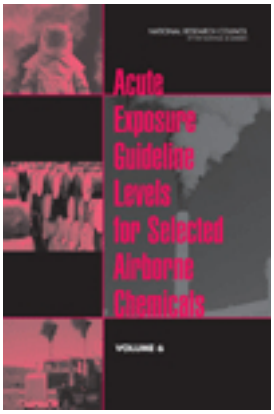

Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 6

Committee on Acute Exposure Guideline Levels, Committee on Toxicology, National Research Council

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 6

Committee on Acute Exposure Guideline Levels

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Preface

Extremely hazardous substances (EHSs)[2] can be released accidentally as a result of chemical spills, industrial explosions, fires, or accidents involving railroad cars and trucks transporting EHSs. Workers and residents in communities surrounding industrial facilities where EHSs are manufactured, used, or stored and in communities along the nation's railways and highways are potentially at risk of being exposed to airborne EHSs during accidental releases or intentional releases by terrorists. Pursuant to the Superfund Amendments and Reauthorization Act of 1986, the U.S. Environmental Protection Agency (EPA) has identified approximately 400 EHSs on the basis of acute lethality data in rodents.

As part of its efforts to develop acute exposure guideline levels for EHSs, EPA and the Agency for Toxic Substances and Disease Registry (ATSDR) in 1991 requested that the National Research Council (NRC) develop guidelines for establishing such levels. In response to that request, the NRC published *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* in 1993.

Using the 1993 NRC guidelines report, the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances—consisting of members from EPA, the Department of Defense (DOD), the Department of Energy (DOE), the Department of Transportation, other federal and state governments, the chemical industry, academia, and other organizations from the private sector—has developed acute exposure guideline levels (AEGLs) for approximately 200 EHSs.

In 1998, EPA and DOD requested that the NRC independently review the AEGLs developed by NAC. In response to that request, the NRC organized within its Committee on Toxicology the Committee on Acute Exposure Guideline Levels, which prepared this report. This report is the sixth volume in the

[2]As defined pursuant to the Superfund Amendments and Reauthorization Act of 1986.

series *Acute Exposure Guideline Levels for Selected Airborne Chemicals*. It reviews the AEGLs for allylamine, ammonia, aniline, arsine, crotonaldehyde, *trans* and *cis* + *trans*, 1, 1-dimethylhydrazine, 1, 2-dimethylhydrazine, iron pentacarbonyl, methyl hydrazine, nickel carbonyl, phosphine, and 8 metal phosphides for scientific accuracy, completeness, and consistency with the NRC guideline reports.

This report was reviewed in draft by individuals selected for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report: Deepak K. Bhalla, Wayne State University; David W. Gaylor, Gaylor and Associates, LLC; and Samuel Kacew, University of Ottawa.

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by Robert Goyer, University of Western Ontario (Emeritus). Appointed by the National Research Council, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

After the review of the draft was completed, the committee evaluated AEGLs that were developed for 8 metal phosphides. Because the acute toxicity of metal phosphides results from the phosphine generated from hydrolysis of the metal phosphides, their AEGL values are likewise based upon phosphine AEGLs. Therefore Chapter 10 of this report was expanded to present AEGL values for phosphine and the metal phosphides. We wish to thank Ian Greaves, University of Minnesota, and Wallace Hayes, Harvard School of Public Health, for their review of this revised chapter. The review was overseen by Samuel Kacew.

The committee gratefully acknowledges the valuable assistance provided by the following persons: Ernest Falke, Marquea D. King, Iris A. Camacho, and Paul Tobin (all from EPA); George Rusch (Honeywell, Inc.); Cheryl Bast, Sylvia Talmage, Robert Young, and Sylvia Milanez (all from Oak Ridge National Laboratory). We are grateful to James J. Reisa, director of the Board on Environmental Studies and Toxicology (BEST), for his helpful comments. Other staff members who contributed to this effort are Raymond Wassel (senior program officer), Aida Neel (program associate), Ruth Crossgrove (senior editor), Radiah Rose (senior editorial assistant), and Mirsada Karalic-Loncarevic (manager, Technical Information Center). The committee particularly acknowledges

Kulbir Bakshi, project director for the committee, for bringing the report to completion. Finally, we would like to thank all members of the committee for their expertise and dedicated effort throughout the development of this report.

Donald E. Gardner, *Chair*
Committee on Acute Exposure
Guideline Levels

William E. Halperin, *Chair*
Committee on Toxicology

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

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Introduction

This report is the sixth volume in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals*.

In the Bhopal disaster of 1984, approximately 2,000 residents living near a chemical plant were killed and 20,000 more suffered irreversible damage to their eyes and lungs following accidental release of methyl isocyanate. The toll was particularly high because the community had little idea what chemicals were being used at the plant, how dangerous they might be, or what steps to take an emergency. This tragedy served to focus international attention on the need for governments to identify hazardous substances and to assist local communities in planning how to deal with emergency exposures.

In the United States the Superfund Amendments and Reauthorization Act (SARA) of 1986 required that the U.S. Environmental Protection Agency (EPA) identify extremely hazardous substances (EHSs) and, in cooperation with the Federal Emergency Management Agency and the U.S. Department of Transportation, assist local emergency planning committees (LEPCs) by providing guidance for conducting health hazard assessments for the development of emergency response plans for sites where EHSs are produced, stored, transported, or used. SARA also required that the Agency for Toxic Substances and Disease Registry (ATSDR) determine whether chemical substances identified at hazardous waste sites or in the environment present a public health concern.

As a first step in assisting the LEPCs, EPA identified approximately 400 EHSs largely on the basis of their immediately dangerous to life and health values, developed by the National Institute for Occupational Safety and Health in experimental animals. Although several public and private groups, such as the Occupational Safety and Health Administration and the American Conference of Governmental Industrial Hygienists, have established exposure limits for some substances and some exposures (e.g., workplace or ambient air quality), these limits are not easily or directly translated into emergency exposure limits for exposures at high levels but of short duration, usually less than 1 hour (h), and

only once in a lifetime for the general population, which includes infants (from birth to 3 years of age), children, the elderly, and persons with diseases, such as asthma or heart disease.

The National Research Council (NRC) Committee on Toxicology (COT) has published many reports on emergency exposure guidance levels and spacecraft maximum allowable concentrations for chemicals used by the U.S. Department of Defense (DOD) and the National Aeronautics and Space Administration (NRC 1968, 1972, 1984a,b,c,d, 1985a,b, 1986a,b, 1987, 1988, 1994, 1996a,b, 2000). COT has also published guidelines for developing emergency exposure guidance levels for military personnel and for astronauts (NRC 1986b, 1992). Because of COT's experience in recommending emergency exposure levels for short-term exposures, in 1991 EPA and ATSDR requested that COT develop criteria and methods for developing emergency exposure levels for EHSs for the general population. In response to that request, the NRC assigned this project to the COT Subcommittee on Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. The report of that subcommittee, *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993), provides step-by-step guidance for setting emergency exposure levels for EHSs. Guidance is given on what data are needed, what data are available, how to evaluate the data, and how to present the results.

In November1995 the National Advisory Committee (NAC)[1] for Acute Exposure Guideline Levels for Hazardous Substances was established to identify, review, and interpret relevant toxicologic and other scientific data and to develop acute exposure guideline levels (AEGLs) for high-priority, acutely toxic chemicals. The NRC's previous name for acute exposure levels—community emergency exposure levels (CEELs)—was replaced by the term AEGLs to reflect the broad application of these values to planning, response, and prevention in the community, the workplace, transportation, the military, and the remediation of Superfund sites.

AEGLs represent threshold exposure limits (exposure levels below which adverse health effects are not likely to occur) for the general public and are applicable to emergency exposures ranging from 10 minutes (min) to 8 h. Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 min, 30 min, 1 h, 4 h, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million [ppm] or milligrams per cubic meter [mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory

[1]NAC is composed of members from EPA, DOD, many other federal and state agencies, industry, academia, and other organizations. The NAC roster is shown on page 9.

effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

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

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

Airborne concentrations below AEGL-1 represent exposure levels that can produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic nonsensory adverse effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

As described in *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993) and the NRC guidelines report, *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals* (NRC 2001a), the first step in establishing AEGLs for a chemical is to collect and review all relevant published and unpublished information. Various types of evidence are assessed in establishing AEGL values for a chemical. These include information from (1) chemical-physical characterizations, (2) structure-activity relationships, (3) in vitro toxicity studies, (4) animal toxicity studies, (5) controlled human studies, (6) observations of humans involved in chemical accidents, and (7) epidemiologic studies. Toxicity data from human studies are most applicable and are used when available in preference to data from in vivo and in vitro studies. Toxicity data from inhalation exposures are most useful for setting AEGLs for airborne chemicals because inhalation is the most likely route of exposure and because extrapolation of data from other routes would lead to additional uncertainty in the AEGL estimate.

For most chemicals, actual human toxicity data are not available or critical information on exposure is lacking, so toxicity data from studies conducted in

laboratory animals are extrapolated to estimate the potential toxicity in humans. Such extrapolation requires experienced scientific judgment. The toxicity data for animal species most representative of humans in terms of pharmacodynamic and pharmacokinetic properties are used for determining AEGLs. If data are not available on the species that best represents humans, data from the most sensitive animal species are used. Uncertainty factors are commonly used when animal data are used to estimate risk levels for humans. The magnitude of uncertainty factors depends on the quality of the animal data used to determine the no-observed-adverse-effect level (NOAEL) and the mode of action of the substance in question. When available, pharmacokinetic data on tissue doses are considered for interspecies extrapolation.

For substances that affect several organ systems or exert multiple effects, all endpoints (including reproductive (in both genders), developmental, neurotoxic, respiratory, and other organ-related effects are evaluated, the most important or most sensitive effect receiving the greatest attention. For carcinogenic chemicals, excess carcinogenic risk is estimated, and the AEGLs corresponding to carcinogenic risks of 1 in 10,000 (1×10^{-4}), 1 in 100,000 (1×10^{-5}), and 1 in 1,000,000 (1×10^{-6}) exposed persons are estimated.

REVIEW OF AEGL REPORTS

As NAC began developing chemical-specific AEGL reports, the EPA and DOD asked the NRC to review independently the NAC reports for their scientific validity, completeness, and consistency with the NRC guideline reports (NRC 1993, 2001a). The NRC assigned this project to the COT Committee on Acute Exposure Guideline Levels. The committee has expertise in toxicology, epidemiology, occupational health, pharmacology, medicine, pharmacokinetics, industrial hygiene, and risk assessment.

The AEGL draft reports are initially prepared by ad hoc AEGL development teams consisting of a chemical manager, two chemical reviewers, and a staff scientist of the NAC contractor—Oak Ridge National Laboratory. The draft documents are then reviewed by NAC and elevated from "draft" to "proposed" status. After the AEGL documents are approved by NAC, they are published in the *Federal Register* for public comment. The reports are then revised by NAC in response to the public comments, elevated from "proposed" to "interim" status, and sent to the NRC Committee on Acute Exposure Guideline Levels for final evaluation.

The NRC committee's review of the AEGL reports prepared by NAC and its contractors involves oral and written presentations to the committee by the authors of the reports. The NRC committee provides advice and recommendations for revisions to ensure scientific validity and consistency with the NRC guideline reports (NRC 1993, 2001a). The revised reports are presented at subsequent meetings until the subcommittee is satisfied with the reviews.

Because of the enormous amount of data presented in AEGL reports, the NRC committee cannot verify all of the data used by NAC. The NRC committee relies on NAC for the accuracy and completeness of the toxicity data cited in the AEGL reports.

Thus far, the committee has prepared five reports in the series Acute Exposure Guideline Levels for Selected Airborne Chemicals (NRC 2001b, 2002, 2003, 2004, 2007). This report is the sixth volume in that series. AEGL documents for allylamine, ammonia, aniline, arsine, crotonaldehyde, cis/trans-, crotonaldehyde, trans-iso, 1, 1-dimethylhydrazine, iron pentacarbonyl, methyl hydrazine, nickel carbonyl, phosphine, and 8 metal phosphides are each published as an appendix to this report. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

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6

Dimethylhydrazine[1]

Acute Exposure Guideline Levels

UPDATE OF DIMETHYLHYDRAZINE AEGLS

In Volume 1 of the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2000), AEGL values were developed for 30 minutes (min), and 1, 4, and 8 hours (h). Since that time AEGL values have also been developed for 10-min exposures. This document updates Volume 1 to include 10-min values. The summary below is from Volume 1, with additional discussion to address the development of 10-min values.

SUMMARY

Dimethylhydrazine occurs as a symmetrical (1,2-dimethylhydrazine) and an unsymmetrical (1,1-dimethylhydrazine) isomer. Unless otherwise specified, in this document dimethylhydrazine refers to unsymmetrical dimethylhydrazine. Both compounds are clear, colorless liquids. Unsymmetrical dimethylhydrazine is a component of rocket fuel 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 is limited to small quantities, and it is usually considered a research chemical. Because data are limited for 1,2-dimethylhydrazine, the AEGL values for both isomers are based on 1,1-dimethylhydrazine. Limited data suggest that 1,1-dimethylhydrazine may be somewhat more toxic than 1,2-dimethylhydrazine.

[1]This document was prepared by AEGL Development Team member Richard Thomas of the National Advisory Committee on Acute Exposure Guideline Levels for Hazardous Substances (NAC) and Robert Young of the Oak Ridge National Laboratory. The NAC reviewed and revised the document, which was then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC Committee concludes that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NAC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

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. The limited data for humans suggest that the nonlethal toxic response to acute inhalation of dimethylhydrazine is qualitatively similar to that observed in animals (no information was available regarding lethal responses in humans). In the absence of quantitative data for humans, the use of animal data is considered a credible approach for developing AEGL values.

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 less than 100 ppm multiplied by hours. At cumulative exposures at or only slightly greater than 100 ppm-h, more notable effects have been reported, including muscle fasciculation, behavioral changes, tremors, and convulsions. At only slightly higher exposures, lethality has been demonstrated. The available data suggest that there is very little margin between exposures resulting in no significant toxicity and those causing substantial lethality (the lethal concentration for 50% of the animals was ≈900-2,000 ppm-h).

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. U.S. Environmental Protection Agency (EPA) inhalation slope factors are currently unavailable for dimethylhydrazine.

AEGL-1 values for dimethylhydrazine are not recommended because of inadequate data to develop health-based criteria and because the concentration-response relationship for dimethylhydrazine indicated that a very narrow margin exists between exposures that produce no toxic response and those that result in significant toxicity.

Behavioral changes and muscle fasciculations in dogs exposed for 15 min to 360 ppm of 1,1-dimethylhydrazine (Weeks et al. 1963) served as the basis for deriving AEGL-2 values. Available lethality data in dogs and rats indicated a near-linear temporal relationship (n = 0.84 and 0.80 for dogs and rats, respectively). For temporal scaling ($C^1 \times t = k$) to derive values for AEGL-specific exposure durations, a linear concentration-response relationship, n = 1, was used. (C = exposure concentration, t = exposure duration, and k = a constant). An uncertainty factor of 3 for interspecies variability was applied because the

toxic response to dimethylhydrazine was similar across the species tested. This was especially true for lethality responses (LC_{50} values for various time periods ranging from 5 min to 4 h) among rats, mice, dogs, and hamsters. A comparison of LC_{50} values for the same exposure durations in these species did not vary by more than 3-fold. An uncertainty factor of 10 was retained for intraspecies variability, however, based primarily on the varied toxic responses observed in dogs, from extremely severe (vomiting, tremors, convulsions, and death) to no observable effects. Additionally, Weeks et al. indicated that dogs that had been previously stressed (auditory stimuli) may have potentiated their response to dimethylhydrazine. Based on these data, it was assumed that humans may be equally divergent in their response to dimethylhydrazine as a result of similar stresses.

The AEGL-3 was derived from the 1-h 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-dimethylhydrazine, the 1-h LC_{50} of 981 ppm was adjusted downward to estimate the lethality threshold of 327 ppm. An uncertainty factor of 3 for interspecies variability was applied for several reasons. The 4-h LC_{50} values for mice, rats, and hamsters differ by a factor of approximately 2 and were consistent with the dog data when extrapolated from 1 h using $n = 1$. The more sensitive species, the dog, was used to derive the AEGL-3 values. An uncertainty factor of 10 for intraspecies variability was retained for several reasons. A broad spectrum of effects was seen, including behavioral effects, hyperactivity, fasciculations, tremors, convulsions, and vomiting. The mechanism of toxicity is uncertain, and sensitivity among individuals may vary. Following identical exposures, the responses of the dogs varied from one of extreme severity (vomiting, tremors, convulsions, and death) to no observable effects. Temporal scaling as previously described was applied to obtain exposure values for AEGL-specific exposure periods.

Verified inhalation and oral slope factors were unavailable from EPA for dimethylhydrazine. A cancer assessment based on the carcinogenic potential (withdrawn cancer slope factors) of dimethylhydrazine revealed that AEGL values for a 10^{-4} carcinogenic risk exceeded the AEGL- 2 values that were based on noncancer end points. Because the cancer risk for dimethylhydrazine was estimated from nonverified cancer estimates, and because AEGLs are applicable to rare events or single once-in-a-lifetime exposures to a limited geographic area and small population, the AEGL values based on noncarcinogenic end points were considered more appropriate. A summary of AEGL values is shown in Table 6-1.

TABLE 6-1 Summary of AEGL Values for 1,1- and 1,2-Dimethylhydrazines

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR	NR	NR	NR	NR	Not recommended due to insufficient data; concentration-response relationships suggest little margin between exposures causing minor effects and those resulting in serious toxicity.[a]
AEGL-2 (disabling)	18 ppm (44 mg/m^3)	6 ppm (14.7 mg/m^3)	3 ppm (7.4 mg/m^3)	0.75 ppm (2 mg/m^3)	0.38 ppm (1 mg/m^3)	Behavioral changes and muscle fasciculations in dogs exposed to 360 ppm for 15 min (Weeks et al. 1963).
AEGL-3 (lethal)	65 ppm (159 mg/m^3)	22 ppm (54 mg/m^3)	11 ppm (27 mg/m^3)	2.7 ppm (6.6 mg/m^3)	1.4 ppm (3.4 mg/m^3)	Lethality threshold of 327 ppm for 1 h estimated from 1-h LC_{50} in dogs (Weeks et al. 1963).

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

NR: not recommended. Numerical values for AEGL-1 are not recommended (1) because of the lack of available data, (2) because an inadequate margin of safety exists between the derived AEGL-1 and the AEGL-2, or (3) because the derived AEGL-1 is greater than the AEGL-2. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.

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