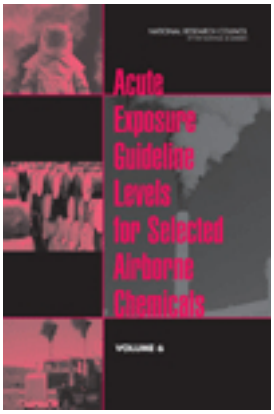

Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 6

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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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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8

Monomethylhydrazine[1]

Acute Exposure Guideline Levels

UPDATE OF MONOMETHYLHYDRAZINE AEGLS

In Volume 1 of the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2000), acute exposure guideline level (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, reference with additional discussion to address the development of 10-min values.

SUMMARY

Monomethylhydrazine 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, fluorine), spontaneous ignition may occur.

Human volunteers exposed to 90 ppm of monomethylhydrazine for 10 min reported minor irritation as the only effect (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 re-

[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).

sponses, 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. Exposure concentration-exposure time relationships appear to follow a linear relationship, 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 and monomethylhydrazine concentrations of 2 ppm and 5 ppm, there was no evidence of treatment-related carcinogenicity in dogs or rats even after a 1-year postexposure observation period. However, mice exposed to 2 ppm 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. Recommendation of AEGL-1 values for monomethylhydrazine would be inappropriate. This conclusion was based on the fact that notable toxicity may occur at or below the odor threshold. Exposure concentration-exposure duration relationships for monomethylhydrazine indicated little margin between exposures that produce no adverse health effect and those that result in significant toxicity.

The AEGL-2 values were derived by a 3-fold reduction of the AEGL-3 values. This approach for estimating a threshold for irreversible effects was used in the absence of exposure-response data related to irreversible or other serious long-lasting effects. It is believed that a 3-fold reduction in the estimated threshold for lethality is adequate to reach the AEGL-2 threshold level because of the steep dose-response relationship.

For AEGL-3, lethality data (1-h LC_{50} of 82 ppm) for squirrel monkeys (Haun et al. 1970) were downwardly adjusted by a factor of 3 to estimate a lethality threshold (27.3 ppm). Temporal scaling to obtain time-specific AEGL values was described by $C^1 \times t = k$ (where C = exposure concentration, t = exposure duration, and k = a constant). The lethality data for the species tested indicated a near-linear relationship between concentration and time (n = 0.97 and 0.99 for monkeys and dogs, respectively). The derived exposure values were adjusted by a total uncertainty factor of 10. An uncertainty factor of 3 was applied for interspecies variability with the following justification. One-hour LC_{50}s were determined for the monkey, dog, rat, and mouse. The LC_{50} values ranged from 82 ppm in the squirrel monkey to 244 ppm in the mouse, differing by a factor of approximately 3. The squirrel monkey data (1-h LC_{50} = 82 ppm) were used to determine the AEGL-3 because this species appeared to be the most sensitive to monomethylhydrazine toxicity and because it was the species most closely related to humans. An uncertainty factor of 3 for protection of sensitive individuals was applied to reflect individual variability of less than an order of magnitude. Although the mechanism of toxicity is uncertain and sensitivity among individuals may vary, the exposure-response relationship for each spe-

cies tested is very steep, suggesting limited variability in the toxic response to monomethylhydrazine. Furthermore, it is likely that acute toxic responses are, at least initially, a function of the extreme reactivity of monomethylhydrazine. Interaction of the highly reactive monomethylhydrazine with tissues (e.g., pulmonary epithelium) is not likely to vary greatly among individuals.

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 monomethylhydrazine may provide insight into understanding and defining the threshold between nonlethal and lethal exposures.

Inhalation or oral slope factors were not available for monomethylhydrazine. A cancer assessment based on the carcinogenic potential of dimethylhydrazine revealed that AEGL values for a 10^{-4} carcinogenic risk exceeded the AEGL-3 values that were based on noncancer end points. Furthermore, the available data for hydrazine and its methylated derivatives suggest that the tumorigenic response observed for these compounds results from long-term, repeated exposures that cause repetitive tissue damage. 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. The AEGL values and toxicity end points are summarized in Table 8-1.

TABLE 8-1 Summary of AEGL Values for Monomethylhyrazine[a]

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1	NR	NR	NR	NR	NR	Not recommended due to inadequate data; concentration-response relationships suggest little margin between exposures that cause minor effects and those that result in serious toxicity.[b]
AEGL-2	5.3 ppm (10 mg/m^3)	1.8 ppm (3.4 mg/m^3)	0.90 ppm (1.7 mg/m^3)	0.23 ppm (0.43 mg/m^3)	0.11 ppm (0.21 mg/m^3)	3-fold reduction in AEGL-3
AEGL-3	16 ppm 30 mg/m^3	5.5 ppm 10.3 mg/m^3	2.7 ppm 5.1 mg/m^3	0.68 ppm 1.3 mg/m^3	0.34 ppm 0.64 mg/m^3	1-h LC_{50} of 82 ppm reduced 3-fold to estimate a lethality threshold; uncertainty factor = 10

[a]Each uncertainty factor of 3 is the geometric mean of 10, which is 3.16; hence, 3.16 × 3.16 = 10.
[b]Refer to AEGL-1 for hydrazine if hydrazine is also present.

(Continued)

TABLE 8-1 Continued

Note: 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) 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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