Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 19

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VOLUME 19

Committee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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Preface

Extremely hazardous substances (EHSs)[1] 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. Subsequently, *Standard Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Substances* was published in 2001, providing updated procedures, methodologies, and other guidelines used by the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances and the Committee on Acute Exposure Guideline Levels (AEGLs) in developing the AEGL values.

Using the 1993 and 2001 NRC guidelines reports, the NAC—consisting of members from EPA, the Department of Defense (DOD), the Department of Energy (DOE), the Department of Transportation (DOT), other federal and state governments, the chemical industry, academia, and other organizations from the private sector—has developed AEGLs for more than 270 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 (COT) the Committee on Acute Exposure Guideline Levels, which prepared this report. This report is the nineteenth volume in that

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

series. AEGL documents for the cyanide salts, diketene, methacrylaldehyde, pentaborane, tellurium hexafluoride, and tetrafluoroethylene are each published as an appendix in 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.

The committee's review of the AEGL documents involved both oral and written presentations to the committee by the authors of the documents. The committee examined the draft documents and provided comments and recommendations for how they could be improved in a series of interim reports. The authors revised the draft AEGL documents based on the advice in the interim reports and presented them for reexamination by the committee as many times as necessary until the committee was satisfied that the AEGLs were scientifically justified and consistent with the 1993 and 2001 NRC guideline reports. After these determinations have been made for an AEGL document, it is published as an appendix in a volume such as this one.

The interim report of the committee that led to this report was reviewed in draft form 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 the committee interim report, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents A. Wallace Hayes (Harvard School of Public Health), Sam Kacew (University of Ottawa), and Judith Zelikoff (New York University).

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 this volume before its release. The review of the interim report was overseen by Robert Goyer (University of Western Ontario [retired]). Appointed by the NRC, he was responsible for making certain that an independent examination of the interim 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.

The committee gratefully acknowledges the valuable assistance provided by Ernest Falke and Iris A. Camacho from EPA. The committee also acknowledges Susan Martel, the project director for her work this project. Other staff members who contributed to this effort are James J. Reisa (director of the Board on Environmental Studies and Toxicology), Radiah Rose (manager of editorial projects), Mirsada Karalic-Loncarevic (manager of the Technical Information

Center), and Tamara Dawson (program associate). Finally, I would like to thank all members of the committee for their expertise and dedicated effort throughout the development of this report.

Edward C. Bishop, *Chair*
Committee on Acute Exposure
Guideline Levels

DEDICATION

The Committee on Acute Exposure Guideline Levels dedicates this volume to our late colleague Dr. Donald E. Gardner. Don was a member of the committee for 12 years, and served as chair for 8 of those years. He was a distinguished toxicologist, respected leader, and valued friend.

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 19

National Research Council Committee Review of Acute Exposure Guideline Levels for Selected Airborne Chemicals

This report is the nineteenth 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 in 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. 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 (NASA) (NRC 1968, 1972, 1984a,b,c,d, 1985a,b, 1986a, 1987, 1988, 1994, 1996a,b, 2000a, 2002a, 2007a, 2008a). COT has also published guidelines for developing emergency exposure guidance levels for military personnel and for astronauts (NRC 1986b, 1992, 2000b). 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 November 1995, 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:

[1]NAC completed its chemical reviews in October 2011. The committee was composed of members from EPA, DOD, many other federal and state agencies, industry, academia, and other organizations. From 1996 to 2011, the NAC discussed over 300 chemicals and developed AEGLs values for at least 272 of the 329 chemicals on the AEGLs priority chemicals lists. Although the work of the NAC has ended, the NAC-reviewed technical support documents are being submitted to the NRC for independent review and finalization.

AEGL-1 is the airborne concentration (expressed as ppm [parts per million] or mg/m^3 [milligrams per cubic meter]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory 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 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 animal studies 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 have multiple effects, all end points (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, 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 were initially prepared by ad hoc AEGL development teams consisting of a chemical manager, chemical reviewers, and a staff scientist of the NAC contractors—Oak Ridge National Laboratory and subsequently SRC, Inc. The draft documents were then reviewed by NAC and elevated from "draft" to "proposed" status. After the AEGL documents were approved by NAC, they were published in the *Federal Register* for public comment. The reports were 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 committee 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 and the contractors for the accuracy and completeness of the toxicity data cited in the AEGL reports. Thus far, the committee has prepared eighteen reports in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2001b, 2002b, 2003, 2004, 2007b, 2008b, 2009, 2010a,b, 2011, 2012a,b,c, 2013a,b, 2014a,b,c). This report is the nineteenth volume in that series. AEGL documents for the cyanide salts, diketene, methacrylaldehyde, pentaborane, tellurium hexafluoride, and tetrafluoroethylene are each published as an appendix in 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.

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Appendixes

3

Methacrylaldehyde[1]

Acute Exposure Guideline Levels

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P.L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review, and interpret relevant toxicologic and other scientific data and develop AEGLs for high-priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min and 1, 4, 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 or milligrams per cubic meter [ppm or 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 effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

[1]This document was prepared by the AEGL Development Team composed of Tom Marshall (Oak Ridge National Laboratory), Lisa Ingerman (SRC, Inc.), Julie Klotzbach (SRC, Inc.), Chemical Manager Susan Ripple (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances), and Ernest V. Falke (U.S. Environmental Protection Agency). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

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

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

Airborne concentrations below the AEGL-1 represent exposure concentrations that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, nonsensory 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 concentrations 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 idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Methacrylaldehyde is a colorless liquid at ambient temperature and pressure. It is an intermediate in the production of methacrylonitrile and methacrylic acid, and has been found in the emissions from automobile exhaust, liquid floor wax, steel-protective paints, and trees. Production of methacrylaldehyde in the United States (other than as a chemical intermediate) was discontinued in the late 1970s because better catalysts in propylene oxidation became available for the production of copolymers and resins. Methacrylaldehyde is highly irritating to mucous membranes, especially the upper respiratory tract and eyes (HSDB 2002). Data on the acute lethality of methacrylaldehyde in animals are sparse. Inhalation studies indicate that it is an irritant and that the upper respiratory tract is the target for toxicity in laboratory animals. Irritant effects were evident in studies of durations ranging from a single 6-h exposure to repeated exposures for 2-13 weeks.

The AEGL-1 values for methacrylaldehyde are based on ocular irritation in healthy human subjects (Nojgaard et al. 2005). The nondominant eyes of 10 men were exposed for 20 min to methacrylaldehyde at concentrations of 0, 0.089, 0.189, and 0.286 ppm in eight sessions. Blinking frequency was recorded as a measure of irritation and the subjects described the intensity of any ocular discomfort or irritation during the exposures. The number of complaints about irritation and its intensity were not different at any concentration relative to that described by the control group. The relative change in blinking frequency was statistically higher (18%; $p = 0.001$) during exposure at 0.286 ppm. The no-

observed-adverse-effect level (NOAEL) for blinking frequency was 0.189 ppm, which served as the point-of-departure for all of the AEGL-1 values for methacrylaldehyde. No uncertainty factors were applied because the blinking frequency is not a perceived effect but an objective measurement that precedes perceived irritation. The same AEGL-1 value was used for all durations because mild irritation is not expected to vary over time.

The AEGL-2 values are based on sensory irritation observed in a study by Coombs et al. (1994), in which Sprague-Dawley rats were exposed to methacrylaldehyde at 1, 4.9, and 15.3 ppm for 6 h/day, 5 days/week for 13 weeks. Animals exposed at the two highest concentrations were observed keeping their eyes half-closed or closed during exposure and animals exposed at 15.3 ppm occasionally exhibited salivation. No signs of ocular irritation were observed at 1 ppm. Lesions of the upper airways were evidence that the upper respiratory tract is also a target for toxicity. No relevant single exposure or short-term exposure studies were available. Because half-closed or closed eyes may be impairments for escape, 1 ppm was used as the point-of-departure. Typically, two uncertainty factors of 3 would be used for direct-acting irritants; one to account for interspecies differences and one to account for intraspecies variability. However, adjusting the 1-ppm point-of-departure by a total uncertainty factor of 10 would result in values lower than 0.189 ppm, the concentration which did not result in perceived irritation or change in blinking frequency in the Nojgaard et al. (2005) study used as the basis of the AEGL-1 values. Thus, a total uncertainty factor of 3 was used. Time scaling was not performed because half-closed or closed eyes are signs of contact irritation.

The AEGL-3 values are based on a study of a single 6-h exposure to methacrylaldehyde at 77 ppm, which resulted in 90% mortality in rats (Coombs et al. 1992). No deaths were observed in rats exposed at 19 ppm for 6 h/day, 5 days/week for 2 weeks (Coombs et al. 1992) or in rats exposed at 15.3 ppm for 6 h/day, 5 days/week for 13 weeks (Coombs et al. 1994). The concentration of 19 ppm was selected as the point-of-departure for AEGL-3 values. Selecting a no-effect level as the basis of the AEGL-3 values is supported by the steep concentration-response relationship; a 4-fold increase in concentration resulted in a 90% increase in mortality. AEGL-3 values were time-scaled using the equation $C^n \times t = k$ (ten Berge et al. 1986). Default values of $n = 3$ for extrapolating to shorter durations and $n = 1$ for extrapolating to longer durations were used. The 30-min AEGL-3 value was adopted as the 10-min value because extrapolation from a 6-h point-of-departure to a 10-min guideline is not recommended (NRC 2001). A total uncertainty factor of 10 was applied; a factor of 3 was used to account for interspecies differences and a factor of 3 was used to account for intraspecies variability. Factors of 10 were considered unnecessary because the toxic effects of methacrylaldehyde appear to be related to contact irritation, so effects are not expected to differ substantially between species or among individuals.

The AEGL values for methacrylaldehyde are presented in Table 3-1.

1. INTRODUCTION

Methacrylaldehyde is a colorless liquid at ambient temperature and pressure. It is highly irritating to mucous membranes, especially the upper respiratory tract and eyes (HSDB 2002). Production of methacrylaldehyde in the United States other than as a chemical intermediate was discontinued in the late 1970s because better catalysts in propylene oxidation became available in the production of copolymers and resins. It is an intermediate in the production of methacrylonitrile and methacrylic acid. It has been found in the emissions from automobile exhaust, liquid floor wax, steel protective paints, and trees. The chemical and physical properties of methacrylaldehyde are presented in Table 3-2.

TABLE 3-1 AEGL Values for Methacrylaldehyde

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	0.20 ppm (0.58 mg/m^3)	0.20 ppm (0.58 mg/m^3)	0.20 ppm (0.58 mg/m^3)	0.20 ppm (0.58 mg/m^3)	0.20 ppm (0.58 mg/m^3)	Eye blinking frequency in human subjects (Nojgaard et al. 2005)
AEGL-2 (disabling)	0.33 ppm (0.96 mg/m^3)	0.33 ppm (0.96 mg/m^3)	0.33 ppm (0.96 mg/m^3)	0.33 ppm (0.96 mg/m^3)	0.33 ppm (0.96 mg/m^3)	No-effect level for ocular irritation in rats (Coombs et al. 1994)
AEGL-3 (lethal)	4.3 ppm (12 mg/m^3)	4.3 ppm (12 mg/m^3)	3.5 ppm (10 mg/m^3)	2.2 ppm (6.4 mg/m^3)	1.4 ppm (4.1 mg/m^3)	No deaths in rats (Coombs et al. 1992)

TABLE 3-2 Chemical and Physical Properties of Methacrylaldehyde

Parameter	Value	References
Synonyms	Methacrolein; 2-methylpropenal; methacraldehyde; 2-methyl-2-propenal; 2-methylacrolein; isobutenal; methacrolein	Borchers 2012
CAS registry no.	78-85-3	Borchers 2012
Chemical formula	C_4H_6O	HSDB 2002
Molecular weight	70.09	Borchers 2012
Physical state	Colorless liquid	HSDB 2002
Melting point	-81°C	HSDB 2002
Boiling point	68.4°C	HSDB 2002
Density/specific gravity (water = 1)	0.849 at 25°C	HSDB 2002
Vapor density (air = 1)	2.4	HSDB 2002
Solubility in water	5.9% (59,000 mg/L) at 20°C; miscible with water, ethanol, and ether	HSDB 2002
Vapor pressure	155 mm Hg at 25 °C	HSDB 2002
Lower explosive limit (volume % in air)	2.6	IPCS 1995
Conversion factors	1 ppm = 2.9 mg/m^3 1 mg/m^3 = 0.35 ppm	HSDB 2002

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No studies of the acute lethality of methacrylaldehyde in humans were found.

2.2. Nonlethal Toxicity

2.2.1. Clinical Studies

The nondominant eye of 10 healthy men was exposed for 20 min to methacrylaldehyde at concentrations of 0, 0.089, 0.189, and 0.286 ppm (Nojgaard et al. 2005). Methacrylaldehyde vapors were mixed with clean air that was adjusted to a flow rate that generated the desired concentration. Exposures were conducted using a clear plastic eyepiece though which the vapors passed after mixing with clean air at 20% relative humidity. Concentrations delivered to the eyepiece were measured at a point in the delivery system before reaching the eyepiece. Blinking frequency was recorded as a measure of irritation and the subjects reported the perceived intensity of any eye discomfort or irritation during the exposure sessions. The subjects were recorded by a digital video camera and the same researcher viewed all of the videos and counted the number of blinks per session. The subjects were asked to rate perceived irritation of the eye, eyelid, or skin as none, weak, moderate, or strong. A baseline for blinking frequency was established by having four successive stages in each exposure session: an acclimatization stage, which included 3 min of clean air; an initial baseline recording with 8 min of clean air; a 20 min stage of chemical or clean air; and a final 8 min of clean air. The latter stage was divided into 4 min of recovery and 4 min of a final baseline recording. The number of complaints about irritation and its perceived intensity were not different at any concentration relative to the control exposure (see Table 3-3). The relative change in blinking frequency was statistically higher (18%; $p = 0.001$) during exposure at the highest concentration of 0.286 ppm. The NOAELs were 0.286 ppm for perceived irritation and 0.189 ppm for blinking frequency. A mixture of limolene oxidation products and ozone was tested separately in this study. The results showed that those materials increased blinking frequency by as much as 34%, and also showed that lower relative humidity (20% vs. 50%) exacerbated the response.

2.3. Neurotoxicity

No studies of the neurotoxicity of methacrylaldehyde in humans were found.

TABLE 3-3 Results of Blinking Frequency Tests in Humans Exposed to Methacrylaldehyde

Test Parameter	Control	0.089 ppm	0.189 ppm	0.286 ppm
Subjects perceiving irritation	3/10	4/10	5/10	4/10
Perceived intensity	<weak	<weak, weak	<weak, weak	<weak, weak
Relative change in blinking frequency (%)[a]	-9	10	8	18[b]
95% Confidence interval (%)	-19 to 3	-2 to 23	-2 to 20	7 to 30
p-value[c]	0.14	0.09	0.13	0.001

[a]Change relative to baseline of each subject calculated using log-transformed data.
[b]p = 0.001.
[c]Calculated by repeated-analysis using ANOVA software program.
Source: Adapted from Nojgaard et al. 2005.

2.4. Developmental and Reproductive Toxicity

No studies of the developmental or reproductive toxicity of methacrylaldehyde in humans were found.

2.5. Genotoxicity

No studies of the genotoxicity of methacrylaldehyde in humans were found.

2.6. Carcinogenicity

No studies of the carcinogenicity of methacrylaldehyde in humans were found.

2.7. Summary

The single human study on methacrylaldehyde indicates that it is a direct-acting irritant, confirming that effects in people are similar to those observed in animal studies.

3. ANIMAL TOXICITY DATA

The results of toxicity studies of laboratory animals exposed to methacrylaldehyde by inhalation are summarized in Table 3-4.

TABLE 3-4 Result of Toxicity Studies of Methacrylaldehyde

Species	Exposure Duration	Concentration (ppm)	End Point	Reference
Mouse	30 min	2.0	NOAEL (10% decrease in respiratory rate)	Larsen and Nielsen 2000
		4.4	LOAEL (30% decrease in respiratory rate)	
		6.6	40% decrease in respiratory rate	
		10.2	50% decrease in respiratory rate	
		13.1	55% decrease in respiratory rate	
		26.3	70% decrease in respiratory rate	
		1.3 (95% CI: 0.8-2.1)	RD_0	
Rat	4 h	125	Lethal to 2/6, 3/6, or 4/6 rats	Carpenter et al. 1949
Rat	4 h	195	LC_{50}; severe irritation of respiratory tract	BG Chemie 1995
Rat	6 h	77	Lethal to 9/10 in 48 h; acute irritation, pulmonary lesions	Coombs et al. 1992
		5	NOAEL; eyes half-closed during exposure	
	6 h/d, 5 d/wk for 2 wk	19	LOAEL; multiple clinical signs related to respiratory irritation, respiratory tract lesions	
Rat	6 h/d, 5 d/wk for 13 wk	1.0	NOEL	Coombs et al. 1994
		4.9	NOAEL; eyes half-closed during exposure	
		15.3	LOAEL; multiple clinical signs related to respiratory irritation, respiratory tract lesions, evidence of reversal 4 wk after exposure	
Rat	Unknown	10	Maternal toxicity	BG Chemie 1995
		20	Maternal and fetal toxicity (reduced birth weight)	

Abbreviations: CI, confidence interval; LOAEL, lowest-observed-adverse-effect level; NOAEL, no-observed-adverse-effect level; NOEL, no-observed-effect level; RD_0, extrapolated threshold concentration for reduction in respiratory rate.

3.1. Acute Lethality

3.1.1. Rats

Carpenter et al. (1949) exposed six Sherman rats (sex not specified) to methacrylaldehyde at a nominal concentration of 125 ppm for 4 h in a glass inhalation chamber, and observed the survivors for 14 days. The report indicates that two, three, or four of the rats died. No other information was provided. The concentration of 125 ppm is assumed to be an approximate LC_{50} in Sherman rats.

An unconfirmed 4-h LC_{50} of 195 ppm is reported in a secondary source (BG Chemie 1995). BG Chemie is the German Employment Accident Insurance Fund of the Chemical Industry. The organization, which includes a scientific advisory committee, assesses the hazard of chemicals in the workplace, plans toxicity studies, and contracts the conduct of those studies to laboratories.

3.2. Nonlethal Toxicity

3.2.1. Rats

In a 2-week inhalation exposure study in Sprague-Dawley rats, a single 6-h exposure to methacrylaldehyde at 77 ppm, the highest concentration tested, resulted in death or a moribund condition in nine of 10 rats (five male, four female) within 2 days of exposure (Coombs et al. 1992). The cause of death was lesions in the respiratory tract, which were comprised of necrosis of the olfactory and respiratory epithelium in the nasal turbinates, extensive epithelial ulceration of the larynx and trachea, and necrosis of the bronchiolar epithelium of the lungs. The other two concentrations tested were 5 and 19 ppm, and groups of five male and five female rats were exposed at those concentrations for 6 h/day, 5 days/week for the full 2 weeks. Closed eyes or half-closed eyes were noted in the rats during each exposure period; rats in the 19-ppm group also adopted a hunched position during the exposure. Minimal hyperplasia of the respiratory epithelium of the nasal turbinates and laryngeal epithelia were observed at 19 ppm; no respiratory lesions were observed at 5 ppm.

Coombs et al. (1994) exposed groups of 10 male and 10 female Sprague-Dawley rats by inhalation to methacrylaldehyde at 0, 1, 4.9, and 15.3 ppm for 6 h/day, 5 days/week for 13 weeks. Additional groups of control rats and rats exposed at 15.3 ppm were maintained and observed for 4 weeks after exposure ended. Animals exposed at 4.9 or 15.3 ppm were observed keeping their eyes half-closed during exposure days 1-6 or for most of the study, respectively; salivation was observed occasionally in the 15.3-ppm group. Weight gain and food consumption were decreased in both males and females at the highest concentration. Lesions in the respiratory tract comprised of inflammation of the olfactory epithelium and metaplastic changes in the dorsal meatus and dorsal central nasal septum were observed in male and female rats exposed at 15.3 ppm. Similar changes were found in the larynx of some animals at that concentration. Clear

signs of repair and recovery from the lesions were found during the 4-week observation period. The NOAEL was 4.9 ppm and the LOAEL was 15.3 ppm for olfactory lesions. For ocular irritation, the NOAEL was 1 ppm.

3.2.2. Mice

Larsen and Nielsen (2000) studied the effects of inhaled methacrylaldehyde on the respiratory tract of male mice (strain not specified; four per group) exposed at 0, 2.0, 4.4, 6.6, 10.2, 13.1, or 26.3 ppm for 30 min. Sensory irritation as indicated by a decreased respiratory rate, airflow limitation as indicated by the expiration flow rate at half of the tidal volume, and pulmonary irritation as indicated by the time-of-pause between the end of expiration and the beginning of inspiration were evaluated. Methacrylaldehyde caused a concentration-dependent decrease in respiratory rate of about 30, 40, 50, 55, and 70% at 4.4, 6.6, 10.2, 13.1, and 26.3 ppm, respectively. An RD_{50} (concentration that reduces the respiratory rate by 50%) of 10.4 ppm and an RD_0 (extrapolated threshold concentration for reduction in respiratory rate) of 1.3 ppm were calculated for that indicator of sensory irritation. No response was seen in the indicators for pulmonary irritation. The investigators concluded that methacrylaldehyde is a potent sensory irritant and that desensitization does not occur in mice because the level of sensory irritation was constant during exposure.

3.3. Developmental and Reproductive Toxicity

No studies of the developmental or reproductive toxicity of methacrylaldehyde were found.

3.4. Genotoxicity

Only in vitro mutagenicity data are available on methacrylaldehyde and the results are equivocal. Methacylaldehyde produced positive results in *Salmonella typhimurium* strains TA100 (Eder et al. 1990, 1993, 1994) and TA104 (Mersch-Sunderman et al. 1992) without S-9 activation, but had negative results in strain TA 98 (Kato et al. 1989). Neudecker et al. (1991) showed that the addition of S-9 activation reduced methacrylaldehyde mutagenicity even when the liver preparation was boiled or when epoxide hydrolase was inhibited. That indicates that the positive results seen in this bacterial assay are of a direct-acting nature. Methacrylaldehyde was weakly positive in an *Escherichia coli* WP2 *uvr*A assay without activation (Kato et al. 1989). Several studies have shown methacrylaldehyde to be inactive in the SOS chromotest (Benamira and Marnett 1992; Mersch-Sunderman 1992; Eder et al. 1990, 1993, 1994). Weak activity for DNA damage was indicated in the comet assay using rat hepatocytes (Kuchenmeister et al. 1998), and a marginally positive result was obtained in studies of DNA adduct formation (Eder et al. 1993).

3.5. Chronic Toxicity and Carcinogenicity

No studies of the chronic toxicity or carcinogenicity of methacrylaldehyde were found.

3.6. Summary

Acute lethality data from animal studies are sparse. Nonlethal inhalation studies indicate that methacrylaldehyde is an irritant and that the upper respiratory tract is the target for toxicity. Signs of respiratory irritation in rats were gasping and closed or half-closed eyes during inhalation exposure. At higher concentrations, lesions of the upper airways were evident. Data in mice show that methacrylaldehyde suppresses respiration in a manner that indicates significant irritation. Genotoxicity data are equivocal. No data on the reproductive toxicity, developmental toxicity, or carcinogenicity of methacrylaldehyde were available.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No studies on the metabolism and disposition of methacrylaldehyde were available. According to HSDB (2002), the fate of methacrylaldehyde is probably similar to other short chain aldehydes that are readily oxidized by aldehyde dehydrogenase to organic acids, which can then serve as substrates for fatty oxidation and the Krebs cycle. A second pathway is for aldehydes to be inactivated by reaction with sulfhydryl groups, particularly glutathione.

4.2. Mechanism of Toxicity

The short chain alkenes related to acrolein are known to react with sulfhydryl groups (Beauchamp et al. 1985). Acrolein is the most toxic of the 2-alkenals (including methacrylaldehyde, crotonaldehyde, pentenal, and hexenal) and is also the most reactive toward sulfhydryl groups. The respiratory irritancy of acrolein and related aldehydes may be due to reactivity toward sulfhydryl groups in receptor proteins in the nasal mucosa.

4.3. Structure-Activity Relationships

Neudecker et al. (1991) showed that relative to acrolein the size of the alkylating substituent influences the direct mutagenicity of the aldehyde, with activity decreasing in the order of 2-methylacrolein, 2-ethylacolein, and 2-propylacrolein.

4.4. Other Relevant Information

4.4.1. Species Variability

Studies in rats and mice (Table 3-4) do not indicate much variability in the toxic effects of methacrylaldehyde. That is likely due to the direct irritating effect of methacrylaldehyde on the airways.

4.4.2. Concentration-Exposure Duration Relationship

The concentration-exposure duration relationship for many irritant and systemically-acting vapors and gases may be described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). To obtain health-protective AEGL values in the absence of an empirically derived scaling exponent, temporal scaling may be performed using default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations (NRC 2001).

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

The only human toxicity study of methacrylaldehyde shows that the chemical has the potential for ocular irritation (Nojgaard et al. 2005). The nondominant eyes of 10 men were exposed for 20 min to methacrylaldehyde at concentrations of 0, 0.089, 0.189, and 0.286 ppm in eight sessions. Blinking frequency was recorded as a measure of irritation and the subjects described the intensity of any ocular discomfort or irritation during the exposures. The number of complaints about irritation and its intensity were not different at any concentration relative to that described by the control group. The relative change in blinking frequency was statistically higher (18%; p = 0.001) during exposure at 0.286 ppm. The NOAEL for blinking frequency was 0.189 ppm.

5.2. Animal Data Relevant to AEGL-1

Data in rats show that inhaled methacrylaldehyde is a contact irritant. For a 2-week exposure, the NOAEL was 4.9 ppm and the LOAEL was 19 ppm for respiratory-tract lesions (Coombs et al. 1992). A 13-week study in rats demonstrated a NOAEL of 5 ppm and a LOAEL of 15.3 ppm for olfactory lesions and a NOAEL of 1 ppm for ocular irritation (Coombs et al. 1994).

5.3. Derivation of AEGL-1 Values

The point-of-departure for the AEGL-1 values for methacrylaldehyde is the NOAEL of 0.189 ppm for blinking frequency in human subjects (Nojgaard et al. 2005). No uncertainty factors were applied because blinking frequency is not a perceived effect, but is rather an objective measurement that precedes perceived irritation. The same concentration was used for all durations because mild irritation is not expected to vary over time. The AEGL-1 values for methacrylaldehyde are presented in Table 3-5.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data relevant to deriving AEGL-2 values for methacrylaldehyde were found.

6.2. Animal Data Relevant to AEGL-2

Data in rats show that inhaled methacrylaldehyde is a contact irritant. For a 2-week exposure to methacrylaldehyde, the NOAEL and LOAEL for respiratory-tract lesions in rats was 5 and 19 ppm, respectively (Coombs et al. 1992). In another study, Sprague-Dawley rats were exposed to methacrylaldehyde at 1, 4.9, and 15.3 ppm for 6 h/day, 5 days/week for 13 weeks. At the two highest concentrations, the animals kept their eyes half-closed or closed during exposure. Salivation (indicative of substantial sensory irritation) was observed occasionally in animals exposed at 15.3 ppm. No signs of ocular irritation were observed at 1 ppm. The upper respiratory tract is also a target of toxicity for methacrylaldehyde, as evidenced by olfactory lesions found in rats exposed at 15.3 ppm. Data in mice show that methacrylaldehyde suppresses respiration in a manner that indicates significant irritation (Larsen and Nielsen 2000).

6.3. Derivation of AEGL-2 Values

The AEGL-2 values for methacrylaldehyde are based on a NOAEL of 1 ppm for ocular irritation in rats (Coombs et al. 1994). Typically, two uncertainty factors of 3 would be applied to determine AEGL values for direct-acting irritants; one to account for interspecies differences and one to account for intraspecies variability. However, adjusting the 1-ppm point-of-departure by a total uncertainty factor of 10 would result in values lower than 0.189 ppm, which is a NOAEL for ocular irritation in humans (Nojgaard et al. 2005) and the basis of the AEGL-1 values for methacrylaldehyde. Thus, a total uncertainty factor of 3 was applied instead. Time scaling was not performed because mild ocular irritation is not expected to vary over time. The AEGL-2 values for methacrylaldehyde are presented in Table 3-6, and the calculations are presented in Appendix A.

TABLE 3-6 AEGL-2 Values for Methacrylaldehyde

10 min	30 min	1 h	4 h	8 h
0.33 ppm (0.96 mg/m^3)	0.33 ppm (0.96 mg/m^3)	0.33 ppm (0.96 mg/m^3)	0.33 ppm (0.96 mg/m^3)	0.33 ppm (0.96 mg/m^3)

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data relevant to deriving AEGL-3 values for methacrylaldehyde were found.

7.2. Animal Data Relevant to AEGL-3 Values

Data in rats show that inhaled methacrylaldehyde is a sufficiently severe contact irritant that it causes serious effects, including lethality (Table 3-4). A single exposure of rats to methacrylaldehyde at 77 ppm for 6 h resulted in 90% mortality (Coombs et al. 1992). No deaths were observed in rats exposed at 19 ppm for 6 h/day, 5 days/week for 2 weeks or in rats exposed at 15.3 ppm 6 h/day, 5 days/week for 13 weeks (Coombs et al. 1994). Other supporting studies include an assumed 4-h LC_{50} in Sherman rats of about 125 ppm (nominal) reported by Carpenter et al. (1949), and an unconfirmed 4-h LC_{50} of 195 ppm reported in a secondary source (BG Chemie 1995).

7.3. Derivation of AEGL-3 Values

On the basis of the study by Coombs et al. (1992), the 2-week NOAEL for lethality of 19 ppm was selected as the point-of-departure for AEGL-3 values for methacrylaldehyde. Time scaling was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986). Data on methacrylaldehyde were inadequate for deriving an empirical value for the exponent n, so default values of n = 3 to extrapolate to shorter durations and n = 1 to extrapolate to longer durations were used. A total uncertainty factor of 10 was applied; a factor of 3 to account for interspecies differences and a factor of 3 to account for intraspecies variability. Factors of 10 were considered unnecessary because the toxic effects of methacrylaldehyde appear to be related to contact irritation, so effects are not expected to differ substantially between species or among individuals. Furthermore, use of a factor of 10 for either the interspecies or intraspecies uncertainty factor would result in AEGL-3 values that are less consistent with the available data. (A total uncertainty factor of 30 yields AEGL-3 values of 1.4 ppm for the 10- and 30-min durations, 1.1 ppm for the 1-h duration, 0.7 ppm for the 4-h duration, and 0.47 ppm for the 8-h duration. No effects were observed in rats exposed at 1.0 ppm for 6 h/day, 5 days/week for 13 weeks, and half-closed eyes and respiratory irritation were observed in rats similarly exposed at 4.9 ppm).

The AEGL-3 values for methacrylaldehyde are presented in Table 3-7, and the calculations are provided in Appendix A.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

The AEGL values for methacrylaldehyde are presented in Table 3-8. The AEGL-1 values are based on a study of ocular irritation in healthy human subjects, which identified a NOAEL and a LOAEL for blinking frequency (Nojgaard et al. 2005). The AEGL-2 values are based on a study by Coombs et al. (1994), in which Sprague-Dawley rats exposed to methacrylaldehyde had clinical signs of ocular irritation. The AEGL-3 values are based on a concentration of methacrylaldehyde not resulting in deaths in rats exposed for 6 h/day, 5 days/week for 13 weeks (Coombs et al. 1992).

8.2. Other Standards and Guidelines

No other standards or guidelines for methacrylaldehyde were found.

8.3. Data Adequacy and Research

Human data appropriate for derivation of AEGL-1 values for methacrylaldehyde were available from a well-conducted study. However, no information was available concerning effects in young, elderly, or asthmatic individuals. Minimal animal data were available for derivation of AEGL-2 or AEGL-3 values.

TABLE 3-7 AEGL-3 Values for Methacrylaldehyde

10 min	30 min	1 h	4 h	8 h
4.3 ppm (12 mg/m^3)	4.3 ppm (12 mg/m^3)	3.5 ppm (10 mg/m^3)	2.2 ppm (6.4 mg/m^3)	1.4 ppm (4.1 mg/m^3)

TABLE 3-8 AEGL Values for Methacrylaldehyde

Classification	10 min	30min	1h	4h	8 h
AEGL-1 (nondisabling)	0.20 ppm (0.58 mg/m^3)	0.20 ppm (0.5860 mg/m^3)	0.20 ppm (0.58 mg/m^3)	0.20 ppm (0.58 mg/m^3)	0.20 ppm (0.58 mg/m^3)
AEGL-2 (disabling)	0.33 ppm (0.96 mg/m^3)	0.33 ppm (0.96 mg/m^3)	0.33 ppm (0.96 mg/m^3)	0.33 ppm (0.96 mg/m^3)	0.33 ppm (0.96 mg/m^3)
AEGL-3 (lethal)	4.3 ppm (12 mg/m^3)	4.3 ppm (12 mg/m^3)	3.5 ppm (10 mg/m^3)	2.2 ppm (6.4 mg/m^3)	1.4 ppm (4.1 mg/m^3)

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APPENDIX A

DERIVATION OF AEGL VALUES FOR METHACRYLALDEHYDE

Derivation of AEGL-1 Values

Key study:	Nojgaard, J.K., K.B. Christensen, and P. Wolkoff. 2005. The effect on human blink frequency of exposure to limonene oxidation products and methacrolein. Toxicol Lett. 156(2):241-251.
Toxicity end point:	Blinking frequency, NOAEL = 0.189 ppm
Time scaling:	None
Uncertainty factors:	None
Modifying factor:	None
Calculations:	
10-min AEGL-1:	0.189 ppm (rounded to 0.20 ppm)
30-min AEGL-1:	0.189 ppm (rounded to 0.20 ppm)
1-h AEGL-1:	0.189 ppm (rounded to 0.20 ppm)
4-h AEGL-1:	0.189 ppm (rounded to 0.20 ppm)
8-h AEGL-1:	0.189 ppm (rounded to 0.20 ppm)

Derivation of AEGL-2 Values

Key study:	Coombs, D.W., T.J. Kenny, D. Crook, and W.A. Gibson. 1994. Methacrolein (BG No. 108) 13-week Inhalation Toxicity Study in Rats. BGH 50/932334. Study performed on behalf of the BG Chemie, Heidelberg, Germany, by Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England.
Toxicity end point:	No signs of ocular irritation in rats at 1 ppm
Time scaling:	None
Uncertainty factors:	3 for interspecies differences and intraspecies variability

Modifying factor:	None
10-min AEGL-2:	1 ppm ÷ 3 = 0.33 ppm
30-min AEGL-2:	1 ppm ÷ 3 = 0.33 ppm
1-h AEGL-2:	1 ppm ÷ 3 = 0.33 ppm
4-h AEGL-2:	1 ppm ÷ 3 = 0.33 ppm
8-h AEGL-2:	1 ppm ÷ 3 = 0.33 ppm

Derivation of AEGL-3 Values

Key study:	Coombs, D.W., T.J. Kenny, and C.J. Hardy. 1992. Methacrolein (BG No. 108) 2-week Repeat Dose Preliminary Inhalation Toxicity Study in Rats. BGH 50/932334. BGH 40/920648. Study performed on behalf of the BG Chemie, Heidelberg, Germany, by Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England.
Toxicity end point:	No deaths in rats exposed at 19 ppm for 6 h/day, 5 days/week for 2 weeks
Time scaling:	$C^n \times t = k$ (ten Berge et al.1986); default values of n = 3 for extrapolation to shorter durations and n = 1 for longer durations. The 30-min value was adopted as the 10-min value because of the uncertainty associated with extrapolating a 6-h point-of-departure to a 10-min value (NRC 2001). $(19 \text{ ppm})^3 \times 6 \text{ h} = 41{,}154 \text{ ppm-h}$ $(19 \text{ ppm})^1 \times 6 \text{ h} = 114 \text{ ppm-h}$
Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability
Modifying factor:	None
10-min AEGL-3:	4.3 ppm (same as the 30-min AEGL-3 value)
30-min AEGL-3:	$C^3 \times 0.5 \text{ h} = 41{,}154 \text{ ppm-h}$ $C^3 = 82{,}308 \text{ ppm}$ $C = 43.5 \text{ ppm}$ $43.5 \text{ ppm} \div 10 = 4.3 \text{ ppm}$

1-h AEGL-3: $C^3 \times 1\ h = 41{,}154$ ppm-h
$C^3 = 41{,}154$ ppm
$C = 34.5$ ppm
$34.5\ ppm \div 10 = 3.5$ ppm

4-h AEGL-3: $C^3 \times 4\ h = 41.154$ ppm-h
$C^3 = 10{,}288$ ppm
$C = 21.7$ ppm
$21.7\ ppm \div 10 = 2.2$ ppm

8-h AEGL-3: $C^1 \times 8\ h = 114$ ppm-h
$C = 14.25$ ppm
$14.25\ ppm \div 10 = 1.4$ ppm

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR METHACRYLALDEHYDE

Derivation Summary

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
0.20 ppm (0.58 mg/m^3)	0.20 ppm (0.58 mg/m^3)	0.20 ppm (0.58 mg/m^3)	0.20 ppm (0.58 mg/m^3)	0.20 ppm (0.58 mg/m^3)

Key reference: Nojgaard, J.K., K.B. Christensen, and P. Wolkoff. 2005. The effect on human blink frequency of exposure to limonene oxidation products and methacrolein. Toxicol Lett. 156(2):241-251.

Test species/Strain/Number: 10 healthy men

Exposure route/Concentration/Duration: Ocular exposure via eyepiece; 0, 0.089, 0.189, and 0.286 ppm for 20 min.

Effects:
0.089 ppm = NOAEL
0.189 ppm = NOAEL for increased blinking frequency
0.286 ppm = LOAEL for increased blinking frequency
0.286 ppm = NOAEL for perceived ocular irritation

End point/Concentration/Rationale: Blinking frequency as a measure of ocular irritation; NOAEL = 0.189 ppm

Uncertainty factors/Rationale: No uncertainty factors were necessary because blinking frequency is not a perceived effect, but an objective measurement that precedes perceived irritation.

Modifying factor: None

Animal-to-human dosimetric adjustment: None

Time scaling: None; the same value was applied to all durations because mild irritation is not expected to vary over time.

Data adequacy: Well-conducted human study.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.33 ppm (0.96 mg/m^3)	0.33 ppm 0.96 mg/m^3)	0.33 ppm (0.96 mg/m^3)	0.33 ppm (0.96 mg/m^3)	0.33 ppm (0.96 mg/m^3)

Key reference: Coombs, D.W., T.J. Kenny, D. Crook, and W.A. Gibson. 1994. Methacrolein (BG No. 108) 13-week Inhalation Toxicity Study in Rats. BGH 50/932334. Study performed on behalf of the BG Chemie, Heidelberg, Germany, by Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England.

Test species/Strain/Number: Rat; Sprague-Dawley; 10 males and 10 females/group

(Continued)

AEGL-2 VALUES Continued

Exposure route/Concentrations/Durations: Inhalation; 1, 4.9, and 15.3 ppm for 6 h/day, 5 days/week for 13 weeks
Effects: Half-closed or closed eyes were observed during exposure days 1-6 in rats exposed at 4.9 ppm and for most of the study in rats exposed at 15.3 ppm. Histopathologic evidence of respiratory-tract irritation was found at the end of the 13-week exposure period in rats exposed at 15.3 ppm.
End point/Concentration/Rationale: NOAEL for ocular irritation of 1 ppm, because ocular irritation could impair ability to escape.
Uncertainty factors/Rationale: Total uncertainty factor: 3 Studies of human volunteers and rodents indicate that methacrylaldehyde is a direct-acting irritant. Repeated exposure studies in rats show that the eyes and upper respiratory tract are targets for acute and subchronic toxicity. Data in mice show that methacrylaldehyde suppresses respiration in a manner consistent with significant irritation. Typically, two factors of 3 would be used for direct-acting irritants; one to account for interspecies differences and one to account for intraspecies variability. However, adjusting the 1-ppm point-of-departure by a total uncertainty factor of 10 would result in values lower than 0.189 ppm, the NOAEL for ocular irritation in humans (Nojgaard et al. 2005) and the basis for the AEGL-1 values for methacrylaldehyde.
Modifying factor: None
Animal-to-human dosimetric adjustment: None
Time scaling: Not performed because mild ocular irritation is unlikely to vary with exposure duration.
Data adequacy: Well-conducted subchronic study. No single or short-term exposure studies were available.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
4.3 ppm (12 mg/m^3)	4.3 ppm (12 mg/m^3)	3.5 ppm (10 mg/m^3)	2.2 ppm (6.4 mg/m^3)	1.4 ppm (4.1 mg/m^3)

Key reference: Coombs, D.W., T.J. Kenny, and C.J. Hardy. 1992. Methacrolein (BG. No. 108) 2-week repeat dose preliminary inhalation toxicity study in rats BGH 50/932334. BGH 40/920648. Study performed on behalf of the BG Chemie, Heidelberg, Germany, by Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England.
Test species/Strain/Number: Rat; Sprague-Dawley; 5 males and 5 females/group
Exposure route/Concentrations/Durations: Inhalation; 5, 19, and 77 ppm for 6 h/day, 5 days/week for 2 weeks.
Effects: No deaths observed at 19 ppm. After a single exposure to methacrylaldehyde at 77 ppm for 6 h, nine of 10 rats died or were moribund within 48 h.
End point/Concentration/Rationale: No deaths at 19 ppm.
Uncertainty factors/Rationale: Total uncertainty factor: 10

(Continued)

AEGL-3 VALUES Continued

Interspecies: 3, because methacrylaldehyde is a direct-acting irritant and its effects are unlikely to differ substantial between species.
Intraspecies: 3, because methacrylaldehyde is a direct-acting irritant and its effects are unlikely to differ among individuals.
Studies of human volunteers and rodents indicate that methacrylaldehyde is a direct-acting irritant. Repeated exposure studies in rats show that the eyes and upper respiratory tract are targets for acute and subchronic toxicity. Data in mice show that methacrylaldehyde suppresses respiration in a manner consistent with significant irritation. Furthermore, use of a default value of 10 for either the interspecies or intraspecies uncertainty factor would result in AEGL-3 values that are less consistent with the available data. (Use of a total uncertainty factor of 30 would yield AEGL-3 values of 1.4 ppm for the 10- and 30-min durations, 1.1 ppm for the 1-h duration, 0.7 ppm for the 4-h duration, and 0.47 ppm for the 8-h duration. No effects were found in rats exposed at 1.0 ppm for 6 h/day, 5 days/week for 13 weeks. Half-closed eyes were observed during exposure and reversible respiratory lesions were found in rats similarly exposed at 4.9 ppm).

Modifying factor: None

Animal-to-human dosimetric adjustment: None

Time scaling: $C^n \times t = k$ (ten Berge et al.1986); data on methacrylaldehyde were in adequate to derive an empirical value for the exponent n, so default values of n = 3 for extrapolation to shorter durations and n = 1 for extrapolation to longer durations were used (NRC 2001). The 30-min value was adopted as the 10-min value because of the uncertainty associated with extrapolating a 6-h point-of-departure to a 10-min value (NRC 2001).

Data adequacy: The inhalation study that demonstrated lethality after a single 6-h exposure to methacrylaldehyde was well conducted. The cause of death was lesions in the respiratory tract, comprised of necrosis of the olfactory and respiratory epithelium in the nasal turbinates, extensive epithelial ulceration of the larynx and trachea, and necrosis of the bronchiolar epithelium in the lung. No deaths were observed at the other two concentrations tested (5 and 19 ppm for 6 h/day, 5 days/week) for the full 2 weeks.

APPENDIX C

CATEGORY PLOT FOR METHACRYLALDEHYDE

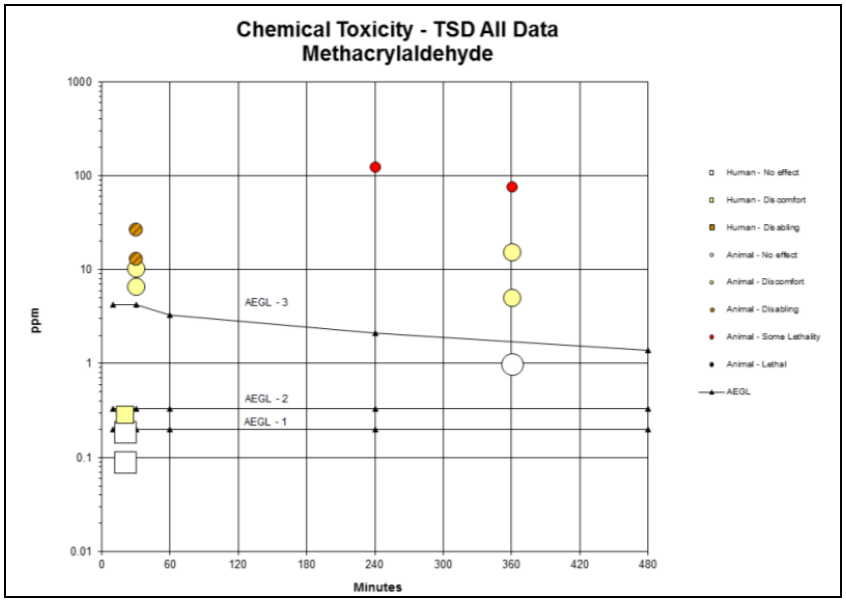

FIGURE C-1 Category plot of toxicity data and AEGL values for methacrylaldehyde.

TABLE C-1 Date Used in Category Plot for Methacrylaldehyde

Source	Species	ppm	Minutes	Category	Comments
AEGL-1		0.2	10	AEGL	
AEGL-1		0.2	30	AEGL	
AEGL-1		0.2	60	AEGL	
AEGL-1		0.2	240	AEGL	
AEGL-1		0.2	480	AEGL	
AEGL-2		0.33	10	AEGL	
AEGL-2		0.33	30	AEGL	
AEGL-2		0.33	60	AEGL	
AEGL-2		0.33	240	AEGL	
AEGL-2		0.33	480	AEGL	
AEGL-3		4.2	10	AEGL	
AEGL-3		4.2	30	AEGL	
AEGL-3		3.5	60	AEGL	

(Continued)

TABLE C-1 Continued

AEGL-3		2.2	240	AEGL	
AEGL-3		1.4	480	AEGL	
Nojgaard et al. 2005	Human	0.089	20	0	
Nojgaard et al. 2005	Human	0.189	20	0	
Nojgaard et al. 2005	Human	0.286	20	1	Increased blinking frequency
Coombs et al. 1992	Rat	1.0	360	0	
Coombs et al. 1992, 1994	Rat	5	360	1	Half-closed or closed eyes
Coombs et al. 1992	Rat	15.3	360	1	Ocular and respiratory irritation
Coombs et al. 1994	Rat	19	360	1	Ocular and respiratory irritation
Coombs et al. 1992	Rat	77	360	SL	90% lethality
Carpenter et al. 1949	Rat	125	240	SL	2/6, 3/6, or 4/6 deaths
Larsen and Nielsen 2000	Mouse	2.0	30	0	
Larsen and Nielsen 2000	Mouse	4.4	30	1	30% decrease in respiratory rate
Larsen and Nielsen 2000	Mouse	6.6	30	1	40% decrease in respiratory rate
Larsen and Nielsen 2000	Mouse	10.2	30	1	50% decrease in respiratory rate
Larsen and Nielsen 2000	Mouse	13.1	30	2	55% decrease in respiratory rate
Larsen and Nielsen 2000	Mouse	26.3	30	2	70% decrease in respiratory rate

For category: 0 = no effect, 1 = discomfort, 2 = disabling, SL = some lethality, 3 = lethality.