 and a total uncertainty factor of 30 applied. An uncertainty factor of 10 for interspecies variability was applied to account for a deficiency in data pertaining to species variability and also variability in the data that are available. An uncertainty factor of 3 was applied for intraspecies variability because the toxic response to hydrazine is not likely to vary considerably among individuals of the same species, including susceptible individuals.

The AEGL–3 values were derived based upon a rat inhalation study (HRC, 1993) that provided data to estimate a lethality threshold (LC^{01} = 337 ppm). Temporal scaling was again applied using the exponential expression $C^2 \times t = k$. Dosimetric conversion using a regional gas dose methodology (U.S. EPA 1994) was applied and resulting exposure values adjusted by a total uncertainty factor of 30. An uncertainty factor of 10 for interspecies variability was applied to account for a deficiency in data pertaining to species variability and also variability in the data that are available. An uncertainty factor of 3 was applied for intraspecies variability because the toxic response to hydrazine is not likely to vary considerably among individuals of the same species.

An estimation of AEGLs based upon carcinogenic potential resulting from a one-time, short term exposure was conducted using the inhalation cancer slope factor for hydrazine. The assessment revealed that AEGLs derived from noncarcinogenic toxicity endpoints were lower values and so the AEGL–3 values were based on the noncarcinogenic endpoint.

The proposed AEGLs, their respective toxicity endpoints and references are summarized below.

SUMMARY OF PROPOSED AEGL VALUES FOR HYDRAZINE

Classi-fication	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	0.1 ppm (0.1 mg/m^3)	0.1 ppm (0.1 mg/m^3)	0.1 ppm (0.1 mg/m^3)	0.1 ppm (0.1 mg/m^3)	Eye and facial irritation inmonkeys (House, 1964)[a]
AEGL–2	8 ppm (10 mg/m^3) ..	6 ppm (8 mg/m^3)	3 ppm (4 mg/m^3)	2 ppm (3 mg/m^3)	Nasal lesions (Latendresse et al., 1995)
AEGL–3	47 ppm (61 mg/m^3)	33 ppm (43 mg/m^3)	17 ppm (22 mg/m^3)	12 ppm (16 mg/m^3)	Lethality in rats (HRC, 1993)

[a] Because the contact irritation response to the extremely reactive hydrazine is concentration dependent rather than time-dependent, the AEGL–1 is the same of all time periods.

[1] Each uncertainty factor of 3 is actually the geometric mean of 10 which is 3.16, hence 3.16 x 3.16 = 10.

References

1. House, W.B. 1964. Tolerance criteria for continuous exposure inhalation exposure to toxic materials. Part III. Effects on animals of 90-day exposure to hydrazine, unsymmetrical dimethylhydrazine (UMDH), decaborane, and nitrogen dioxide. ASD–TR–61–519 (iii). Wright-Patterson AFB, OH. 84 pp.

2. HRC (Huntington Research Centre, Ltd.). 1993. Hydrazine 64% aqueous solution: acute inhalation toxicity in rats 1-hr exposure. Huntington Research Centre, Cambridge, England. CMA 8/930523.

3. Latendresse, J.R., Marit, G.B., Vernot, E.H., Haun, C.C., and Flemming, C.D. 1995. Oncogenic potential of hydrazine in the nose of rats and hamsters after 1 or 10 1-hr exposures. *Fundamental and Applied Toxicology* 27:33–48.

4. 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.

5. U.S. EPA 1994. EPA/600/8–90/066F, Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry.

Methylhydrazine

Methylhydrazine is a clear, colorless liquid used extensively in military applications as a missile and rocket propellant, in chemical power sources, and as a solvent and chemical intermediate. Upon contact with strong oxidizers (e.g., hydrogen peroxide, nitrogen tetroxide, chlorine, and fluorine) spontaneous ignition may occur.

Human volunteers exposed to 90 ppm methylhydrazine for 10 mins reported minor irritation as the only effect of exposure (MacEwen et al., 1970).

Toxicity data are available for multiple laboratory species including, rhesus monkeys, squirrel monkeys, beagle dogs, rats, mice, and hamsters. Nonlethal toxic effects include irritation of the respiratory tract, hemolytic responses, and some evidence of renal and hepatic toxicity. Lethal exposures are usually preceded by convulsions. Lethal toxicity varies somewhat among species. One-hour LC_{50} values of 162, 82, 96, 244, 122, and 991 ppm have been determined for rhesus monkeys, squirrel monkeys, beagle dogs, rats, mice, and hamsters, respectively. Concentration-time relationships appear to follow Haber's Law although there appears to be a critical threshold for lethality with little margin between exposures causing only minor, reversible effects, and those resulting in lethality.

In a 1-year inhalation bioassay using dogs, rats, mice, and hamsters, methylhydrazine concentrations of 2 ppm and 5 ppm, there was no evidence of treatment-related carcinogenicity in dogs or rats even after a 1-year post exposure observation period. However, mice exposed to 2 ppm for the same duration exhibited an increased incidence of lung tumors, nasal adenomas, nasal polyps, nasal osteomas, hemangioma, and liver adenomas and carcinomas. In hamsters exposed to 2 or 5 ppm, there was an increase in nasal polyps and nasal adenomas (5 ppm only), interstitial fibrosis of the kidney, and benign adrenal adenomas.

It was the consensus of the NAC/AEGL Committee that the setting of AEGL–1 values for methylhydrazine would be inappropriate. This conclusion was based on the occurrence of toxic effects at or below the odor threshold, and a concentration-response relationship for methylhydrazine that indicated little margin between exposures producing no toxic response and those resulting in significant toxicity.

The AEGL–2 values were derived by applying a modifying factor of 3 to each of the AEGL–3 values. This estimate of a threshold for irreversible effects was justified because of the absence of exposure-response data related to irreversible or other serious, long-lasting effects and the steep dose-response relationship indicated by the data that was available on methylhydrazine. For AEGL–3, lethality data (1-hr LC_{50} of 82 ppm) for squirrel monkeys (Haun et al., 1970) was adjusted using a modifying factor of 3 to estimate a lethality threshold (27 ppm). The lethality data for the species tested indicated a linear relationship between concentration and time. Therefore, temporal scaling to obtain time-specific AEGL values was described as $C^1 \times t = k$ where the exponent n = 1. The derived exposure values were adjusted by a total uncertainty factor of 10. An uncertainty factor of 3 was applied for interspecies variability because a sensitive nonhuman primate was used to estimate the lethality threshold, and an uncertainty factor of 3 was used for intraspecies variability due to the steep exposure-response relationship.[2]

The AEGL values reflect the steep exposure-response relationship exhibited by the toxicity data. Additional information regarding the mechanism(s) of action and metabolism of methylhydrazine may provide insight into understanding and defining the threshold between nonlethal and lethal exposures.

An estimation of AEGLs based upon carcinogenic potential resulting from a one-time, short-term exposure was conducted and the assessment revealed that AEGLs derived from carcinogenic toxicity for a 10^{-4} carcinogenic risk exceeded AEGL–3 values based on non cancer endpoints.

SUMMARY OF PROPOSED AEGL VALUES FOR METHYLHYDRAZINE

Classi-fication	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	NA	NA	NA	NA	Inappropriate because notable toxicity may occur at concentrations below the odor threshold; concentration-response relationships suggest little margin between exposures causing minor effects and those resulting in serious toxicity.[a]
AEGL–2	2 ppm (3.8 mg/m^3)	1 ppm (1.9 mg/m^3)	0.2 ppm (0.4 mg/m^3)	0.1 ppm (0.2 mg/m^3)	Three-fold reduction in AEGL–3.
AEGL–3	6 ppm (11.3 mg/m^3)	3 ppm (5.6 mg/m^3)	0.7 ppm (1.1 mg/m^3)	0.3 ppm (0.6 mg/m^3)	1-hr LC_{50} of 82 ppm reduced 3-fold to estimate a lethality threshold; UF–10

[a] Refer to AEGL–1 for hydrazine if hydrazine is also present.

[2]Each uncertainty factor of 3 is the geometric mean of 10 which is 3.16; hence, 3.16. x 3.16 = 10.

References

1. Haun, C.C., MacEwen, J.D., Vernot, E.H., and Egan, G.F. 1970. Acute inhalation toxicity of monomethylhydrazine vapor. *American Industrial Hygiene Association Journal* 31:667–677.

2. MacEwen, J.D., Theodore, J., and Vernot, E.H. 1970. Human exposure to EEL concentrations of monomethylhydrazine. Proceedings. First Annual Conference on Environmental Toxicology. AMRL–TR–70–102, Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, OH.

Nitric Acid

Nitric acid is a highly corrosive, strongly oxidizing acid. The course of toxicity following inhalation exposure to nitric acid is consistent between humans and animals. Nitric acid fumes may cause immediate irritation of the respiratory tract, pain, and dyspnea which are followed by a period of recovery that may last several weeks. After this time, a relapse may occur with death caused by bronchopneumonia and/or pulmonary fibrosis. For exposure to nonlethal concentrations, allergic or asthmatic individuals appear to be a sensitive subpopulation.

For derivation of the AEGL values, both human and animal data were utilized. For AEGL–1, humans exposed to 1.6 ppm (4.13 mg/m^3) for 10 mins showed no changes in pulmonary function (Sackner and Ford, 1981). An uncertainty factor of 3 was applied to account for sensitive populations, since the mechanism of action of an irritant gas is not expected to vary greatly among individuals. Scaling to the 30-min, 1-, 4-, and 8-hr exposure periods was not performed because this was a no effect level and irritation is generally concentration dependent but not time dependent. The derived AEGL–1 value is above the odor threshold which provides a warning of exposure before an individual would experience notable discomfort.

AEGL–2 values were derived from data on human studies (Diem, 1907). Individuals exposed to 12 ppm (31 mg/m^3) nitric acid for 1 hour experienced respiratory irritation, pressure in the chest, slight stabbing pains in the trachea and larynx, coughing, marked secretion from the nose and salivary glands, burning of the eyes and lacrimation, and burning and itching of facial skin. An uncertainty factor of 3 was applied to the 1-hr exposure level reported in this study and scaling of the value to 30 mins, 4 hrs, and 8 hrs was accomplished as described below.

Very little data were available for determining AEGL–3 levels. Human case reports of severe injury or death did not contain exposure concentrations and in most animal studies, nitric acid was administered by intratracheal instillation. Extrapolation from a mortality versus concentration curve in the published literature indicated that the LC_0 was approximately one-third the LC_{50} value of 138 ppm (356 mg/m^3) for the rat. This concentration was reported as nitrogen dioxide (NO_2) instead of total nitric acid. From the estimated LC_0 an uncertainty factor of 3 was applied to account for sensitive individuals. Due to the steepness of the dose-response curve for nitric acid, application of additional uncertainty factors would lower the AEGL–3 values below the values derived for AEGL–2 which were based on human data and, since the mechanism of action appears to be the same in both humans and animals with the production of both pulmonary edema and bronchiolitis obliterans, additional uncertainty factors were not used.

The concentration-exposure time relationship is described by the equation $c^n t = k$. Although insufficient data on nitric acid were available to calculate the exponent n, structure-activity relationships indicated that nitric acid and NO_2 have parallel dose-response curves for a 30-min exposure. Therefore, for extrapolation to the various time points for the AEGL–2 and –3 levels, a previously published n of 3.5 derived from NO_2 data was used.

The calculated values for the three AEGL classifications for the four time periods are listed in the table below.

SUMMARY TABLE OF PROPOSED AEGL VALUES FOR NITRIC ACID

Classi-fication	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	0.5 ppm (1.3mg/m^3).	0.5 ppm (1.3mg/m^3).	0.5 ppm (1.3mg/m^3).	0.5 ppm (1.3mg/m^3).	No observed effect level (NOEL) for changes in pulmonary function in humans (Sackner and Ford, 1981); UF=3
AEGL–2	5 ppm (13mg/m^3)	4 ppm (10mg/m^3)	3 ppm (8mg/m^3)	2 ppm (5mg/m^3)	Irritation with cough; burning of eyes and skin; lacrimationand salivation (Diem, 1907); UF=3
AEGL–3	15 ppm (39mg/m^3)	13 ppm (34mg/m^3)	8 ppm (21mg/m^3)	7 ppm (18mg/m^3)	LC_0 estimated from a 30-min LC_{50} in the rat (Gray et al., 1954); UF=3

References

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Phosphine

Phosphine is a colorless gas used as a fumigant against insects and rodents in stored grain. The pesticide is usually applied as a metal phosphide and reacts with moisture to liberate phosphine gas. Phosphine is also used in the semiconductor industry. Information concerning human exposure to phosphine is of limited use in derivation of AEGL values since exposure duration and concentration are not precisely reported. Appropriate animal data are more abundant; however, data consistent with the definition of AEGL–1 values are not available. Therefore, due to insufficient data, AEGL–1 values were not derived.

The AEGL–2 was based on a NOEL for renal and pulmonary pathology in Fischer 344 rats exposed to 3.1 ppm phosphine 6 hrs/day, 5 days/week for 13 weeks (Newton et al, 1993). Scaling to the 30-min, 1-, 4-, and 8-hr exposures was accomplished using the $c^n \times t = k$ relationship, where n = 2. 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 1 to 3.5 (ten Berge et al 1986). For scaling the AEGL values for phosphine across time, the mid-point value of 2 was used as the exponent n because no exposure versus time data were available. An uncertainty factor of 3 was used for interspecies extrapolation since the rat is the most sensitive species. An uncertainity factor of 10 was used for intraspecies extrapolation since the data indicate that children are more sensitive than adults when exposed to phosphine.

The AEGL–3 was based on a NOEL for lethality (18 ppm phosphine) in Sprague Dawley rats exposed to phosphine for 6 hrs. Scaling to the 30-min, 1-, 4-, and 8-hr exposures was accomplished using the $c^n \times t = k$ relationship, where n = 2. An uncertainty factor of 3 was used for interspecies extrapolation since the rat is the most sensitive species and an uncertainity factor of 10 was used for intraspecies extrapolation since data indicate that children are more sensitive than adults when exposed to phosphine.

The calculated values are listed in the table below.

SUMMARY TABLE OF PROPOSED AEGL VALUES PHOSPHINE

Classification	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1 (Nondisabling)	.....	.....	.....	.....	Appropriate data not available
AEGL–2 (Disabling)	0.36 ppm (0.52 mg/m^3).	0.25 ppm (0.35 mg/m^3).	0.13 ppm (0.18mg/m^3).	0.09 ppm (0.13 mg/m^3).	NOEL for renal and pulmonary pathology in rats exposed to 3.1 ppm phosphine, 6 hr/day, 5 days/week for 13 weeks (Newton et al., 1993)
AEGL–3 (Lethality) ..	2.1 ppm (2.9 mg/m^3)	1.5 ppm (2.1 mg/m^3)	0.74 ppm (1.0 mg/m^3).	0.52 ppm (0.73 mg/m^3).	NOEL for lethality in rats exposed to 18 ppm phosphine for 6 hr.(Newton, 1991)

References

1. Newton, P.E. 1991. Acute Inhalation exposures of rats to phosphine. Biology Dynamics, Inc. East Millstone, NJ. Project No. 90–8271.

2. Newton, P.E., Schroeder, R.E., Sullivan, J.B., Busey, W.M., and Banas, D.A. 1993. Inhalation toxicity of phosphine in the rat: acute, subchronic, and developmental. *Inhalation Toxicology* 5:223–239.

V. Public Record and Electronic Submission

The official record for this notice, as well as the public version, has been established for this notice under docket control number (OPPTS–00218; FRL–5737–3) (including comments and data submitted electronically as described below). A public version of this record, including printed, paper versions of electronic comments, which does not include any information claimed as CBI, is available for inspection from 12 noon to 4 p.m., Monday through Friday, excluding legal holidays. The official record is located in the TSCA Nonconfidential Information Center, Rm. NE–B607, 401 M St., SW., Washington, DC.

Electronic comments can be sent directly to EPA at:

oppt.ncic@epamail.epa.gov

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 disks in WordPerfect in 5.1/6.1 file format or ASCII file format. All comments and data in electronic form must be identified by the docket control number (OPPTS–00218; FRL–5737–3). Electronic comments on this notice may be filed online at many Federal Depository Libraries.

All comments which contain information claimed as CBI must be clearly marked as such. Three sanitized copies of any comments containing information claimed as CBI must also be submitted and will be placed in the public record for this notice. Persons submitting information on any portion of which they believe is entitled to treatment as CBI by EPA must assert a business confidentiality claim in accordance with 40 CFR 2.203(b) for each such portion. This claim must be made at the time that the information is submitted to EPA. If a submitter does not assert a confidentiality claim at the time of submission, EPA will consider this as a waiver of any confidentiality claim and the information may be made available to the public by EPA without further notice to the submitter.

List of Subjects

Environmental protection, Hazardous substances.

Dated: October 20, 1997.

Lynn R. Goldman,

Assistant Administrator for Prevention, Pesticides and Toxic Substances.

[FR Doc. 97–28642 Filed 10–29–97; 8:45 am]

BILLING CODE 6560–50–F