Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 17

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)[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. 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 seventeenth vol

ume in that series. AEGL documents for acrylonitrile, carbon tetrachloride, cyanogen, epichlorohydrin, ethylene chlorohydrin, toluene, trimethylacetyl chloride, hydrogen bromide, and boron tribromide 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. AEGL reports for additional chemicals will be presented in subsequent volumes.

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

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 reports of the committee that led to this report were 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 reports, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents for acrylonitrile (interim reports 19b, 21a, and 22), carbon tetrachloride (interim reports 13, 14, 18, and 22), cyanogen (interim report 19a), epichlorohydrin (interim reports 15, 19a, 20a, and 21a), ethylene chlorohydrin (interim reports 20a and 21a), toluene (interim reports 12, 18, and 22), trimethylacetyl chloride (interim reports 20a and 21a), hydrogen bromide (interim reports 16, 18, and 22), and boron tribromide (interim reports 19a and 22): Deepak Bhalla (Wayne State University), Harvey Clewell (The Hamner Institutes for Health Sciences), Jeffrey Fisher (U.S. Food and Drug Administration), David Gaylor (Gaylor and Associates, LLC), Sam Kacew (University of Ottawa), A. Wallace Hayes (Harvard School of Public Health), Rogene Henderson (Lovelace Respiratory Research Institute [retired]), James McDougal (Wright State University [retired]), Charles Reinhardt (DuPont Haskell Laboratory [retired]), Andrew Salmon (California Environmental Protection Agency), Joyce Tsuji (Exponent, Inc.), Bernard Wagner (New York University Medical Center [retired]), 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 re

lease. The review of interim reports was overseen by David Gaylor (Gaylor and Associates, LLC), Sidney Green, Jr., (Howard University), and Robert Goyer (University of Western Ontario [retired]). Appointed by the NRC, they were responsible for making certain that an independent examination of the interim reports 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

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

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

This report is the seventeenth 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)[3] 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

[3] 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.

varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

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) chemicalphysical 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 noobserved-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 sixteen 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, 2014). This report is the seventeenth volume in that series. AEGL documents for acrylonitrile, carbon tetrachloride, cyanogen, epichlorohydrin, ethylene chlorohydrin, toluene, trimethylacetyl chloride, hydrogen bromide, and boron tribromide 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. AEGL reports for additional chemicals will be presented in subsequent volumes.

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Appendixes

7

Trimethylacetyl Chloride[4]

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

[4] This document was prepared by the AEGL Development Team composed of Cheryl Bast (Oak Ridge National Laboratory), Heather Carlson-Lynch (SRC, Inc.), Lisa Ingerman (SRC, Inc.), Chemical Manager George Rusch (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).

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 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

Trimethylacetyl chloride is a clear colorless liquid. It is corrosive and is a moisture-sensitive lachrymator. Trimethylacetyl chloride is used as an intermediate in the preparation of trialkylacetic acids, which are used in polymers, pharmaceuticals, agricultural chemicals, cosmetics, and metal-working fluids.

Data were insufficient to derive AEGL-1 values for trimethylacetyl chloride. Therefore, AEGL-1 values are not recommended.

In the absence of appropriate chemical-specific data on trimethylacetyl chloride, the AEGL-3 values were divided by 3 to derive AEGL-2 values. That approach is justified by the steep concentration-response curve. In a mouse irritation study, a 30-min exposure to trimethylacetyl chloride at 115 ppm resulted in 25% mortality, and a 1.6 increase in the concentration resulted in a 3-fold increase in mortality (75% mortality at 180 ppm) (Hardy and Kieran, 1992). Rats or mice exposed to trimethylacetyl chloride at 78, 115, 180, and 249 ppm for 30 min to 6 h experienced 0, 25, 75, and 100% mortality, respectively (Eastman Kodak 1992; Hardy and Kieran 1992).

An exposure to trimethylacetyl chloride causing no death in rats (78 ppm for 6 h) (Eastman Kodak 1992) was used as the point of departure for the AEGL-3 values. Rough coat, labored breathing, and body weight loss were noted at that

concentration, and 100% mortality was noted at the next highest concentration tested (249 ppm for 3.5 h). Values were scaled across time using the equation $C^n \times t = k$, with default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations to derive values protective of human health (NRC 2001). The 30-min value was adopted as the 10min value because of the added uncertainty of extrapolating a 6-h point of departure to a 10-min AEGL-3 value. Two uncertainty factors of 10 were applied; one factor to account for interspecies differences and one factor to account for the absence of information available to describe interindividual variability. Although clinical signs and pathology from the available data set suggest contact irritation and corrosion (labored breathing, gasping, and corneal opacity in rats, and decreased respiratory rate, lung necrosis, and increased lung weight in mice) and that type of portal-of-entry effect is not expected to vary greatly between species, the available data are not sufficient to conclusively describe the mechanism of toxicity. In addition, RD_{50} (concentration that reduces the respiratory rate by 50%) data suggest that the mouse is more sensitive than the rat (estimated 30-min LC_{50} value of 101-182 ppm from the mouse RD_{50} study [Hardy and Kieran 1992]). A modifying factor of 3 was applied to account for the sparse database. Therefore, the total adjustment is 300. The AEGL values for trimethylacetyl chloride are presented in Table 7-1.

1. INTRODUCTION

Trimethylacetyl chloride is a clear colorless liquid (Hardy and Kieran 1992). It is corrosive and is a moisture-sensitive lachrymator (ChemFinder 2007). Trimethylacetyl chloride is used as an intermediate in the preparation of trialkylacetic acids, which are used in polymers, pharmaceuticals, agricultural chemicals, cosmetics, and metal-working fluids. The chemical and physical properties of trimethylacetyl chloride are presented in Table 7-2.

TABLE 7-2 Chemical and Physical Properties of Trimethylacetyl Chloride

Parameter	Value	References
Synonyms	Pivaloyl chloride; 2,2-dimethyl-propanoyl chloride	ChemFinder 2007
CAS registry no.	3282-30-2	ChemFinder 2007
Chemical formula	C_5H_9ClO	ChemFinder 2007
Molecular weight	120.58	ChemFinder 2007
Physical state	Clear, colorless liquid	Hardy and Kieran 1992
Melting point	-56°C	ChemFinder 2007
Boiling point	105°C	ChemFinder 2007
Flash point	19°C	ChemFinder 2007

Density	0.979	ChemFinder 2007
Solubility in water	Moisture sensitive	ChemFinder 2007
Vapor pressure	27 mm Hg at 20°C	ChemFinder 2007
Conversion factors	1 ppm = 4.9 mg/m^3 1 mg/m^3 = 0.20 ppm	

2. HUMAN TOXICITY DATA

No human toxicity data or odor threshold data on trimethylacetyl chloride were found.

3. ANIMAL TOXICITY DATA

3.1. Acute Toxicity

Groups of three rats were exposed to trimethylacetyl chloride at 78 ppm for 6 h or at 249 ppm for 3.5 h, followed by a 14-day observation period (Eastman Kodak 1992). No further experimental details were provided. Rats in the 249-ppm group exhibited dark eyes, labored breathing, loss of coordination, gasping, and jumping during exposure. All three were prostrate 3 h into exposure and dead within 3.5 h of exposure. Corneal opacity was found at death. No mortality was observed at 78 ppm. However, clinical signs including rough coat and labored breathing, and an average weight loss of 8 g in the 14-day follow-up period were observed.

In an RD_{50} irritancy test, groups of four male albino mice were exposed to trimethylacetyl chloride at 0, 115, 180, or 634 ppm (analytic concentrations) for 30 min, followed by a 24-h observation period (Hardy and Kieran 1992). Flow rate was 13 L/min, and the test atmosphere was analyzed by gas chromatography. The study followed GLP guidelines. An RD_{50} of 290 ppm was calculated. Mortality occurred at all test concentrations; one of four rats died at 115 ppm, three of four at 180 ppm, and three of four at 634 ppm. Absolute lung weight and relative lung-to-body-weight ratios were increased in a concentrationdependent manner in animals surviving 24 h. Microscopic lung pathology in animals surviving 24 h included vascular congestion, alveolar edema, single cell necrosis of bronchiolar epithelium, alveolar duct necrosis, debris in the alveolar ducts, and generalized necrosis of bronchiolar epithelium. Because the RD_{50} was also associated with lethality in the test population, it was not used for the development of AEGL values. An LC_{50} value of 101-182 ppm for 30 min was estimated by the study authors. (The benchmark dose modeling failed because the lower limit included zero.)

3.2. Developmental and Reproductive Toxicity

No data on developmental or reproductive toxicity on trimethylacetyl chloride were found.

3.3. Genotoxicity

No genotoxicity data on trimethylacetyl chloride were found.

3.4. Chronic Toxicity and Carcinogenicity

No data on chronic toxicity or carcinogenicity of trimethylacetyl chloride were found.

3.5. Summary

Animal toxicity data on trimethylacetyl chloride are sparse. Clinical signs and lung pathology in rats and mice are consistent with severe irritation and corrosion. No data on developmental or reproductive toxicity, genotoxicity, or chronic toxicity and carcinogenicity were available.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No information concerning the metabolism and disposition of trimethylacetyl chloride was found.

4.2. Mechanism of Toxicity

Acute inhalation exposure to trimethylacetyl chloride appears to cause irritation (Hardy and Kieran 1992; Eastman Kodak 1992).

4.3. Structure-Activity Relationships

No information was available on structure-activity relationships relevant to trimethylacetyl chloride.

4.4. Other Relevant Information

4.4.1. Species Variability

No information was available on species variability in response to trimethylacetyl chloride.

4.4.2. Susceptible Populations

No information was available on populations sensitive to trimethylacetyl chloride toxicity. However, clinical signs are consistent with irritation. Therefore, effects are not expected to vary widely among individuals.

4.4.3. Time Scaling

The concentration-time 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). Data on trimethylacetyl chloride were inadequate to derive an empirical value for n, so default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations were used (NRC 2001).

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

No human data relevant to development of AEGL-1 values for trimethylacetyl chloride were available.

5.2. Animal Data Relevant to AEGL-1

No animal data relevant to development of AEGL-1 values for trimethylacetyl chloride were available.

5.3. Derivation of AEGL-1 Values

No human or animal data were available for derivation of AEGL-1 values for trimethylacetyl chloride. Therefore, AEGL-1 values are not recommended.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data relevant to development of AEGL-2 values for trimethylacetyl chloride were available.

6.2. Animal Data Relevant to AEGL-2

No mortality was observed in rats exposed to trimethylacetyl chloride at 78 ppm for 6 h. Rough coat, labored breathing, and body weight loss were noted at that concentration (Eastman Kodak 1992). Mortality (100%) was noted at the next highest concentration tested (249 ppm for 3.5 h). No lower concentrations were tested.

6.3. Derivation of AEGL-2 Values

No suitable data that provided a point of departure for deriving AEGL-2 values for trimethylacetyl chloride were available. In the absence of appropriate chemical-specific data, the AEGL-3 values were divided by 3 to estimate AEGL-2 values for trimethylacetyl chloride. That approach is justified by the steep concentration-response curve. In the mouse irritation study, a 30-min exposure to trimethylacetyl chloride at 115 ppm resulted in 25% mortality, and 1.6 increase in the concentration resulted in a 3-fold increase in mortality (75% mortality at 180 ppm) (Hardy and Kieran 1992). Rats or mice exposed to trimethylacetyl chloride at 78, 115, 180, and 249 ppm for 30 min to 6 h experienced 0, 25, 75, and 100% mortality, respectively (Eastman Kodak 1992; Hardy and Kieran 1992). AEGL-2 values for trimethylacetyl chloride are presented in Table 7-3.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data relevant to development of AEGL-3 values for trimethylacetyl chloride were available.

7.2. Animal Data Relevant to AEGL-3

No mortality was observed in rats exposed to trimethylacetyl chloride at 78 ppm for 6 h. Rough coat, labored breathing, and body weight loss were noted at that concentration (Eastman Kodak 1992). Mortality (100%) was noted at the next highest concentration tested (249 ppm for 3.5 h). No other concentrations were tested.

7.3. Derivation of AEGL-3 Values

The concentration of trimethylacetyl chloride causing no death in rats (78 ppm for 6 h) (Eastman Kodak 1992) was used as the point of departure for the AEGL-3 values. Rough coat, labored breathing, and body weight loss were found at that concentration, and mortality (100%) was noted at the next highest concentration tested (249 ppm for 3.5 h). Two uncertainty factors of 10 were applied; one factor to account for interspecies differences and one factor due to the absence of information available to describe interindividual variability. Although clinical signs and pathology from the sparse data set suggest contact irritation and corrosion (labored breathing, gasping, and corneal opacity in rats, and decreased respiratory rate, lung necrosis, and increased lung weight in mice) and that type of portal-of-entry effect is not expected to vary greatly between species, the available data are not sufficient to conclusively describe the mechanism of toxicity. In addition, the RD_{50} data on trimethylacetyl chloride suggest that the mouse is more sensitive than the rat (estimated 30-min LC_{50} value of 101-

182 ppm from the mouse RD_{50} study [Hardy and Kieran 1992]). A modifying factor of 3 was applied to account for the sparse database. Therefore, the total adjustment was 300.

Time scaling was performed using the equation $C^n \times t = k$, with default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations to derive values protective of human health (NRC 2001). The 30-min value for trimethylacetyl chloride was adopted as the 10-min value because of the added uncertainty of extrapolating a 6-h point of departure to a 10-min AEGL-3 value.

The AEGL-3 values for trimethylacetyl chloride are presented in Table 74, and the calculations are presented in Appendix A.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

AEGL values for trimethylacetyl chloride are presented in Table 7-5. AEGL-1 values are not recommended due to insufficient data. AEGL-2 values were derived by taking one-third of the AEGL-3 values, and AEGL-3 values were based on an exposure causing no death in rats exposed to trimethylacetyl chloride for 6 h.

TABLE 7-3 AEGL-2 Values for Trimethylacetyl Chloride

10 min	30 min	1 h	4 h	8 h
0.20 ppm (0.98 mg/m^3)	0.20 ppm (0.98 mg/m^3)	0.16 ppm (0.78 mg/m^3)	0.10 ppm (0.49 mg/m^3)	0.07 ppm (0.34 mg/m^3)

TABLE 7-4 AEGL-3 Values for Trimethylacetyl Chloride

10 min	30 min	1 h	4 h	8 h
0.60 ppm (2.9 mg/m^3)	0.60 ppm (2.9 mg/m^3)	0.47 ppm (2.3 mg/m^3)	0.30 ppm (1.5 mg/m^3)	0.20 ppm (0.98 mg/m^3)

TABLE 7-5 AEGL Values for Trimethylacetyl Chloride

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]

AEGL-2 (disabling)	0.20 ppm (0.98 mg/m^3)	0.20 ppm (0.98 mg/m^3)	0.16 ppm (0.78 mg/m^3)	0.10 ppm (0.49 mg/m^3)	0.07 ppm (0.34 mg/m^3)
AEGL-3 (lethal)	0.60 ppm (2.9 mg/m^3)	0.60 ppm (2.9 mg/m^3)	0.47 ppm (2.3 mg/m^3)	0.30 ppm (1.5 mg/m^3)	0.20 ppm (0.98 mg/m^3)

a Not recommended. Absence of an AEGL-1 value does not imply that exposures below the AEGL-2 value are without adverse effect.

8.2. Other Standards and Guidelines

There are no other exposure standards or guidelines for trimethylacetyl chloride.

8.3. Data Adequacy and Research Needs

There are no human data on trimethylacetyl chloride, and there are no animal data relevant to AEGL-1 or AEGL-2 end points. Available toxicity data on trimethylacetyl chloride are limited to unpublished lethality data in groups of three rats exposed to two concentrations for 3.5 or 6 h (Eastman Kodak 1992) and a 30-min RD_{50} test in mice, in which mortality occurred at all exposure concentrations (Hardy and Kieran 1992). There are no data on nonlethal toxicity in animals, metabolism, or disposition of trimethylacetyl chloride in humans or animals, or on the mechanism of action of the chemical. Additional research on workplace exposures (if applicable), acute inhalation toxicity in animals, toxicokinetics, and mechanism of action would enhance confidence in the AEGL values.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR TRIMETHYLACETYL CHLORIDE

Derivation of AEGL-1 Values

Data are insufficient to derive AEGL-1 values for trimethylacetyl chloride. Therefore, AEGL-1 values are not recommended.

Derivation of AEGL-2 Values

Data are insufficient to derive AEGL-2 values for trimethylacetyl chloride. Therefore, AEGL-2 values were derived by taking one-third of the respective AEGL-3 values. That approach is justified by the steep concentration-response for the chemical.

10-min AEGL-2:	0.60 ppm ÷ 3 = 0.20 ppm
30-min AEGL-2:	0.60 ppm ÷ 3 = 0.20 ppm
1-h AEGL-2:	0.47 ppm ÷ 3 = 0.16 ppm
4-h AEGL-2:	0.30 ppm ÷ 3 = 0.10 ppm
8-h AEGL-2:	0.20 ppm ÷ 3 = 0.07 ppm

Derivation of AEGL-3 Values

Key study:	Eastman Kodak Co. 1992. Initial Submission: Acute Inhalation Toxicity Study with Pivaloyl Chloride in Rats. Submitted to EPA, Washington, DC, by Eastman Kodak Co, Rochester, NY with Cover Letter Dated August 10, 1992. EPA Document No. 88-920005125. Microfiche No. OTS0544099.
Toxicity end point:	No death in rats (78 ppm for 6 h)

Time scaling:	$C^n \times t = k$ (ten Berge et al. 1986), with default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations to derive values protective of human health (NRC 2001). $(78 \text{ ppm})^3 \times 6 \text{ h} = 2{,}847{,}312 \text{ ppm-h}$ $(78 \text{ ppm})^1 \times 6 \text{ h} = 468 \text{ ppm-h}$
Uncertainty factors:	10 for interspecies differences 10 for intraspecies variability
Modifying factor:	3 for sparse database
10-min AEGL-3:	0.60 ppm (set equal to the 30-min AEGL-3 value)
30-min AEGL-3:	$C^3 \times 0.5 \text{ h} = 2{,}847{,}312 \text{ ppm-h}$ $C^3 = 5{,}694{,}624 \text{ ppm}$ $C = 179 \text{ ppm}$ $179 \text{ ppm} \div 300 = 0.60 \text{ ppm}$
1-h AEGL-3:	$C^3 \times 1 \text{ h} = 2{,}847{,}312 \text{ ppm-h}$ $C^3 = 2{,}847{,}312 \text{ ppm}$ $C = 142 \text{ ppm}$ $142 \text{ ppm} \div 300 = 0.47 \text{ ppm}$
4-h AEGL-3:	$C^3 \times 4 \text{ h} = 2{,}847{,}312 \text{ ppm-h}$ $C^3 = 718{,}578 \text{ ppm}$ $C = 89.3 \text{ ppm}$ $89.3 \text{ ppm} \div 300 = 0.30 \text{ ppm}$
8-h AEGL-3:	$C^1 \times 8 \text{ h} = 468 \text{ ppm-h}$ $C = 58.5 \text{ ppm}$ $58.5 \text{ ppm} \div 300 = 0.20 \text{ ppm}$

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR TRIMETHYLACETYL CHLORIDE

Derivation Summary

AEGL-1 VALUES

Data were insufficient to derive AEGL-1 values for trimethylacetyl chloride. Therefore, AEGL-1 values are not recommended for trimethylacetyl chloride.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.20 ppm (0.98 mg/m^3)	0.20 ppm (0.98 mg/m^3)	0.16 ppm (0.78 mg/m^3)	0.10 ppm (0.49 mg/m^3)	0.07 ppm (0.34 mg/m^3)

Data adequacy: Data on trimethylacetyl chloride are sparse. AEGL-2 values were derived by dividing the AEGL-3 values for trimethylacetyl chloride by 3. That approach is supported by the steep concentration-response curve (0% mortality in rats exposed at 78 ppm for 6 h and 100% mortality at 249 ppm for 3.5 h (Eastman Kodak 1992); 25% mortality in mice exposed at 115 ppm and 75% mortality at 180 ppm for 30 min (Hardy and Kieran 1992).

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
0.60 ppm (2.9 mg/m^3)	0.60 ppm (2.9 mg/m^3)	0.47 ppm (2.3 mg/m^3)	0.30 ppm (1.5 mg/m^3)	0.20 ppm (0.98 mg/m^3)

Key reference: Eastman Kodak Co. 1992. Initial Submission: Acute Inhalation Toxicity Study with Pivaloyl Chloride in Rats. Submitted to EPA, Washington, DC, by Eastman Kodak Co, Rochester, NY with Cover Letter Dated August 10, 1992. EPA Document No. 88-920005125. Microfiche No. OTS0544099.

Test species/Strain/Number: Rat; strain and sex not specified; 3/group

Exposure route/Concentrations/Durations: Inhalation; various concentrations for up to 6 h

Effects:
249 ppm for 3.5 h: 3/3 rats died; clinical signs included labored breathing, loss of coordination, gasping, and corneal opacity.
78 ppm for 6 h: No mortality; rough coat, labored breathing, and body weight loss.

End point/Concentration/Rationale: No mortality in rats exposed at 78 ppm for 6 h; considered a threshold for lethality.

Uncertainty factors/Rationale: Total uncertainty factor of 100.
Interspecies: 10, RD_{50} data suggest that the mouse is more sensitive than the rat (estimated 30-min LC_{50} value of 101-182 ppm from the mouse RD_{50} study) (Hardy and Kieran 1992)

Intraspecies: 10

Modifying factor: 3, because of the sparse database.

Animal-to-human dosimetric adjustment: None

Time scaling: $C^n \times t = k$, with default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations to derive values protective of human health (NRC 2001). The 30-min value was adopted as the 10-min value because of the added uncertainty of extrapolating the 6-h point of departure to the 10-min AEGL3 value.

Data adequacy: Sparse data set. Values are considered protective. The 30-min AEGL-3 value is approximately 75-fold lower than the estimated 30-min LC_{50} of 101-182 ppm from the mouse RD_{50} study (Hardy and Kieran 1992), and the 4-h AEGL-3 value is approximately 250-fold lower than the 249 ppm that caused 100% mortality in rats exposed to trimethylacetyl chloride for 3.5 h (Eastman Kodak 1992).

APPENDIX C

CATEGORY PLOT FOR TRIMETHYLACETYL CHLORIDE

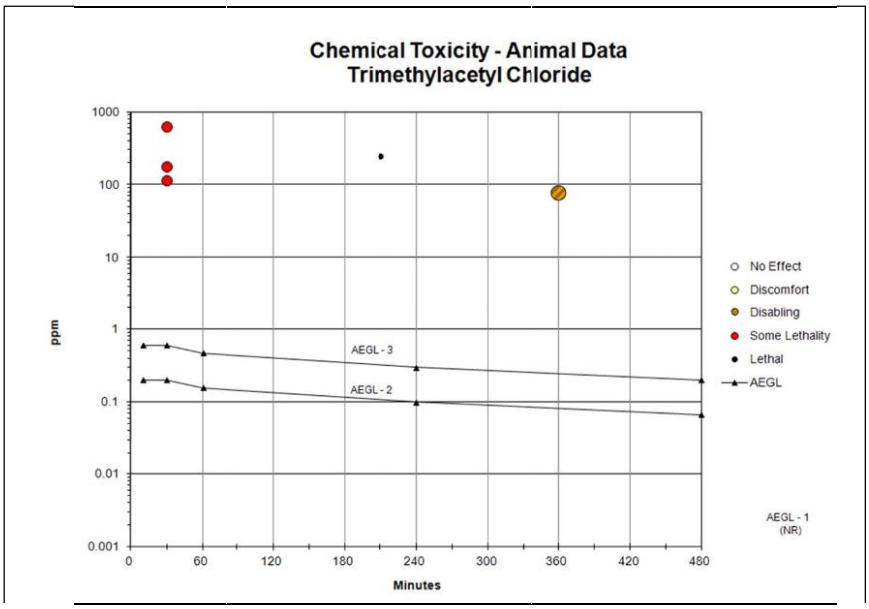

FIGURE C-1 Category plot of toxicity data and AEGL values for trimethylacetyl chloride.

TABLE C-1 Data Used in the Category Plot for Trimethylacetyl Chloride

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Effect
AEGL-2				0.20	10	AEGL	
AEGL-2				0.20	30	AEGL	
AEGL-2				0.16	60	AEGL	
AEGL-2				0.10	240	AEGL	
AEGL-2				0.07	480	AEGL	
AEGL-3				0.60	10	AEGL	
AEGL-3				0.60	30	AEGL	
AEGL-3				0.47	60	AEGL	
AEGL-3				0.30	240	AEGL	
AEGL-3				0.20	480	AEGL	
Eastman Kodak 1992	Rat		1	78	360	2	Rough coat, labored breathing, body weight loss.
Eastman Kodak 1992	Rat		1	249	210	3	Mortality 3/3
Hardy and Kieran 1992	Mouse		1	115	30	SL	Mortality 1/4
Hardy and Kieran 1992	Mouse		1	180	30	SL	Mortality 3/4
Hardy and Kieran 1992	Mouse		1	634	30	SL	Mortality 3/4

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