Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 16

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 sixteenth volume

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

in that series. AEGL documents for selected aliphatic nitriles, benzonitrile, methacrylonitrile, allyl alcohol, hydrogen selenide, ketene, and tear gas 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.

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 selected aliphatic nitriles (interim reports 19b and 21b), benzonitrile (interim reports 19b and 21b), methacrylonitrile (interim reports 19a, 20a, and 21a), allyl alcohol (interim reports 10, 12, 14, 18, and 21a), hydrogen selenide (interim report 16), ketene (interim reports 17 and 21a), and tear gas (interim reports 19a and 21a): Deepak Bhalla (Wayne State University), Harvey Clewell (The Hamner Institutes for Health Sciences), Jeffrey Fisher (U.S. Food and Drug Administration), Sidney Green (Howard University), 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), Kenneth Still (Portland State University), 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 release. The review of interim reports was overseen by David Gaylor (Gaylor and

Associates, LLC), Robert Goyer (University of Western Ontario [retired]), and David H. Moore (Battelle Memorial Institute). 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 sixteenth 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 fifteen 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). This report is the sixteenth volume in that series. AEGL documents for selected aliphatic nitriles, benzonitrile, methacrylonitrile, allyl alcohol, hydrogen selenide, ketene, and tear gas 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.

REFERENCES

NRC (National Research Council). 1968. Atmospheric Contaminants in Spacecraft. Washington, DC: National Academy of Sciences.

NRC (National Research Council). 1972. Atmospheric Contaminants in Manned Spacecraft. Washington, DC: National Academy of Sciences.

NRC (National Research Council). 1984a. Emergency and Continuous Exposure Limits for Selected Airborne Contaminants, Vol. 1. Washington, DC: National Academy Press.

NRC (National Research Council). 1984b. Emergency and Continuous Exposure Limits for Selected Airborne Contaminants, Vol. 2. Washington, DC: National Academy Press.

NRC (National Research Council). 1984c. Emergency and Continuous Exposure Limits for Selected Airborne Contaminants, Vol. 3. Washington, DC: National Academy Press.

NRC (National Research Council). 1984d. Toxicity Testing: Strategies to Determine Needs and Priorities. Washington, DC: National Academy Press.

NRC (National Research Council). 1985a. Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 4. Washington, DC: National Academy Press.

NRC (National Research Council). 1985b. Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 5. Washington, DC: National Academy Press.

NRC (National Research Council). 1986a. Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 6. Washington, DC: National Academy Press.

NRC (National Research Council). 1986b. Criteria and Methods for Preparing Emergency Exposure Guidance Level (EEGL), Short-Term Public Emergency Guidance Level (SPEGL), and Continuous Exposure Guidance level (CEGL) Documents. Washington, DC: National Academy Press.

NRC (National Research Council). 1987. Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 7. Washington, DC: National Academy Press.

NRC (National Research Council). 1988. Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 8. Washington, DC: National Academy Press.

NRC (National Research Council). 1992. Guidelines for Developing Spacecraft Maximum Allowable Concentrations for Space Station Contaminants. Washington, DC: National Academy Press.

NRC (National Research Council). 1993. Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. Washington, DC: National Academy Press.

NRC (National Research Council). 1994. Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol. 1. Washington, DC: National Academy Press.

NRC (National Research Council). 1996a. Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol. 2. Washington, DC: National Academy Press.

NRC (National Research Council). 1996b. Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol. 3. Washington, DC: National Academy Press.

NRC (National Research Council). 2000a. Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol. 4. Washington, DC: National Academy Press.

NRC (National Research Council). 2000b. Methods for Developing Spacecraft Water Exposure Guidelines. Washington, DC: National Academy Press.

NRC (National Research Council). 2001a. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. Washington, DC: National Academy Press.

NRC (National Research Council). 2001b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 1. Washington, DC: National Academy Press.

NRC (National Research Council). 2002a. Review of Submarine Escape Action Levels for Selected Chemicals. Washington, DC: The National Academies Press.

NRC (National Research Council). 2002b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol 2. Washington, DC: The National Academies Press.

NRC (National Research Council). 2003. Acute Exposure Guideline Levels for Selected Airborne Chemical, Vol. 3. Washington, DC: The National Academies Press.

NRC (National Research Council). 2004. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 4. Washington, DC: The National Academies Press.

NRC (National Research Council). 2007a. Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants, Vol. 1. Washington, DC: The National Academies Press.

NRC (National Research Council). 2007b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 5. Washington, DC: The National Academies Press.

NRC (National Research Council). 2008a. Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants, Vol. 2. Washington, DC: The National Academies Press.

NRC (National Research Council). 2008b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 6. Washington, DC: The National Academies Press.

NRC (National Research Council). 2009. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 7. Washington, DC: The National Academies Press.

NRC (National Research Council). 2010a. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 8. Washington, DC: The National Academies Press.

NRC (National Research Council). 2010b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 9. Washington, DC: The National Academies Press.
NRC (National Research Council). 2011. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 10. Washington, DC: The National Academies Press.
NRC (National Research Council). 2012a. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 11. Washington, DC: The National Academies Press.
NRC (National Research Council). 2012b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 12. Washington, DC: The National Academies Press.
NRC (National Research Council). 2012c. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 13. Washington, DC: The National Academies Press.
NRC (National Research Council). 2013a. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 14. Washington, DC: The National Academies Press.
NRC (National Research Council). 2013b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 15. Washington, DC: The National Academies Press.

Appendixes

6

Ketene[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

[1]This document was prepared by the AEGL Development Team composed of Peter Bos (RIVM, The Dutch National Institute of Public Health and the Environment), Lisa Ingerman (SRC, Inc.), Chemical Manager James Holler (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

Ketene is a colorless gas with a sharp, penetrating odor that can be detected at a concentration of 12 ppm but not at 1 ppm. It is an unstable, readily polymerizing compound and cannot be stored in the gaseous state. Ketene reacts with water to form acetic acid, and the reaction is accelerated by the presence of alkali; it will acetylate amino groups, phenolic hydroxyl groups, and sulfhydryl groups in aqueous solution (Cameron and Neuberger 1937). It is soluble in acetone, benzene, ether, and chloroform wherein it can react with a variety of compounds, such as amines, alcohols, and acids. Ketene is used as an acetylating agent in chemical synthesis, especially in synthesis of acetic acid and acetate esters.

Human data on the acute toxicity of ketene are not available. Neurotoxicity, developmental and reproductive toxicity, genotoxicity, and carcinogenicity have not been examined in humans.

Five studies examined the toxicity of ketene in various animal species. These studies indicate that the inhalation route of exposure is of particular concern for ketene and that the chemical has similarities to phosgene in clinical effects and mode of action. Ketene is a respiratory poison that can exhibit delayed toxicity to alveolar structures (mainly capillaries) to produce death by pulmonary edema. Ketene has been shown to acetylate free amino (and other functional) groups of proteins in aqueous solution. Like phosgene, the pulmonary effects of inhalation exposure to ketene may be manifested in the absence of direct irri-

tation by ketene or its breakdown product, acetic acid. For all species tested, the toxicologic profile of ketene is similar. Ketene is lethal at high concentrations; at lower concentrations, minor irritation during exposure and central nervous system impairment have been observed. However, severe damage to the lungs (at the alveolar level) may manifest as long as 24 h after exposure. The central nervous system effects are likely due to cerebral anoxia secondary to alveolar damage. Toxicity is greatest in mice, followed by rats, guinea pigs, cats, and rabbits. Ketene appears to exhibit a steep concentration-response relationship.

Data were insufficient for deriving AEGL-1 values for ketene. No human or animal data on AEGL-1 severity effects following exposure to ketene were available. No overt signs of toxicity were observed in mice exposed at 1 ppm for 7 h in a repeated-exposure study (Treon et al. 1949). Pulmonary damage was reported at the end of the exposure period; however, whether pulmonary damage would occur following a single exposure is unknown. Because of the uncertainty of whether the lowest concentration tested (1 ppm) would result in effects which exceeded the AEGL-1 definition, derivation of AEGL-1 values is not recommended for ketene. Although ketene reportedly has a distinct, penetrating floral odor (Health Council of the Netherlands 2001), neither an odor threshold nor a level of odor awareness are available. Thus, whether odor detection and minor irritation would provide adequate warning of ketene exposure is uncertain, especially given the potential for sensitive subpopulations (asthmatics) and delayed severe pulmonary toxicity (including lethality) after ketene exposure.

Data on AEGL-2 severity effects in humans and animals were not available. As discussed in consideration of AEGL-1 values, uncertainty is associated with using the lowest test concentration of 1 ppm in the repeated-exposure study in mice (Treon et al. 1949) to derive AEGL-2 values. Therefore, AEGL-2 values for ketene were based on a 3-fold reduction of AEGL-3 values. This approach is used to estimate a threshold for irreversible effects and is considered appropriate given the apparent steep concentration-response curve for ketene (lethality in mice was 0/10 at 1 ppm for 7 h; 7/10 at 23 ppm for 30 min; and 10/10 at 50 ppm for 50 min).

AEGL-3 values are based on the mouse studies of Treon et al. (1949). A 50-min exposure to ketene at 50 ppm caused 100% mortality in mice. A 30-min exposure at 23 ppm was lethal to 7/10 mice, but a 2-h exposure at this concentration was 100% lethal. A 4.5-h exposure at 12 ppm (the next lower test concentration) did not result in deaths, but 3/7 mice died during a 5.5-h exposure at the same concentration on the subsequent day of exposure. Because the time of death during the second exposure was not reported, whether the deaths were a delayed effect of the first exposure or caused by the second exposure is uncertain. In a second repeated-exposure study (Treon et al. 1949), no deaths occurred in mice after a single 7-h exposure at 1 ppm and 1/10 mice died 3 days after the tenth exposure. The concentration of 1 ppm was considered a threshold for lethal effects caused by a single exposure to ketene and was chosen as the point of departure for calculating AEGL-3 values. A total uncertainty factor of 10 was used. Mice appeared to be the most susceptible species, so an interspecies factor

of 3 was considered adequate to account for interspecies differences. An intraspecies factor of 3 was used because the mode of action (acylation of functional groups on proteins and enzymes in the lung) is not expected to vary greatly among individuals. Human studies examining the toxicity of phosgene, which appears to have a mode of action similar to ketene, did not identify sensitive subpopulations and used an intraspecies uncertainty factor of 3 in the derivation of the AEGL-2 and AEGL-3 values (NRC 2002). AEGL-3 values were derived by time scaling according to the equation $C^n \times t = k$, using default values of n = 3 to extrapolate from longer to shorter durations and n = 1 to extrapolate from shorter to longer durations. The 10-min AEGL-3 value was set equal to the 30-min value because of the uncertainty associated with extrapolating a 7-h point of departure to a 10-min AEGL value.

The AEGL values for ketene are presented in Table 6-1.

1. INTRODUCTION

Ketene is a colorless gas (Hasek 1981; Taylor 1950; HSDB 2005) with a sharp, penetrating odor (Health Council of the Netherlands 2001) that can be detected at 12 ppm but not at 1 ppm (Treon et al. 1949). It is an unstable, readily polymerizing compound (Hasek 1981; HSDB 2005), and cannot be stored in the gaseous state. Ketene reacts with water to form acetic acid, and the process is accelerated by the presence of alkali (Treon et al. 1949). It is soluble in acetone, benzene, ether, and chloroform (Cameron and Neuberger 1937). When in a solution of inert solvents, ketene can react with a variety of compounds, such as amines, alcohols, and acids. Ketene reacts with water to form acetic acid and will acetylate amino groups, phenolic hydroxyl groups, and sulfhydryl groups in aqueous solution (Cameron and Neuberger 1937). Ketene polymerizes slowly at 0°C and more quickly at room temperature. Polymerization is catalyzed by pyridine, dust particles, and rubber (Cameron and Neuberger 1937).

Ketene is manufactured by pyrolysis of acetic acid at 700-800°C under reduced pressure (10-50 kPa or 0.1-0.5 atm) (Hasek1981). A phosphate ester is injected to provide an acidic catalyst. After removal of water and unconverted acetic acid, gaseous ketene is absorbed immediately in an appropriate reaction medium (e.g., acetic anhydride is prepared by passage into a mixture of acetic acid and anhydride). Very pure ketene is best obtained from pyrolysis of acetic anhydride.

In the laboratory, ketene is prepared easily in a “ketene lamp”, in which acetone vapors are passed over an electrically-heated tungsten wire at about 700°C (Cameron and Neuberger 1937; Hasek1981). The major problem with this production is contamination of ketene with large amounts of methane produced in equivalent amounts (Cameron and Neuberger 1937) and other gaseous byproducts. If the temperature is increased further, ketene decomposes into ethylene and carbon monoxide. A substantially better product is obtained by pyrolysis of diketene (the commercially available dimer of ketene) or acetic anhy-

dride, the latter material easily affords a ketene stream of better than 99% purity (Hasek 1981).

Ketene is used as an acetylating agent in chemical synthesis, especially of acetic acid and acetate esters (Health Council of the Netherlands 2001). The chemical and physical properties of ketene are presented in Table 6-2.

2. HUMAN TOXICITY DATA

No human data on ketene were found.

TABLE 6-1 AEGL Values for Ketene

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	Insufficient data
AEGL-2 (disabling)	0.08 ppm (0.14 mg/m^3)	0.08 ppm (0.14 mg/m^3)	0.063 ppm (0.11 mg/m^3)	0.040 ppm (0.069 mg/m^3)	0.029 ppm (0.050 mg/m^3)	One third of AEGL-3 values (NRC 2001)
AEGL-3 (lethal)	0.24 ppm (0.41 mg/m^3)	0.24 ppm (0.41 mg/m^3)	0.19 ppm (0.33 mg/m^3)	0.12 ppm (0.21 mg/m^3)	0.088 ppm (0.15 mg/m^3)	Nonlethal exposure of mice, 1 ppm for 7 h (Treon et al. 1949)

[a]Not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects. A penetrating odor was reported for ketene, but neither an odor threshold nor a level of odor awareness are available. Therefore, whether the distinct floral odor of ketene will be noticeable by individuals is unclear.

TABLE 6-2 Chemical and Physical Properties for Ketene

Parameter	Value	Reference
Synonyms	Ethenone; carbomethene	HSDB 2005
CAS registry no.	463-51-4	HSDB 2005
Chemical formula	C_2H_2O	HSDB 2005
Molecular weight	42.04	HSDB 2005
Physical state	Gas	HSDB 2005
Color	Colorless	HSDB 2005
Odor	Penetrating	HSDB 2005
Melting point	-150°C	HSDB 2005
Boiling point	-56°C	HSDB 2005
Solubility	Fairly soluble in acetone	HSDB 2005
Vapor density (air = 1)	1.45	HSDB 2005
Vapor pressure	1.4×10^4 mm Hg at 25°C	HSDB 2005
Conversion factors	1 mg/m^3 = 0.582 ppm 1 ppm = 1.719 mg/m^3	NIOSH 2011

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Monkeys

Treon et al. (1949) exposed (whole body) monkeys (one animal per concentration, sex and strain not specified) to ketene at nominal concentrations of 50, 200, 750, and 1,500 ppm for 10 min under static conditions. The desired atmosphere was obtained by introducing a calculated volume of freshly generated ketene gas (purity: 98-99%) into the chamber. At the lowest concentration of 50 ppm, the exposed monkey survived without noteworthy signs of intoxication. At higher concentrations, all monkeys died within 7.67, 1.95, and 0.6 h after exposure, respectively (see Table 6-3). Symptoms of toxicity were similar at the various concentrations, but the onset of symptoms was shorter with higher concentrations. The only sign of intoxication during exposure was coughing at 1,500 ppm. Toxicity was characterized by dyspnea (rapid and labored breathing) and cyanosis culminating in fatal edema of the lungs (nasal discharge, slightly sanguineous fluid expelled from the mouth). Death was preceded by evidence of irritation (probably anoxic) of the central nervous system, which included lethargy, weakness, laying down inside position, closed eyes, and convulsive movements of the head. The observed clinical effects were confirmed by evidence of gross and microscopic pathologic changes in the lungs (generalized alveolar edema and congestion, occasional cases of an emphysematous condition at the periphery of the lobes, and distended alveolar spaces with fluid) and brain (meningeal and cerebral edema and congestion, accompanied by neuronal chromatolysis indicating the presence of cerebral anoxia). No significant changes in other organs were found.

Treon et al. (1949) exposed one monkey (sex and strain not specified) to ketene at 23 ppm for 4 h on two consecutive days and one monkey received 14 exposures of 1 ppm for 7 h/day, 5 days/week, followed by another 55 exposures after a 9-day interval (see Table 6-4). At the start of each experiment, ketene (purity: 98-99%) was injected in the chamber from a syringe to obtain the desired concentration. Because no analytic method was available to measure such low concentrations, estimates were calculated from measurements of the rate at which ketene flowed from the reservoir into a measured air stream (nominal concentrations). During the first 4-h exposure period, the monkey exposed at 23 ppm showed adverse clinical effects, including irritation of the eyes, coughing, and lethargy, especially signs related to the lungs and brain. Clinical effects were more pronounced during the second 4-h exposure (some nasal discharge, irregular and labored respiration, more severe coughing, and frothy fluid from the mouth). It was unclear whether microscopic examinations were performed on the tissues of this animal, but it was reported that in general all test species, except guinea pigs, showed alveolar edema and acute pulmonary congestion after repeated exposure to ketene at concentrations above 12 ppm. The monkey recovered and survived. No clinical signs were observed in the monkey exposed repeatedly to ketene at 1 ppm.

TABLE 6-3 Acute Lethality Data from Studies of Animals Exposed to Static Concentrations of Ketene for 10 Minutes

Concentration (ppm)	Mortality	Time of death (h)
Monkeys (n = 1)		
50	0/1	–
200	1/1	7.67
750	1/1	1.95
1,500	1/1	0.6
Cats (n = 1)		
200	0/1	–
750	1/1	2.83[a]
1,250	1/1	58.7
1,500	1/1	17
Rabbits (n = 1-2)		
200	0/2	–
250	0/2	–
375	0/2	–
500	0/2	–
750	0/2	–
1,000	1/2	0.8
1,250	2/2	2.8 and 3.07
1,500	1/1	1.3
Guinea pigs (n = 2)		
100	0/2	–
200	0/2	–
250	0/2	–
375	0/2	–
500	1/2	5.5
750	1/2	1.6
1,000	2/2	2.0 and 6.0
1,250	2/2	2.16 and 9.1
Rats (n = 2)		
100	0/2	–
200	0/2	–
250	0/2	–
375	2/2	3.25 and 9.67
500	2/2	4.45 and 6.75
750	2/2	3.7 and 5.5
1,000	2/2	2.0 and 2.6
1,250	2/2	0.95 and 1.95
Mice (n = 10-20)		
25	0/10	–
50	8/20	1.1-7.75 (6 mice); 16.2-16.4 (2 mice)
75	10/10	1.5-4.5 (7 mice); 12-22.5 (2 mice); 60 (1 mouse)
100	10/10	1.05-3.05 (9 mice); 7.5-16 (1 mouse)

[a]The cat had an obstruction of the bowel.
Source: Adapted from Treon et al. 1949.

TABLE 6-4 Acute Lethality Data from Studies of Animals Exposed to Dynamic Concentrations of Ketene for 10 Minutes

	Intended Exposure			
Concentration (ppm)	(time/day)	(day)	Mortality	Time of Death
Monkeys (n = 1)				
23	4 h	2	0/1	–
1	7 h	14	0/1[a]	–
1	7 h	55	0/1[a]	–
Cats (n = 1-2)				
23	4 h	2	0/1	–
23	6.5 h	2	0/1	–
12	4.5-6 h[b]	15	1/1	After fifth exposure
1	7 h	14	0/2	–
1	7 h	55	0/2	–
Rabbits (n = 4-5)				
50	50 min	1	0/4	–
53	100 min	1	3/4	1.87-3.57 h (2 rabbits), 135.5 h (1 rabbit)
23	4 h	2	4/4	1.5-8 d after second exposure
23	6.5 h	2	2/4	24 min after first exposure and during second exposure
12	4.5-6 h[b]	15	4/4	During or after fifth exposure (3 rabbits); during ninth exposure (1)
1	7 h	14	0/4	–
1	7 h	55	3/5	During ninth exposure (1 rabbit); after twenty-third exposure (1 rabbit); after thirty-ninth exposure (1 rabbit)
Guinea pigs (n = 2)				
50	50 min	1	0/2	–
53	100 min	1	2/2	4.04 and 4.32 h
23	120 min	1	0/2	–

Guinea pigs (n = 2)				
23	4 h	2	2/2	Less than 7.3 h after first exposure
1	7 h	14	0/2	–
1	7 h	55	0/2	–
Rats (n = 2)				
50	50 min	1	0/2	–
53	100 min	1	2/2	1.37 and 3.04 h
23	4 h	2	0/2	–
23	6.5 h	2	2/2	0 and 55 min after first exposure
12	4.5-6 h[b]	15	1/2	After sixth exposure
1	7 h	14	0/2	–
1	7 h	55	0/2	–
Mice (n = 7-10)				
50	50 min	1	10/10	0-94 min (7 mice); 5.25-8.25 h (3 mice)
53	100 min	1	10/10	0-92 min
23	30 min	1	7/10	1.05-4.2 h (5 mice); 7 h (1 mouse), 16 h (1 mouse)
23	120 min	1	10/10	1.85-6.85 h
23	4 h	2	10/10	During first exposure (3 mice); less than 7 h after first exposure (7 mice)
12	4.5-6 h[b]	15	4/7	During second exposure (3 mice); during seventh exposure (1 mouse)
1	7 h	14	1/10	3 days after tenth exposure
1	7 h	55	1/10	1 day after forty-ninth exposure

[a]The same monkey was exposed in both of these experiments, with a 9-day interval between them.
[b]Animals were exposed for 4.5 h on the first day, 5.5 h on the second day, and 6 h on each of 13 other days for 5 days per week.
Source: Adapted from Treon et al. 1949.

3.1.2. Cats

Wooster et al. (1947) exposed groups of 1-2 cats (sex and strain not specified) to ketene vapor (purity not specified). The amount of ketene generated per minute was determined at the beginning and the end of exposure by titration method to calculate the mean ketene concentration during exposure. Cats were exposed (whole body) for 10 min to mean concentrations of 233 ppm (0.40 g/m^3; n = 1), 367 ppm (0.63 g/m^3; n = 2), 623 ppm (1.07 g/m^3; n = 2), and 815 ppm (1.40 g/m^3; n = 1); the observation period was 15 days. Cats showed no signs of irritation during exposure, but salivated profusely. Mortality rates of 0/1, 1/2, 2/2, and 1/1, respectively, were found (see Table 6-5). Cats died within 12 h. Deaths were preceded by convulsive seizures, during which animals gasped for breath. Necropsy revealed trachea and bronchi containing foam and hyperemic lungs containing lobules filled with edema fluid. Microscopically, the perivascular connective tissue of the bronchial and bronchiolar vessels was very edematous, as were many alveoli. No changes in the epithelium of the airways or other organs were found. Toxicity was reported in a general way for several species and without reference to exposure concentrations.

Treon et al. (1949) exposed four cats (one animal per concentration, sex and strain not specified) to ketene (purity: 98-99%) at initial nominal concentrations of 200, 750, 1,250, and 1,500 ppm for 10 min under static conditions. The lowest concentration that caused death was 750 ppm, although it was noticed that the cat had an obstruction of the bowel. Times of death are presented in Table 6-3. Cats displayed signs of illness only after a latency period much longer than that observed for any of the other species tested. Referring to all species tested, general toxicity of ketene was reported to be characterized by dyspnea and cyanosis culminating in fatal edema of the lungs. Death was preceded by evidence of irritation (probably anoxic) of the central nervous system. The lowest concentration that induced edema and congestion of the pulmonary alveoli was 750 ppm.

Treon et al. (1949) exposed cats (one or two cats per concentration, sex and strain not specified) to ketene at nominal concentrations ranging from 1 to 23 ppm for a various number of exposures (see Section 3.1.1 for technical details and Table 6-4 for information on exposure conditions). No mortality was seen in cats exposed at 1 ppm for up to 55 days or in cats exposed for two successive days at 23 ppm (4- or 6.5-h exposures). The only cat that died had received five exposures at 12 ppm for 4.5-6 h. Cats exposed to ketene at 12 or 23 ppm for several hours on successive days exhibited sneezing, coughing, salivation, slight nasal discharge, slight irritation of the eyelids, and labored respiration. Convulsions preceded death in the case of the cat exposed at 12 ppm.

3.1.3. Rabbits and Guinea Pigs

Cameron and Neuberger (1937) studied the noxious properties of ketene in guinea pigs (number, sex, and strain not specified). Ketene was prepared accord

TABLE 6-5 Acute Lethality Data from Studies of Animals Exposed to Ketene for 10 Minutes

Concentration (ppm)	Mortality	Time of Death or Observation Period
Cats (n = 1-2)		
233	0/1	15 d
367	1/2	8-12 h
623	2/2	26 min and 8-12 h
815	1/1	135 min
Rabbits (n = 2)		
652	0/2	10 d
Guinea pigs (n = 2-4)		
367	2/4	8-12 h
	3/4	3 d
623	4/4	8-12 h
652	2/2	8-12 h
Rats (n = 4)		
122	0/4	10 d
250	4/4	150 min
774	4/4	135 min
Mice (n = 20-24)		
70	9/20	115 min
	20/20	240 min
122	16/20	180 min
	18/20	3 d
192	20/20	115 min
349	11/20	55 min
	20/20	80 min
815	24/24	60 min

Source: Adapted from Wooster et al. 1947.

ing to the method of Herriott (1934.) Methane was produced in equivalent amounts using this method, but the authors stated that methane could be ignored because very high concentrations were known to be without effect on white mice. In some experiments (not further specified) ketene was passed through ice-cold liquid paraffin to remove acetone. The exposure chamber was an 18-L glass vessel containing a fan and perforated for some inlets and outlets (glass tubes). The use of rubber was minimized to prevent polymerization of ketene. The system ensured that ketene entered within 30 seconds after commencing the experiment and allowed the concentration to be measured during exposure. A titration method was used, but no details about when the measurements were taken or how many were made were provided. Guinea pigs were exposed (whole body) for 5 min to ketene at 200-300 ppm (whether these were actual or nominal

concentrations was not specified). All animals died within 2-4 h after exposure (see Table 6-6). Animals were quiet, stretched out or huddled together, and showed somewhat decreased respiration, but no obvious dyspnea until 10-15 min before death. Marked dyspnea, violent jumping, clonic spasms, coma, and death with obvious pulmonary edema were observed. The bronchi were unaffected. There was no blistering or burning of the skin or mucous surfaces. Effects on other organs included dilated right hearts, slightly congested brains, and markedly congested arteries and veins accompanied by edema of their walls and sometimes marked hemorrhages. No changes were found in the other organs or tissues, apart from terminal venous congestion. Fetuses from pregnant animals were reported to be unaffected, but no details were provided.

Wooster et al. (1947) exposed two rabbits (sex and strain not specified) for 10 min to a mean nominal concentration of ketene at 652 ppm (1.12 g/m^3) (see Section 3.1.2 for technical details). Both animals survived the 10-day observation period (see Table 6-5). Toxicity results were discussed without reference to species or exposure concentration. It was generally reported that only a few signs of irritation and slight lacrimation during exposure were observed, and that animals tended to keep their eyes closed.

Wooster et al. (1947) exposed groups of four, four, and two guinea pigs (strain and sex not specified) for 10 min to mean nominal concentrations of ketene (purity not given) at 367 ppm (0.63 g/m^3), 623 ppm (1.07 g/m^3), and 652 ppm (1.12 g/m^3), respectively (see Section 3.1.2 for technical details). All animals in the two highest exposure groups died 8-12 h after exposure (see Table 6-5). Two of four guinea pigs in the lowest exposure group died during that timeframe, and a third animal died within 3 days. Signs of irritation and slight lacrimation during exposure were reported. Toxicity symptoms preceding death was similar to those described for the cat, with effects predominantly on the lungs and central nervous system (see Section 3.1.2 for technical details). No changes were seen in other organs. Toxicity was reported without reference to exposure concentrations and in a general way for several species.

TABLE 6-6 Acute Lethality Data in Several Animal Species

Concentration (ppm)	Exposure Duration (min)	Mortality (%)	Time of Death (min)
Guinea pigs (n = unknown)			
200-300	5	100	120-250
Rats (n = unknown)			
200-300	5	100	90-100
Mice (n = 120 mice [total])			
100	5	100	50-250
200-300	5	100	35-65
200-300	20	100	20-65
2,000	20	100	20-103

Source: Adapted from Cameron and Neuberger 1937.

Treon et al. (1949) exposed eight groups of rabbits (two animals per concentration except for one animal in the highest exposure group, sex and strain not specified) to initial nominal concentrations of ketene (purity: 98-99%) at 200, 250, 375, 500, 750, 1,000, 1,250, and 1,500 ppm for 10 min under static conditions. Mortality data are presented in Table 6-3. The lowest lethal concentration was 1,000 ppm; times of death were 0.8 h (1,000 ppm), 2.8 and 3.07 h (1,250 ppm), and 1.3 h (1,500 ppm). Animals that died exhibited coughing, blinking of the eyes, and a slight increase of respiratory rate during exposure. A more severe toxic state developed after latent periods of variable duration, depending on the concentration. Toxicity preceding death was similar that that described for monkeys (see Section 3.1.1 for technical details), with affects predominantly on the lungs and central nervous system. The lowest concentration that induced edema and congestion of the pulmonary alveoli was 1,000 ppm. No significant changes in other organs were found.

Treon et al. (1949) exposed seven groups of rabbits (4-5 animals per group, sex and strain not specified) to nominal concentrations of ketene ranging from 1 to 53 ppm for various exposure durations. Mortality rates and times of death are presented in Table 6-4. Exposure at 50 ppm for 50 min was not lethal to four rabbits, but three of four rabbits died after a 100-min exposure at 53 ppm. A 6.5-h exposure at 23 ppm killed one of four rabbits, and a second animal died during exposure on day 2. Further, all four rabbits died after a 4-h exposure at 23 ppm on two consecutive days. After repeated exposure to ketene at 12 ppm and 23 ppm, the following signs of respiratory illness followed by brain damage were seen: sneezing, rubbing noses, holding heads up and back, labored respiration (also seen in animals that died at 1 ppm), and running movements of the legs. Surviving animals exposed at 1 ppm exhibited no signs of respiratory illness. Microscopic evidence of alveolar edema and acute pulmonary congestion were seen in animals after repeated exposures at 12 ppm and higher.

Treon et al. (1949) exposed eight groups of guinea pigs (two animals per concentration, sex and strain not specified) to initial nominal concentrations of ketene (purity: 98-99%) at 100, 200, 250, 375, 500, 750, 1,000, and 1,250 ppm for 10 min under static conditions. Mortality rates and times of death are presented in Table 6-3. The lowest lethal concentration was 500 ppm, and 100% mortality occurred at 1,250 ppm. Compared with other the species tested, guinea pigs that died exhibited greater individual variability in the length of the latent period prior to the onset of respiratory distress. Otherwise the response of guinea pigs was of the same general type as that of the other species. Toxicity preceding death was similar to that described for monkeys (see Section 3.1.1 for technical details), with effects predominantly on the lungs and central nervous system. The lowest concentration that induced edema and congestion of the pulmonary alveoli was 500 ppm. No significant changes in other organs were found.

Treon et al. (1949) exposed six groups of guinea pigs (two animals per group, sex and strain not specified) to nominal concentrations of ketene ranging from 1 to 53 ppm for various exposure durations. Mortality rates and time of

death are presented in Table 6-4. No deaths occurred after a 50-min exposure at 50 ppm or a 2-h exposure at 23 ppm. After a 100-min exposure at 53 ppm or a 4-h exposure at 23 ppm, 100% mortality was seen. The time that elapsed before signs of respiratory illness were observed was lengthened as the ketene concentration decreased. Microscopic evidence of alveolar edema and acute pulmonary congestion were seen in animals after repeated exposures to ketene at 23 ppm and higher.

3.1.4. Rats

Cameron and Neuberger (1937) tested the effects of 5-min exposures to ketene (purity not specified, but equivalent amounts of methane were reported to be present) at 200-300 ppm on albino rats (number, sex, and strain not specified). Exposure conditions were comparable those used for guinea pigs (see Section 3.1.3 for technical details). All animals died within 90-100 min after exposure (see Table 6-6). Animals were quiet, stretched out or huddled together, and showed somewhat decreased respiration but no obvious dyspnea until 10-15 min before the end of exposure. Toxicity preceding death was similar to that described for guinea pigs (see Section 3.1.3), with effects predominantly on the lungs and central nervous system but also on the heart, arteries, and veins. There was no blistering or burning of the skin or mucous surfaces. No changes were found in the other organs or tissues, apart from terminal venous congestion. It was reported that fetuses from pregnant animals appeared unaffected, but details were not provided.

Wooster et al. (1947) exposed three groups of four rats (sex and strain not specified) for 10 min to mean nominal concentrations of ketene (purity not specified) at 122 ppm (0.21 g/m^3), 250 ppm (0.43 g/m^3), and 774 ppm (1.33 g/m^3) (see Section 3.1.2 for technical details). In the lowest exposure group, all animals survived the 10-day observation period (see Table 6-5). In general, only a few signs of irritation and slight lacrimation during exposure were reported. Animals tended to keep their eyes closed. In the two highest exposure groups, all animals died within 150 or 135 min, respectively. Toxicity preceding death was similar to that described for the cat, with effects predominantly on the lungs and central nervous system affected (see Section 3.1.2). No changes were seen in other organs. Toxicity was reported without reference to exposure concentrations and in a general way for several species.

Treon et al. (1949) exposed eight groups of rats (two animals per concentration, sex and strain not specified) to initial nominal concentrations of ketene (purity: 98-99%) at 100, 200, 250, 375, 500, 750, 1,000, and 1,250 ppm for 10 min under static conditions. Mortality rates and times of death are presented in Table 6-3. The lowest lethal concentration was 375 ppm (100% mortality). Rats that died developed severe respiratory distress after latent periods of variable duration, depending on the concentration. Toxicity preceding death was similar to that described for monkeys (see Section 3.1.1 for technical details), with ef-

fects predominantly on the lungs and central nervous system. The lowest concentration that induced edema and congestion of the pulmonary alveoli was 375 ppm. No significant changes in other organs were found.

Treon et al. (1949) exposed seven groups of rats (two animals per group, sex and strain not specified) to nominal concentrations of ketene ranging from 1 to 53 ppm for various exposure durations. Mortality rates and times of death are presented in Table 6-4. No deaths occurred after a 50-min exposure at 50 ppm or 4-h exposures on two consecutive days at 23 ppm. After a 100-min exposure at 53 ppm or a 6.5-h exposure at 23 ppm, 100% mortality was seen. The time that elapsed before any signs of respiratory illness were observed lengthened as the ketene concentration decreased. Effects on respiration (irregular and labored respiration, gasping, and prostration) were further shown to be dependent on exposure duration. At 23 ppm, no respiratory effects were observed after two exposures of 4 h, but were observed after a single exposure for 6.5 h. At 50-53 ppm, effects were seen after 100 min, but not after 50 min. At 12 ppm, effects on respiration and on the brain (tremors) were seen after the fifth exposure. Microscopic evidence of alveolar edema and acute pulmonary congestion were seen following repeated exposures at 12 ppm and higher.

3.1.5. Mice

Cameron and Neuberger (1937) studied the 5 min-effects of ketene (purity not specified, but equivalent amounts of methane were reported to be present) in more detail using four groups of fully grown male and female white mice (120 mice; strain, sex, and number per group were not specified) under experimental conditions described for guinea pigs (see Section 3.1.3 for technical details and Table 6-6 for information on exposure conditions). All animals died within 4 h, and had variable survival times within and across the groups (see Table 6-6). The investigators were unable to obtain an accurate estimate of the lower range toxicity of ketene, but had reason to believe that a concentration of less than 100 ppm was fatal to mice. Mice that died within 30 min immediately became quiet on exposure and crouched together lying stretched on their bellies. Within 5 min, respiration became more rapid and labored and sometimes noses and eyes were rubbed. After about 10 min, a little frothy fluid appeared at the mouth and nose and respiration became irregular, with the animals often gasping and showing more frequently shallow and rapid breathing. Animals made violent leaps or ran around for a few seconds, then felt on their sides with limbs extended, making jerky movements of their hind limbs. Respiration became slower and deeper, much fluid poured from the nose and mouth, the animal passed into deep coma, and death occurred in 20-30 min from the onset. When mice died after 2-4 h, animals were very quiet, stretched out or huddled together, and showed somewhat decreased respiration but no obvious dyspnea until 10-15 min before death. Toxicity preceding death was similar to that described for guinea pigs (see Section 3.1.3 for technical details), with effects predominantly on the lungs, central

nervous system, the heart, arteries, and veins. There was no blistering or burning of the skin or mucous surfaces. No changes were found in the other organs or tissues, apart from terminal venous congestion. It was reported that fetuses from pregnant animals appeared unaffected, but details were not provided.

Wooster et al. (1947) exposed five groups of 20-24 mice (sex and strain not specified) for 10 min to mean nominal concentrations of ketene (purity not specified) of 70 ppm (0.12 g/m^3), 122 ppm (0.21 g/m^3), 192 ppm (0.33 g/m^3), 349 ppm (0.6 g/m^3), and 815 ppm (1.4 g/m^3) (see Section 3.1.2 for technical details). During exposure only a few signs of irritation and slight lacrimation were reported. Animals tended to keep their eyes closed. With the exception of the 122-ppm group, 100% mortality occurred in the treatment groups. The duration of survival decreased with increasing concentrations (see Table 6-5). At 122 ppm, two animals survived through an observation period of 3 days. Toxicity preceding death was similar to that described for the cat, with effects predominantly on the lungs and central nervous system affected (see Section 3.1.2 for technical details). No changes were seen in other organs. Toxicity was reported without reference to exposure concentrations and in a general way for several species.

Treon et al. (1949) exposed four groups of mice (10-20 per group, sex and strain not specified) to initial nominal concentrations of ketene (purity: 98-99%) at 25, 50, 75, and 100 ppm for 10 min under static conditions. Mortality rates and times of death are presented in Table 6-3. The lowest lethal concentration was 50 ppm, and 100% mortality occurred at 75 ppm and higher. Within the various exposure groups, great variability in time of death was found. Animals that died remained fairly active during exposure. After latent periods of variable duration, the response of mice was of the same general type as that of other species. Toxicity preceding death was similar to that described for monkeys (see Section 3.1.1 for technical details), with effects predominantly in the lungs and central nervous system affected. No significant changes in other organs were found.

Treon et al. (1949) exposed eight groups of mice (7-10 per group, sex and strain not specified) to nominal ketene concentrations ranging from 1 to 53 ppm for various exposure durations. Mortality rates and times of death are presented in Table 6-4. The lowest concentration with acute lethality was 12 ppm (4.5-6 h/day); three of seven mice died during the second exposure period. At 23 ppm, mortality rates of 7/10 and 10/10 were found after 30 min in the groups exposed for 2 and 4 h, respectively. Exposure of 50-100 min at 50-53 ppm resulted in 100% mortality. Clinical effects were dependent on exposure duration. At 12 ppm, only slight nasal irritation was observed after 4.5 h of exposure, followed by labored respiration after the following 5.5 h. At concentrations of 23 ppm and higher, effects were seen on respiration and the brain (convulsions). Animals that died in the 1-ppm group showed some labored respiration. Microscopic evidence of alveolar edema and acute pulmonary congestion were observed in mice following repeated exposures at 12 ppm and higher.

Mendenhall and Stokinger (1959) exposed (whole body) groups of 6-30 male white mice of the HLA (Hamilton Labs., Hamilton, O.) strain for 10 min to ketene at concentrations of 1.1-39.0 ppm to investigate mortality. Ketene was generated with a ketene mantle and the concentration of ketene, methane, and other gases in the effluent was estimated by absorption of ketene in alkali (99.8% efficiency) and measuring the time required for neutralization. Assuming that each molecule of ketene formed was accompanied by 1 molecule of methane, it was calculated that the gas mixture was comprised of 42.0% methane, 42.0% ketene, and 16.0% other gases (mean ketene concentration: s.d. 2.17%, n = 10 analyses). It was assumed that animals were exposed to this mixture. During actual runs, the ketene concentration was estimated spectrophotometrically (precision better than 5%). Exposure of 15 mice in the chamber under usual testing conditions did not show interference with the test for ketene (no effects of exudates on the ketene reagent). This test was part of a tolerance study in which mice exposed to ketene were challenged by a second ketene or ozone exposure after a lapse of some days. The lowest lethal concentration was 5.4 ppm (6.7% mortality). The lowest concentration with 100% mortality was 18.4 ppm. Mortality rates varied from 0$ to 20% at 5.4-11.4 ppm and from 50% to 100% at 14.4-39.0 ppm. Time of death varied between 6 h and "in the second week" post-exposure. An LC_{50} of 16.5 ppm for a 10-min exposure was reported, with confidence limits of 8.8 and 31 (p = 0.05). This estimate of the toxicity of ketene at 10 days after exposure was made by assuming that none of the animals died after the third day as a result of ketene exposure. Death was preceded by concentration-dependent effects on the lungs, with edema starting at 11.4 ppm. The following effects were confirmed by histologic examination conducted (3 h to 4 days post-exposure) in a parallel experiment: no significant changes at 5.8 ppm, marked capillary congestion at 7.2 ppm, and marked capillary engorgement, some patchy edema with hemorrhages, and superficial desquamation of the bronchial tree at 9 ppm.

3.2. Nonlethal Toxicity

3.2.1. Monkeys

Treon et al. (1949) exposed (whole body) four monkeys (one animal per concentration, sex and strain not specified) to ketene at initial nominal concentrations of 50, 200, 750, and 1,500 ppm for 10 min under static conditions. The desired atmosphere was obtained by introducing a calculated volume of freshly generated ketene gas (purity: 98-99%) into the chamber. At the lowest concentration of 50 ppm, the exposed monkey survived (see Table 6-3) without noteworthy signs of intoxication. The higher concentrations were all lethal.

Treon et al. (1949) exposed one monkey to ketene at 23 ppm for 4 h on two consecutive days and another monkey received 14 exposures of 1 ppm for 7 h/day, 5 days/week followed by another 55 exposures after a 9-day interval (see

Table 6-4). The sex and strain of the monkeys were not specified. At the start of each experiment, ketene (purity: 98-99%) was injected into the chamber from a syringe to obtain the desired concentration. Because no analytic method was available to measure these low concentrations, the ketene concentrations were calculated from measurements of the rate at which ketene flowed from the reservoir into a measured air stream (nominal concentrations). The monkey exposed at 23 ppm showed some adverse clinical effects, especially related to lungs and brain (irritation of the eyes, some coughing, and some lethargy) during the first 4-h exposure period. Clinical effects were more pronounced during the second 4-h exposure period (some nasal discharge, irregular and labored respiration, more severe coughing, and frothy fluid from the mouth). It was not clear whether a microscopic examination was performed on this animal, but it was reported in general that all species tested, except guinea pigs, showed alveolar edema and acute pulmonary congestion after repeated exposure to ketene concentrations above 12 ppm. The monkey recovered and survived. No clinical signs were observed in the monkey repeatedly exposed at 1 ppm.

3.2.2. Cats

Wooster et al. (1947) exposed four groups of cats (sex and strain not specified; 1-2 animals/group) to ketene vapor (purity not given). The amount of ketene generated per minute was determined at the beginning and the end of exposure by titration method to calculate the mean ketene concentration during exposure. Cats were exposed (whole body) for 10 min to ketene at mean concentrations of 233 ppm (0.40 g/m^3; n = 1), 367 ppm (0.63 g/m^3; n = 2), 623 ppm (1.07 g/m^3; n = 2), and 815 ppm (1.40 g/m^3; n = 1); the observation period was 15 days. Cats showed no signs of irritation during exposure, but salivated profusely. No deaths occurred at the lowest concentration of 233 ppm (see Table 6-5). Although the description of toxic effects is not detailed, it appeared that surviving animals did not suffer from serious effects.

Treon et al. (1949) exposed four cats (one animal per concentration; sex and strain not specified) to ketene (purity: 98-99%) at initial nominal concentrations of 200, 750, 1,250, and 1,500 ppm for 10 min under static conditions. The highest nonlethal concentration was 200 ppm (see Table 6-3). Cats had signs of illness only after a latency period much longer than that observed in any of the other species tested, but whether slight signs of toxicity occurred at 200 ppm was not reported. The lowest concentration that induced edema and congestion of the pulmonary alveoli was 750 ppm.

Treon et al. (1949) exposed cats (one or two per concentration; sex and strain not specified) to nominal ketene concentrations of 1-23 ppm for a various number of exposures (see Section 3.1.1 for technical details and Table 6-4 for information on exposure conditions). No mortality was seen in cats exposed at 1 ppm for up to 55 days or in cats exposed for two successive days at 23 ppm (4- or 6.5-h exposures). Cats exposed at 12 or 23 ppm for several hours on succes-

sive days exhibited sneezing, coughing, salivation, slight nasal discharge, slight irritation of the eyelids, and labored respiration.

3.2.3. Rabbits and Guinea Pigs

Wooster et al. (1947) exposed two rabbits (sex and strain not specified) for 10 min to ketene at a mean nominal concentration of 652 ppm (1.12 g/m^3) (see Section 3.1.2 for technical details). Both animals survived the 10-day observation period (see Table 6-5). Toxicity results were discussed without reference to species or exposure concentration. It was generally reported that only few signs of irritation and slight lacrimation during exposure were observed. Animals tended to keep their eyes closed.

Wooster et al. (1947) exposed three groups of four, four, and two guinea pigs (strain and sex not specified) for 10 min to ketene (purity not specified) at mean nominal concentrations of 367 ppm (0.63 g/m^3), 623 ppm (1.07 g/m^3), and 652 ppm (1.12 g/m^3), respectively (see Section 3.1.2 for technical details). Only one animal exposed at the lowest concentration survived the 3-day observation period (see Table 6-5). Although the description of toxic effects was not very detailed, it appeared that surviving animals did not suffer from serious effects. In general, only few signs of irritation and slight lacrimation during exposure were reported.

Treon et al. (1949) exposed eight groups of rabbits (two animals per group except for one animal in the highest exposure group; sex and strain not specified) to ketene (purity: 98-99%) at initial nominal concentrations of 200, 250, 375, 500, 750, 1,000, 1,250, and 1,500 ppm for 10 min under static conditions. The mortality data and times of death are presented in Table 6-3. The highest concentration without mortality was 750 ppm. Surviving rabbits did not show noteworthy signs of intoxication.

Treon et al. (1949) exposed seven groups of rabbits (four or five animals per group; sex and strain not specified) to nominal ketene concentrations of 1-53 ppm for various exposure durations. Mortality rates and times of death are presented in Table 6-4. Exposure at 50 ppm for 50 min was not lethal, but three of four rabbits died after a 100-min exposure at 53 ppm. All rabbits exposed at 1 ppm for 7 h/day for 14 exposures survived. These animals exhibited no signs of respiratory illness. Although toxicity was described without specific reference to animal species or concentrations, the description suggested that no severe effects were seen in surviving animals.

Treon et al. (1949) exposed eight groups of guinea pigs (two animals per group; sex and strain not specified) to ketene (purity: 98-99%) at initial nominal concentrations of 100, 200, 250, 375, 500, 750, 1,000, and 1,250 ppm for 10 min under static conditions. Mortality rates and times of death are presented in Table 6-3. The highest nonlethal concentration was 375 ppm. Surviving animals did not show noteworthy signs of intoxication.

Treon et al. (1949) exposed six groups of guinea pigs (two animals per group; sex and strain not specified) to nominal ketene concentrations of 1-53 ppm for various exposure durations. Mortality rates and times of death are presented in Table 6-4. No deaths occurred after a 50-min exposure at 50 ppm or a 2-h exposure at 23 ppm. The time that elapsed before any signs of respiratory illness lengthened as the ketene concentration decreased. Although toxicity was described without specific reference to animal species or concentrations, the description suggested that no severe effects were seen in surviving animals.

3.2.4. Rats

Wooster et al. (1947) exposed three groups of four rats (sex and strain not specified) for 10 min to ketene (purity no specified) at mean nominal concentrations of 122 ppm (0.21 g/m^3), 250 ppm (0.43 g/m^3), and 774 ppm (1.33 g/m^3) (see Section 3.1.2 for technical details). Only the rats in the lowest exposure group survived the 10-day observation period (see Table 6-5). Although the description of toxic effects is not detailed, it appeared that surviving animals did not suffer from serious effects. In general, only few signs of irritation and slight lacrimation during exposure were reported. Animals tended to keep their eyes closed.

Treon et al. (1949) exposed eight groups of rats (two animals per group; sex and strain not specified) to ketene (purity: 98-99%) at initial nominal concentrations of 100, 200, 250, 375, 500, 750, 1,000, and 1,250 ppm for 10 min under static conditions. Mortality rates and times of death are presented in Table 6-3. The highest concentration without mortality was 250 ppm. Surviving rats rubbed their noses during exposure, and later exhibited vigorous breathing associated with signs of moisture of the respiratory passages (rales).

Treon et al. (1949) exposed seven groups of rats (two animals per group; sex and strain not specified) to nominal ketene concentrations of 1-53 ppm for various exposure durations. Mortality rates and times of death are presented in Table 6-4. No deaths occurred after a 50-min exposure ato 50 ppm or 4-h exposures on two consecutive days at 23 ppm. After a 100-min exposure at 53 ppm or a 6.5-h exposure at 23 ppm, 100% mortality was seen. The time that elapsed before any signs of respiratory illness were observed lengthened as the ketene concentration decreased. Effects on respiration (irregular and labored breathing, gasping, and prostration) were further shown to depend on exposure duration. At 23 ppm, no respiratory effects were observed after two exposures of 4 h, but were observed after a single exposure of 6.5 h. At 50-53 ppm, effects were seen after 100 min, but not after 50 min. The description of toxicity suggested that no severe effects were seen in surviving animals.

3.2.5. Mice

Wooster et al. (1947) exposed five groups of 20-24 mice (sex and strain not specified) for 10 min to ketene (purity no specified) at mean nominal concentrations of 70 ppm (0.12 g/m^3), 122 ppm (0.21 g/m^3), 192 ppm (0.33 g/m^3), 349 ppm (0.6 g/m^3), and 815 ppm (1.4 g/m^3) (see Section 3.1.2 for technical details; see Table 6-7). Only two animals from the 122-ppm group survived the observation period of 3 days (see Table 6-5). Although the description of toxic effects is not very detailed, it appeared that surviving animals did not suffer from serious effects. Only a few signs of irritation and slight lacrimation during exposure were reported. Animals tended to keep their eyes closed.

Treon et al. (1949) exposed four groups of mice (10-20 mice per group; sex and strain not specified) to ketene (purity: 98-99%) at initial nominal concentrations of 25, 50, 75, and 100 ppm for 10 min under static conditions. Mortality rates and times of death are presented in Table 6-3. Only at the lowest concentration of 25 ppm was no mortality found. Surviving mice at 25 ppm had labored and irregular respiration and appeared lethargic for several hours; effects after a 10-min exposure at 50 ppm were similar but more severe.

Treon et al. (1949) exposed eight groups of mice (7-10 animals per group; sex and strain not specified) to ketene at nominal concentrations of 1-53 ppm for various exposure durations. Mortality rates and times of death are presented in Table 6-4. Mortality was observed at all concentrations; however, there was latency in pulmonary toxicity. The lowest concentration with acute lethality was 12 ppm (4.5-6 h/day): all mice survived the first 4.5-h exposure period, but three of seven mice died during the second 5.5 h. Slight nasal irritation was found after the first exposure, and was followed by labored respiration after the second exposure. Two animals died after exposure at 1 ppm, but only after repeated (10 and 49 times) 7-h exposures; surviving animals exhibited no overt signs of respiratory illness. The time that elapsed before any signs of respiratory illness lengthened as the ketene concentration decreased.

Mendenhall and Stokinger (1959) exposed (whole body) groups of 6-30 male white mice of the HLA (Hamilton Labs., Hamilton, O.) strain for 10 min to ketene at concentrations of 1.1-39.0 ppm to investigate mortality (see Section 3.1.5 for technical details). It was assumed that animals were exposed to a gas mixture calculated to be comprised of 42.0% methane, 42.0% ketene, and 16.0% other gases (mean ketene concentration: s.d. 2.17%, n = 10 analyses). During actual runs, the ketene concentration was estimated spectrophotometrically (precision better than 5%). No mortality was found in the two lowest exposure groups of 1.1 and 5.0 ppm, as well as in some groups exposed to ketene at 5.4-11.4 ppm (0-20% mortality). At higher concentrations, mortality was 50-100% (see Section 3.1.5). Time of death varied between 6 h and “in the second week” post-exposure. At variable lethal/nonlethal concentrations (parallel experiment;

5.8-11.4 ppm), histologic examination of the lungs performed 3-6 h post-exposure showed capillary congestion at 7.2-9 ppm and increased water content at 11.4 ppm.

3.3. Neurotoxicity

Evidence of neurotoxicity is discussed in conjunction with the studies described in Section 3.2.

TABLE 6-7 Summary of Nonlethal Inhalation Data in Laboratory Animals

Species	LOAEL Without Lethality (ppm)	Exposure Duration	Effect	Reference
Monkey	23	4 h/d, 2 d	Effects related to the lungs and brain (first exposure: irritation of the eyes, some coughing, some lethargy; second exposure: some nasal discharge, irregular and labored respiration, more severe coughing, frothy fluid from the mouth). Alveolar edema, acute pulmonary congestion.	Treon et al. 1949
Cat	233	10 min	Profuse salivation, no signs of irritation, no serious effects.	Wooster et al. 1947
Cat	23 23 12	4 h/d, 2 d 6.5 h/d, 2 d 4.5-6 h/d, 2 d	Sneezing, coughing, salivation, slight nasal discharge, slight irritation of the eyelids, labored respiration.	Treon et al. 1949
Rabbit	652	10 min	Only few signs of irritation, slight lacrimation, closed eyes.	Wooster et al. 1947
Rat	122	10 min	No serious effects, a few signs of irritation and slight lacrimation, closed eyes.	Wooster et al. 1947
Rat	100	10 min	Nose rubbing during exposure, vigorous breathing associated with signs of moisture of the respiratory passages (rales).	Treon et al. 1949
Mouse	122	10 min	No serious effects, a few signs of irritation and slight lacrimation during exposure.	Wooster et al. 1947
Mouse	25	10 min	Labored and irregular respiration, lethargy for several hours.	Treon et al. 1949

3.4. Developmental and Reproductive Toxicity

No studies on the development or reproductive toxicity of ketene were found. However, the mortality study of Cameron and Neuberger (1937) reported that fetuses from pregnant guinea pigs, rats, and mice appeared to be unaffected after ketene exposure (see Sections 3.1.3., 3.1.4., and 3.1.5). No details on the experimental conditions of the developmental study were given.

3.5. Genotoxicity

Jensen et al. 1951) reported that ketene was negative in the Neurospora back-mutation test using the double mutant adenineless, colonial W.40a strain (recovered from the adenineless strain from Beadle's stock crossed to the colonial growing strain 70007A). Additionally, they cited an earlier report by Rapoport (1947, in Russian) that ketene was mutagenic in *Drosophila*.

3.6. Carcinogenicity

No reports on the carcinogenicity ketene were found.

3.7. Summary of Animal Data

Four studies conducted with experimental animals exposed to ketene are available, but the studies are old and the results are not described in great detail.[2] The reports of Cameron and Neuberger (1937), Wooster et al. (1947), and Mendenhall and Stokinger (1957) only involve 5- or 10-min exposures and the exposure concentrations are not always well-described. Wooster et al. (1947) only describe their results in general terms without reference to specific species or concentrations. Treon et al. (1949) provide results of longer exposure periods (several hours to several weeks), but they only report calculated (nominal) concentrations of ketene. The results of Treon et al. (1949) are adequate for deriving AEGL values because the study used ketene of high purity (98-99%), dynamic exposure conditions, longer exposure durations (up to 7 h), and wide concentration ranges for both lethal and nonlethal effects.

The toxicologic profile of inhalation exposure to ketene is generally similar among species tested, involving minor irritation and some central nervous system impairment during exposure, lethality at high exposure concentrations, and severe damage to the lungs (at the alveolar level) that may be manifest as long as 24 h after exposure (Cameron and Neuberger 1937; Potts et al. 1949;

[2]A fifth study by Potts et al. (1949) examined the acute toxicity of ketene (0.5 mg/L [500 mg/m^3 or 291 ppm]) in rats and mice (n = 8). However, the study examined only 1.5-min exposures and was poorly described.

Treon et al. 1949). The minor irritation during exposure may be due to the liberation of acetic acid (Potts et al. 1949), and the central-nervous-system effects reported are likely due to cerebral anoxia secondary to alveolar damage (Treon et al. 1949). Toxicity of ketene is greatest in mice, followed by rats, guinea pigs, cats, and rabbits (Treon et al. 1949).

The inhalation route of exposure is of particular concern for ketene. The available information indicates that the mode of action for ketene is similar to phosgene, which causes delayed toxicity to alveolar structures (mainly capillaries) and produces death by pulmonary edema (Cameron and Neuberger 1937; Potts et al. 1949). In general, severe effects are absent in animals that survive the initial exposure to ketene; however, latent pulmonary toxicity, similar to that observed following phosgene exposure, may result in lethality. In addition, the pulmonary histopathology following ketene exposure was characterized by Potts et al. (1949) as being "severe phosgene poisoning" by the pathologist. A steep concentration-response relationship appeared to be present for ketene.

Data on the developmental and reproductive toxicity, genotoxicity, and carcinogenicity of ketene are in adequate to draw conclusions.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No reports on the metabolism of ketene were found.

4.2. Mechanism of Toxicity

As noted above in Section 3.7, clinical signs and pathologic effects of ketene following inhalation exposure are similar to phosgene, involving death at high concentrations and minor irritation during exposure with some lethality after a latency period at lower concentrations. Ketene, like phosgene, acetylates free amino groups of proteins in aqueous solution (Cameron and Neuberger 1937; Potts et al. 1949). Potts et al. (1949) also provided some evidence that phosgene and ketene may affect enzymatic activity in lung cells in a similar way, suggesting that their modes of action could be similar. Similar to phosgene, the delay in toxicity observed with ketene results from the acylation of essential functional groups of enzymes and proteins in the lung rather than direct irritation by ketene or metabolites (Sciuto 2005). Ketene produces acetic acid as a breakdown product, whereas phosgene produces hydrochloric acid (Potts et al. 1949).

4.3. Structure Activity Relationships

Cameron and Neuberger (1937) grouped ketene (C_2H_2O) with arsines (AsH_3) and phosgene ($COCl_2$) as very poisonous gases, and suggested that phosgene was the most toxic, followed by ketene then arsine (fatal concentra-

tions were >25, ±100, and 250 ppm, respectively). Ketene resembled phosgene in its mode of toxic action (see Section 4.2).

4.3.1. Species Variability

From the static inhalation studies of Treon et al. (1949) (see Section 3.1), there was evidence of a marked difference in the relative susceptibility to ketene among the animal species tested when mortality was the end point. As shown in Table 6-8, two 10-min exposure studies showed that mice were the most susceptible to ketene, followed by monkeys, rats, guinea pigs, cats, and rabbits. Furthermore, a 5-min exposure study by Cameron and Neuberger (1937) had supportive results. Time to death after an exposure to ketene at 200-300 ppm was shortest for mice (35-36 min) followed by rats (90-100 min) and guinea pigs (120-250 ppm).

Differences in species susceptibility were also seen under dynamic inhalation conditions (Treon et al. 1949) (see Section 3.1). Comparison of the lowest acute exposure conditions resulting in lethality (see Table 6-4) indicated that mice (12 ppm for ≥4.5 h) were the most susceptible, followed by guinea pigs (23 ppm for 4 h), rats (23 ppm for 6.5 h) and rabbits (23 ppm for 6.5 h), and cats (12 ppm for 4.5-6 h, after fifth exposure). No monkeys died in this study. Although the relative susceptibility was somewhat different from above, the mouse was the most sensitive species in all studies.

TABLE 6-8 Susceptibility to Ketene

Species	Highest Concentration That Did Not Induce Fatal Pulmonary Edema	Lowest Concentrations That Induced Edema and Congestion of the Pulmonary Alveoli Followed by Death
Data from 10-min Exposure Study by Treon et al. (1949)		
Mouse	25 ppm	50 ppm
Monkey	50 ppm	200 ppm
Rat	250 ppm	375 ppm
Guinea pig	375 ppm	500 ppm
Cat	200 ppm	750 ppm
Rabbit	750 ppm	1,000 ppm
Data from 10-min Exposure Study by Wooster et al. (1947)		
Mouse	Unknown	≤70 ppm
Rat	122 ppm	250 ppm
Guinea pig	Unknown	≤367 ppm
Cat	233 ppm	367 ppm
Rabbit	≥652 ppm	Unknown

4.3.2. Intraspecies Variability and Susceptible Populations

No human data are available on the toxicity of ketene which can be used to evaluate intraspecies variability or identify susceptible populations. The probable mode of action for ketene toxicity (binding to macromolecules in the lung) is unlikely to vary greatly among individuals. A sensitive human subpopulation was not identified in the available literature on phosgene (NRC 2002), which has a similar mode of action.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

No human data on ketene were available.

5.2. Animal Data Relevant to AEGL-1

Four studies were available on the acute toxicity of ketene in experimental animals, but they were rather old and sometimes lack sufficient details (Cameron and Neuberger 1937; Wooster et al. 1947; Treon et al. 1949; Mendenhall and Stokinger 1959). Only the study by Treon et al. (1949) was carried out with ketene of high purity (98-99%). In the other studies, ketene vapor of unknown purity (Wooster et al. 1947) or mixtures of ketene with methane and other gases were used (Cameron and Neuberger 1937; Mendenhall and Stokinger 1959). It was not always clear whether actual or nominal concentrations were reported. Further, toxicity results are not always clearly related to a specific exposure concentration or duration, exposures mostly are of short duration, and exposure concentrations were not regularly measured. No reports on metabolism and mechanism of toxicity were found. Exposures of less than 10 min are of little use for setting AEGLvalues for durations of more than 30 min, but can be used as supporting information for the 10-min AEGL values. Thus, the most appropriate study is the one by Treon et al. (1949), in which several animal species were exposed to ketene concentrations ranging from 1 to 53 ppm for various exposure durations (10 min to 7 h).

Effects reported in the four studies were predominately related to the lungs and brain, and included sneezing, coughing, salivation, nasal discharge, frothy fluid from the mouth, irregular and labored respiration, and lethargy (Cameron and Neuberger 1937; Wooster et al. 1947; Treon et al. 1949; Mendenhall and Stokinger 1959). These effects were dependent on both the exposure concentration and duration. Histopathologic effects found in the lungs included alveolar edema and acute pulmonary congestion. Furthermore, irritation of the eyes, lacrimation, and closed eyes during exposure were reported. Serious effects on the lungs and brain ultimately led to death. Mice appeared to be the most susceptible animal species among those tested. No overt signs of toxicity were observed in

mice exposed to ketene for 7 h at 1 ppm, the lowest concentration tested (Treon et al. 1949). However, the investigators noted that animals repeatedly exposed at 1 ppm exhibited varying degrees of interstitial fibrosis, leukocytic and histiocytic infiltration, atelectasis, and emphysema. It is not known if a single 7-h exposure at 1 ppm would also result in pulmonary damage. As shown in other experiments by Treon et al. (1949), inhalation exposure to ketene can result in latent pulmonary toxicity. Mice exposed at 25 ppm for 10 min (static exposure) showed labored and irregular breathing and appeared lethargic for several hours.

5.3. Derivation of AEGL-1 Values

It was not possible to develop AEGL-1 values for ketene with any scientific rigor. No overt signs of toxicity were observed in mice exposed to ketene at 1 ppm for 7 h; however, the investigators noted serious pulmonary effects following repeated exposure at this concentration. However, it is unknown whether the pulmonary damage occurred following a single exposure or resulted from repeated exposure. Due to the uncertainty of whether the lowest concentration tested (1 ppm) would result in effects which exceeded the AEGL-1 definition, derivation of AEGL-1 values is not recommended for ketene.

Although ketene reportedly possesses a distinct, penetrating floral odor (Health Council of the Netherlands 2001), neither an odor threshold nor a level of odor awareness are available. Thus, it is uncertain whether odor detection and minor irritation would provide adequate warning of ketene exposure, given the potential for sensitive subpopulations (asthmatics) and for delayed, severe pulmonary toxicity (including lethality) associated with ketene exposure.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data on ketene were available.

6.2. Animal Data Relevant to AEGL-2

Of the four lethality studies available on the acute toxicity of ketene (Cameron and Neuberger 1937; Wooster et al. 1947; Treon et al. 1949; Mendenhall and Stokinger 1959), only the study by Treon et al. (1949) was carried out with ketene of high purity (98-99%). In the other studies, ketene vapor of unknown purity (Wooster et al. 1947) or mixtures of ketene with methane and other gases were used (Cameron and Neuberger 1937; Mendenhall and Stokinger 1959). Whether actual or nominal concentrations were reported in these studies was unclear. The nonlethal effects report in these studies included sneezing, coughing, salivation, nasal discharge, ocular irritation, frothy fluid from the mouth, irregular and labored respiration, and lethargy (Cameron and Neuberger

1937; Wooster et al. 1947; Treon et al. 1949; Mendenhall and Stokinger 1959). The effects were predominantly related to the lungs and the brain, and were dependent on the concentration and exposure duration. Histopathologic findings in the lungs included alveolar edema and acute pulmonary congestion. Serious effects on the lungs and brain ultimately led to death. Mice appeared to be the most susceptible species. In the Treon et al. (1949) study, no overt signs of toxicity were observed in mice exposed to ketene at1 ppm for 7 h or at 12 ppm for 4.5 h (the next higher exposure concentration); however, 3/7 mice that were subsequently exposed to ketene the next day at 12 ppm for 5.5 h died. It is unknown if a single exposure at either concentration would result in latent lung damage. Serious lung damage was reported in mice repeatedly exposed to ketene at 1 ppm (Treon et al. 1949).

6.3. Derivation of AEGL-2 Values

Effects on the lungs observed in acute exposure studies of ketene in rodents are the adverse effects most relevant to deriving AEGL-2 values (Cameron and Neuberger 1937; Wooster et al. 1947; Treon et al. 1949; Mendenhall and Stokinger 1959). Although Treon et al. (1949) identified concentrations that did not result in overt signs of toxicity or mortality following a single exposure, it is unknown whether these concentrations would result in latent lung damage. Thus, the data were considered unsuitable for deriving AEGL-2 values. In the absence of relevant data, the AEGL-2 values were estimated by taking 3-fold reduction of the AEGL-3 values (NRC 2001). This reduction is considered an estimate of a threshold for irreversible effects and appropriate because of the apparent steep concentration-response relationship (lethality was 0/10 at 1 ppm for 7 h, 7/10 at 23 ppm for 30 min; 10/10 at 50 ppm for 50 min). The AEGL-2 values for ketene are presented in Table 6-8.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data on ketene were available.

7.2. Animal Data Relevant to AEGL-3

Of the four lethality studies on the acute toxicity of ketene (Cameron and Neuberger 1937; Wooster et al. 1947; Treon et al. 1949; Mendenhall and Stokinger 1959), only the study by Treon et al. (1949) was carried out with ketene of known purity (98-99%). In the other studies, ketene vapor of unknown purity (Wooster et al. 1947) or mixtures of ketene with methane and other gases were used (Cameron and Neuberger 1937; Mendenhall and Stokinger 1959). Whether actual or nominal concentrations of ketene were reported in these studies was not always clear.

TABLE 6-8 AEGL-2 Values for Ketene

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-2	0.08 ppm (0.14 mg/m^3)	0.08 ppm (0.14 mg/m^3)	0.063 ppm (0.11 mg/m^3)	0.040 ppm (0.069 mg/m^3)	0.029 ppm 0.050 mg/m^3)

Mice appeared to be the most susceptible animal species. A 50-min exposure to ketene at 50 ppm caused 100% mortality in mice. A 30-min exposure at 23 ppm was lethal to 7/10 mice, but a longer exposure of 2 h at this concentration was lethal to all 10 mice. A 4.5-h exposure to ketene at 12 ppm (the next lower concentration) did not result in deaths, although 3/7 mice died during a 5.5-h exposure at 12 ppm on the subsequent day (Treon et al. 1949). In a repeated-exposure study, no deaths were observed in mice exposed to ketene at 1 ppm for 7 h (Treon et al. 1949), but 1/10 mice died 3 days after the tenth exposure.

In the Treon et al. (1949) study, no overt signs of toxicity were observed in mice exposed to ketene at 1 ppm for 7 h or at 12 ppm for 4.5 h (the next higher concentration). However, 3/7 mice died during a subsequent exposure at 12 ppm for 5.5 h the next day

7.3. Derivation of AEGL-3 Values

No mortality in mice exposed to ketene at 1 ppm for 7 h in the Treon et al. (1949) repeated-exposure study was selected as the basis of the AEGL-3 values. Although no mice died after a 4.5-h exposure at 12 ppm, 3/7 died during a second exposure for 5.5 h. Because the time of death during the second exposure was not reported, whether the deaths were a delayed effect of the first exposure or caused by the second subsequent exposure is uncertain. Due to this uncertainty, the 1 ppm was selected as the point of departure for calculating AEGL-3 values for ketene. Because mice appeared to be the most susceptible species, an interspecies uncertainty factor of 3 was considered adequate. An intraspecies uncertainty factor of 3 was considered adequate because the mode of action (acylation of functional groups on proteins and enzymes in the lung) is not expected to vary greatly among individuals. Human studies examining the toxicity of phosgene, a chemical which appears to have a mode of action similar to ketene, did not identify sensitive subpopulations. AEGL-2 and AEGL-3 values derived for phosgene used an intraspecies uncertainty factor of 3 (NRC 2002). Thus, a total uncertainty factor of 10 was used to calculate the AEGL-3 values for ketene.

Time scaling was performed using the equation $C^n \times t = k$, where the value of n ranges from 0.8 to 3.5 (ten Berge et al. 1986; NRC 2001). The mortality and time-to-death information in the study by Treon et al. (1949) were inadequate for deriving an empirical value of n. The lowest mortality for a single exposure was 70% (at 23 ppm for 30 min), followed by 100% (four of the five test concentrations that could be used for a derivation resulted in a 100% response). In the absence of adequate data, default values of n = 3 (for extrapolation from a

7-h exposure to 30 min, 1 h, and 4 h) and n = 1 (for extrapolation from a 7-h exposure to 8 h) were used. Because of the uncertainty associated with extrapolating a 7-h exposure to a 10-min value, the 10-min AEGL-3 value was set equal to the 30-min AEGL-3 value. The AEGL-3 values for ketene are presented in Table 6-9.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

The AEGL values for ketene are presented in Table 6-10.

Reports vary concerning the relative toxicity of ketene and phosgene. For example, Potts et al. (1949) report that "the toxicity of ketene for mice seems 20 times as great as that of phosgene" (1.5-min exposure at 500 mg/m^3 [291 ppm] killed 7/8 mice), whereas Treon et al. (1949) reported that "the toxicity of ketene appears to be of the same order of magnitude as that of phosgene". Information from the American Conference of Governmental Industrial Hygienists (ACGIH 2012) suggests that ketene is less toxic on a chronic basis than phosgene (report includes secondary citation to Treon et al. 1949). A comparison of the AEGL-3 values for ketene (Table 6-10) and phosgene (Table 6-11; NRC 2002) is difficult because of differences in the exposure duration associated with the points of departure (7 h for ketene vs. 10 and 30 min for phosgene) and the different n values used for time scaling (default values of n = 3 or n = 1 for ketene vs. n = 1 for all durations for phosgene). However, the 8-h AEGL-3 values, which were both calculated using n = 1 for time scaling, are similar for ketene and phosgene.

TABLE 6-9 AEGL-3 Values for Ketene

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-3	0.24 ppm (0.41 mg/m^3)	0.24 ppm (0.41 mg/m^3)	0.19 ppm (0.33 mg/m^3)	0.12 ppm (0.21 mg/m^3)	0.088 ppm (0.15 mg/m^3)

TABLE 6-10 AEGL Values for Ketene

	Exposure Duration				
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)	0.08 ppm (0.14 mg/m^3)	0.08 ppm (0.14 mg/m^3)	0.063 ppm (0.11 mg/m^3)	0.040 ppm (0.069 mg/m^3)	0.029 ppm (0.050 mg/m^3)
AEGL-3 (lethal)	0.24 ppm (0.41 mg/m^3)	0.24 ppm (0.41 mg/m^3)	0.19 ppm (0.33 mg/m^3)	0.12 ppm (0.21 mg/m^3)	0.088 ppm (0.15 mg/m^3)

[a]Not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects.

TABLE 6-11 AEGL Values for Phosgene

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	Insufficient data
AEGL-2 (disabling)	0.08 ppm (0.14 mg/m^3)	0.08 ppm (0.14 mg/m^3)	0.063 ppm (0.11 mg/m^3)	0.040 ppm (0.069 mg/m^3)	0.029 ppm (0.050 mg/m^3)	One third of AEGL-3 values (NRC 2001)
AEGL-3 (lethal)	0.24 ppm (0.41 mg/m^3)	0.24 ppm (0.41 mg/m^3)	0.19 ppm (0.33 mg/m^3)	0.12 ppm (0.21 mg/m^3)	0.088 ppm (0.15 mg/m^3)	Nonlethal exposure of mice, 1 ppm for 7 h (Treon et al. 1949)

[a]Not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects.

8.2. Comparison with Other Standards and Guidelines

No emergency response planning guidelines have been set for ketene. The immediately dangerous to life or health (IDLH) value for ketene is 5 ppm, and is based on acute inhalation toxicity data in humans and animals (NIOSH 1994). NIOSH (1994) remarked that 5 ppm is the lowest concentration that produces a clinically-relevant physiologic response. Furthermore, it noted that this may be a conservative value due to the lack of relevant acute toxicity data on workers exposed to ketene at concentrations greater than 5 ppm. The 30-min AEGL-2 value, based on a 3-fold reduction in the AEGL-3 value, is approximately 20 times lower than the NIOSH short-term exposure limit (STEL) and the ACGIH STEL values, which are based on pulmonary toxicity observed in short-term exposure studies. The NIOSH IDLH value is approximately 20 times higher than the 30-min AEGL-3 value. The AEGL-3 values are approximately 6-times lower than the occupational standards of the Occupational Safety and Health Administration and the National Institute for Occupational Safety and Health. The threshold limit value for ketene is based on the reasoning that 1 ppm was tolerated for several weeks and up to 6 months without apparent injury in several animal species (Treon et al. 1949). A concentration of 5 ppm was considered the lowest concentration that produced a clinically-relevant physiologic response. A summary of currently available standards and guidelines is presented in Table 6-12.

8.3. Data Quality and Research Needs

The available database on ketene is of poor quality. No human data are available. Animal studies mainly deal with very short exposures (10-20 min). The one study dealing with longer exposures (Treon et al. 1949) did not report actual concentrations of ketene. Data clearly addressing AEGL-1 and AEGL-2 effects are lacking and no appropriate acute toxicity study or odor detection information was available.

TABLE 6-12 Standards and Guidelines for Ketene

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.08 ppm (0.14 mg/m^3)	0.08 ppm (0.14 mg/m^3)	0.063 ppm (0.11 mg/m^3)	0.040 ppm (0.069 mg/m^3)	0.029 ppm 0.050 mg/m^3)
AEGL-3	0.24 ppm (0.41 mg/m^3)	0.24 ppm (0.41 mg/m^3)	0.19 ppm (0.33 mg/m^3)	0.12 ppm (0.21 mg/m^3)	0.088 ppm (0.15 mg/m^3)
IDLH (NIOSH)[a]	–	5 ppm (9 mg/m^3)	–	–	–
TLV-TWA (ACGIH)[b]	–	–	–	–	0.5 ppm (0.86 mg/m^3)
PEL-TWA (OSHA)[c]	–	–	–	–	0.5 ppm (0.9 mg/m^3)
REL-TWA (NIOSH)[d]	–	–	–	–	0.5 ppm (0.9 mg/m^3)
TLV-STEL (ACGIH)[e]	1.5 ppm (2.6 mg/m^3) (15 mins)	–	–	–	–
REL-STEL (NIOSH)[f]	1.5 ppm (3 mg/m^3) (15 mins)	–	–	–	–
MAC (The Netherlands)[g]	–	–	–	–	0.5 ppm (0.9 mg/m^3)

[a]IDLH (immediately dangerous to life or health, National Institute for Occupational Safety and Health [NIOSH 1994]) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms, or any irreversible health effects.

[b]TLV-TWA (threshold limit value - time-weighted average, American Conference of Governmental Industrial Hygienists [ACGIH 2012]) is the time-weighted average concentration for a normal 8-h workday and a 40-h workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[c]PEL-TWA (permissible exposure limit - time-weighted average, Occupational Safety and Health Administration [(29 CFR 1910.1000) [2006]) is defined analogous to the ACGIH TLV-TWA, but is for exposures of no more than 8 h/day, 40 h/week.

[d]REL-TWA (recommended exposure limit - time-weighted average, National Institute for Occupational Safety and Health [NIOSH 2011]) is defined analogous to the ACGIH TLV-TWA.

[e]TLV-STEL (threshold limit value-short-term exposure limit, American Conference of Governmental Industrial Hygienists [ACGIH 2012]) is defined as a 15-min TWA exposure which should not be exceeded at any time during the workday even if the 8-h TWA is within the TLV-TWA. Exposures above the TLV-TWA and up to the STEL should not be longer than 15 min and should not occur more than four times per day. There should be at least 60 min between successive exposures in this range.

[f]REL-STEL (recommended exposure limit – short-term exposure limit, National Institute for Occupational Safety and Health [NIOSH 2011) is defined analogous to the ACGIH TLV-STEL.

[g]MAC (maximaal aanvaaarde concentratie [maximum accepted concentration], SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], Dutch Expert Committee for Occupational Standards, The Netherlands (MSZW 2004) is defined analogous to the ACGIH TLV-TWA.

9. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2012. Ketene (CAS Reg. No. 463-51-4). 2012 TLVs and BEIs Based on the Documentation of the Threshold Limit Values for Chemical Substance and Physical Agents. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

Cameron, G.R., and A. Neuberger. 1937. Ketene as a noxious gas. J. Pathol. Bacteriol. 45(3):658-660.

Hasek, R.H. 1981. Ketenes and related substances. Pp. 874-893 in Kirk-Othmer Encyclopedia of Chemical Technology, 3rd Ed., Vol. 13, J.I. Kroschwitz, and M. Howe-Grant, eds. New York: Wiley.

Health Council of the Netherlands. 2001. Ketene (CAS Reg. No. 463-51-4). Health-based Reassessment of Administrative Occupational Exposure Limits. No. 2000/15OSH/024. Health Council of the Netherlands, The Hague [online]. Available: http://www.gezondheidsraad.eu/sites/default/files/00@15024OSH.PDF [accessed Jan. 9, 2014].

Herriott, R.M. 1934. A convenient ketene generator. J. Gen. Physiol. 18:69-70 (as cited in Cameron and Neuberger 1937).

HSDB (Hazardous Substances Data Bank). 2005. Ketene (CAS Reg. No. 463-51-4). TOXNET Specialized Information Services, U.S. National Library of Medicine, Bethesda, MD [online]. Available: http://toxnet.nlm.nih.gov/ [accessed Jan. 9, 2014].

Jensen, K.A., I. Kirk, G. Kølmark, and M. Westergaard. 1951. Chemically induced mutations in *Neurospora*. Cold Spring Harb. Symp. Quant. Biol. 16:245-261.

Mendenhall, R.M., and H.E. Stokinger. 1959. Tolerance and cross-tolerance development to atmospheric pollutants ketene and ozone. J. Appl. Physiol. 14(6):923-926.

MSZW (Ministerie van Sociale Zaken en Werkgelegenheid). 2004. Nationale MAC-lijst 2004: Keteen. Den Haag: SDU Uitgevers [online]. Available: http://www.lasrook.net/lasrookNL/maclijst2004.htm [accessed Jan. 3, 2014].

NIOSH (National Institute for Occupational Safety and Health). 1994. Documentation for Immediately Dangerous to Life or Health Concentrations (IDLHs): Ketene. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, Cincinnati, OH [online]. Available: http://www.cdc.gov/niosh/idlh/463514.html [accessed Jan. 10, 2014].

NIOSH (National Institute for Occupational Safety and Health). 2011. NIOSH Pocket Guide to Chemical Hazards: Ketene. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, Cincinnati, OH [online]. Available: http://www.cdc.gov/niosh/npg/npgd0367.html [accessed Jan. 10, 2014].

NRC (National Research Council). 1993. Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. Washington, DC: National Academy Press.

NRC (National Research Council). 2001. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. Washington, DC: National Academy Press.

NRC (National Research Council). 2002. Phosgene. Pp. 13-70 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 2. Washington, DC: National Academies Press.

Potts, A.M., F.P. Simon, and R.W. Gerard. 1949. The mechanism of phosgene and diphosgene. Arch. Biochem. 24(2):327-337.

Rapoport, I.A. 1947. Derivatives of carbamic acid and mutations [in Russian]. Biull. Eksp. Biol. Med. 23(3):198-201.

Sciuto, A.M. 2005. Inhalation toxicology of an irritant gas: Historical perspectives, current research, and case studies of phosgene exposure. Pp. 457-482 in Inhalation Toxicology, 2nd Ed., H. Salem, and S.A. Katz, eds. Boca Raton, FL: CRC Press.

Taylor, H. 1950. Non-metallic toxicological hazards: Some of the newer compounds in industry. Br. Med. Bull. 7(1-2):15-18.

ten Berge, W.F., A. Zwart, and L.M. Appelman. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. J. Hazard. Mater. 13(3):301-309.

Treon, J.F., H.E. Sigmon, K.V. Kitzmiller, F.F. Heyroth, W.J. Younker, and J. Cholak. 1949. Physiologic response of animals exposed to air-borne ketene. J. Ind. Hyg. Toxicol. 31(4):209-219.

Wooster, H.A., C.C. Lushbauch, and C.E. Redemann. 1947. The inhalation toxicity of ketene and ketene dimer. J. Ind. Hyg. Toxicol. 29(1):56-57.

APPENDIX A

DERIVATION OF AEGL VALUES FOR KETENE

Derivation of AEGL-1 Values

Due to the uncertainty of whether the lowest concentration of ketene tested of 1 ppm (Treon et al. 1949) would result in effects that exceed the definition of AEGL-1 effects, derivation of AEGL-1 values is not recommended for ketene. Absence of AEGL-1 values does not imply that exposures below the AEGL-2 values are without adverse effects.

Derivation of AEGL-2 Values

Toxicity end point:	3-fold reduction of AEGL-3 values
10-min AEGL-2:	0.24 ppm ÷ 3 = 0.080 ppm (0.14 mg/m^3)
30-min AEGL-2:	0.24 ppm ÷ 3 = 0.080 ppm (0.14 mg/m^3)
1-h AEGL-2:	0.19 ppm ÷ 3 = 0.063 ppm (0.11 mg/m^3)
4-h AEGL-2:	0.12 ppm ÷ 3 = 0.040 ppm (0.069 mg/m^3)
8-h AEGL-2:	0.088 ppm ÷ 3 = 0.029 ppm (0.050 mg/m^3)

Derivation of AEGL-3 for Ketene

Key study:	Treon, J.F., H.E. Sigmon, K.V. Kitzmiller, F.F. Heyroth, W.J. Younker, and J. Cholak. 1949. Physiologic response of animals exposed to air-borne ketene. J. Ind. Hyg. Toxicol. 31(4):209-219.
Toxicity end point:	No mortality in mice exposed to ketene at 1 ppm for 7 h.
Time scaling:	$C^n \times t = k$ (default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolating to longer durations); time scaling not performed for the 10-min AEGL-3 value, because of the uncertainty in extrapolating a 7-h point of departure to a 10-min value.

Uncertainty factors:	3 for interspecies differences 3 for intraspecies variability
Calculations:	$(1\ ppm)^3 \times 7\ h = 7\ ppm\text{-}h$ $(1\ ppm)^1 \times 7\ h = 7\ ppm\text{-}h$
10-min AEGL-3:	0.24 ppm (0.41 mg/m^3) (equal to 30-min value)
30-min AEGL-3:	$C^3 \times 0.5\ h = 7\ ppm\text{-}h$ $C = 2.4\ ppm$ $2.4\ ppm \div 10 = 0.24\ ppm$ (0.41 mg/m^3)
1-h AEGL-3:	$C^3 \times 1\ hr = 7\ ppm\text{-}h$ $C = 1.9\ ppm$ $1.9\ ppm \div 10 = 0.19\ ppm$ (0.33 mg/m^3)
4-h AEGL-3:	$C^3 \times 4\ h = 7\ ppm\text{-}h$ $C = 1.2\ ppm$ $1.2\ ppm \div 10 = 0.12\ ppm$ (0.21 mg/m^3)
8-h AEGL-3:	$C \times 8\ h = 7\ ppm\text{-}h$ $C = 0.875\ ppm$ $0.875 \div 10 = 0.088\ ppm$ (0.15 mg/m^3)

APPENDIX B

ACUTE GUIDELINE LEVELS FOR KETENE

Derivation Summary

AEGL-1 VALUES

AELG-1 values for ketene are not recommended because of insufficient data. Absence of AEGL-1 values does not imply that exposures below the AEGL-2 values are without adverse effects.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.08 ppm (0.14 mg/m^3)	0.08 ppm (0.14 mg/m^3)	0.063 ppm (0.11 mg/m^3)	0.040 ppm (0.069 mg/m^3)	0.029 ppm (0.050 mg/m^3)

Data adequacy: Data consistent with the definition of AEGL-2 values were not available. The AEGL-2 values for ketene were based on a 3-fold reduction of the AEGL-3 values.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
0.24 ppm (0.41 mg/m^3)	0.24 ppm (0.41 mg/m^3)	0.19 ppm (0.33 mg/m^3)	0.12 ppm (0.21 mg/m^3)	0.088 ppm (0.15 mg/m^3)

Key reference: Treon, J.F., H.E. Sigmon, K.V. Kitzmiller, F.F. Heyroth, W.J. Younker, and J. Cholak. 1949. Physiologic response of animals exposed to airborne ketene. J. Ind. Hyg. Toxicol. 31(4): 209-219.

Test species/Strain/Number: Mouse, strain and sex not specified, 10/ group

Exposure route/Concentrations/Durations: Inhalation, 1 ppm for 7 h/day for 14 days

End point/Concentration/Rationale: No deaths were observed after the first day of exposure; 1/10 mice died 3 days after the tenth exposure.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, mouse is the most susceptible animal species for ketene
Intraspecies: 3, mode of action (acylation of functional groups on proteins and enzymes in the lung) is not expected to vary greatly among individuals. Human studies examining the toxicity of phosgene, which appears to have a mode of action similar to ketene, did not identify sensitive subpopulations. An intraspecies uncertainty factor of 3 was used to derive AEGL-2 and AEGL-3 values for phosgene (NRC 2002).

Modifying factor: Not applicable

Animal-to-human dosimetric adjustment: Not applicable

(Continued)

AEGL-3 VALUES Continued

Time scaling: $C^n \times t = k$ (default values of n = 3 for extrapolating to shorter durations and n = 1 for extrapolating to longer durations). Time scaling was not performed for the 10-min AEGL-3 value, because of the uncertainty in extrapolating a 7-h point of departure to a 10-min value. The 10-min AEGL-3 value of 0.24 ppm is supported by the study of Treon et al. (1949), which reported no deaths in mice (0/10) after exposure to ketene at 25 ppm for 10 min.

Data adequacy: The database on ketene is poor. Only four studies were available on the acute toxicity of ketene in laboratory animals; these studies are old and sometimes lack sufficient details. No human data on ketene were available. Although Treon et al. (1949) reported only nominal concentrations of ketene, the results of the study are generally in agreement with other studies. Therefore, the study by Treon et al. (1949) provides an appropriate point of departure for deriving AEGL-3 values because it used ketene of high purity (98-99%), involved dynamic exposure conditions, involved longer exposure durations (up to 7 h), and tested a wide concentration range of ketene.

APPENDIX C

CATEGORY PLOT FOR KETENE

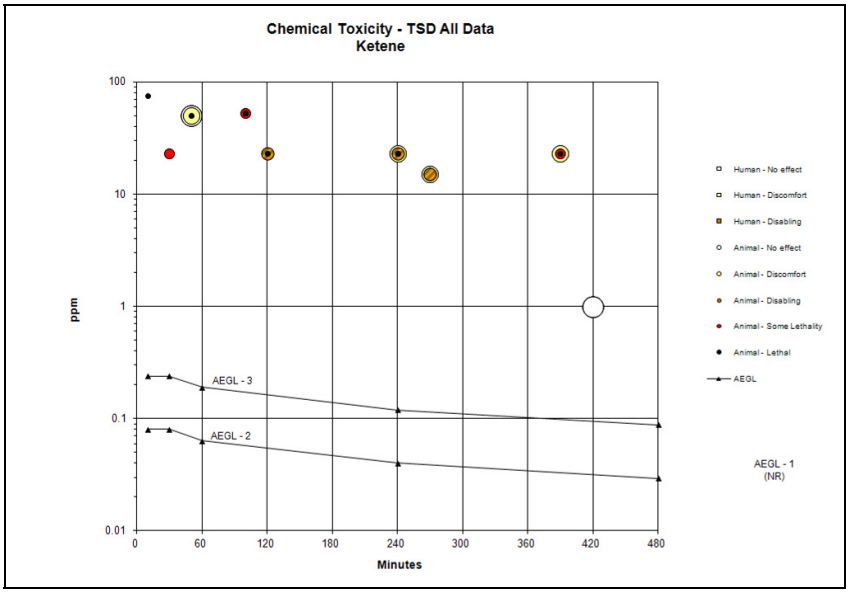

FIGURE C-1 Category plot of toxicity data and AEGL values for ketene.

TABLE C-1 Data Used in Category Plot for Ketene

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
AEGL-2				0.08	10	AEGL	
AEGL-2				0.08	30	AEGL	
AEGL-2				0.063	60	AEGL	
AEGL-2				0.040	240	AEGL	
AEGL-2				0.029	480	AEGL	
AEGL-3				0.24	10	AEGL	
AEGL-3				0.24	30	AEGL	
AEGL-3				0.19	60	AEGL	
AEGL-3				0.12	240	AEGL	
AEGL-3				0.088	480	AEGL	
Treon et al. 1949	Mouse		1	75	10	3	Mortality (10/10)
Treon et al. 1949	Mouse		1	23	30	SL	Mortality (7/10)
Treon et al. 1949	Rabbit		1	50	50	0	
Treon et al. 1949	Rat		1	50	50	0	
Treon et al. 1949	Guinea pig		1	50	50	1	
Treon et al. 1949	Mouse		1	50	50	3	Mortality (10/10)
Treon et al. 1949	Guinea pig		1	53	100	3	Mortality (2/2)
Treon et al. 1949	Rat		1	53	100	3	Mortality (2/2)
Treon et al. 1949	Mouse		1	53	100	3	Mortality (10/10)
Treon et al. 1949	Rabbit		1	53	100	SL	Mortality (3/4)
Treon et al. 1949	Guinea pig		1	23	120	2	
Treon et al. 1949	Mouse		1	23	120	3	Mortality (10/10)
Treon et al. 1949	Cat		1	23	240	1	

Treon et al. 1949	Monkey	1	23	240	2	Adverse clinical effects, ocular irritation, coughing, lethargy
Treon et al. 1949	Guinea pig	1	23	240	3	Mortality (2/2)
Treon et al. 1949	Mouse	1	23	240	3	Mortality (10/10)
Treon et al. 1949	Rabbit	1	15	270	1	
Treon et al. 1949	Mouse	1	15	270	2	
Treon et al. 1949	Rat	1	15	270	2	
Treon et al. 1949	Cat	1	23	390	1	
Treon et al. 1949	Rat	1	23	390	3	Mortality (2/2)
Treon et al. 1949	Rabbit	1	23	390	SL	Mortality (1/4)
Treon et al. 1949	Cat	1	1	420	0	
Treon et al. 1949	Cat	1	1	420	0	
Treon et al. 1949	Monkey	1	1	420	0	
Treon et al. 1949	Mouse	1	23	30	SL	Mortality (7/10)
Treon et al. 1949	Rabbit	1	50	50	0	
Treon et al. 1949	Rat	1	50	50	0	
Treon et al. 1949	Guinea pig	1	50	50	1	
Treon et al. 1949	Mouse	1	50	50	3	Mortality (10/10)
Treon et al. 1949	Guinea pig	1	53	100	3	Mortality (2/2)
Treon et al. 1949	Rat	1	53	100	3	Mortality (2/2)
Treon et al. 1949	Mouse	1	53	100	3	Mortality (10/10)
Treon et al. 1949	Rabbit	1	53	100	SL	Mortality (3/4)
Treon et al. 1949	Guinea pig	1	23	120	2	
Treon et al. 1949	Mouse	1	23	120	3	Mortality (10/10)
Treon et al. 1949	Cat	1	23	240	1	

(Continued)

TABLE C-1 Continued

Source	Species	Sex	No. Exposures	ppm	Minutes	Category	Comments
Treon et al. 1949	Monkey		1	23	240	2	Adverse clinical effects, ocular irritation, coughing, lethargy
Treon et al. 1949	Guinea pig		1	23	240	3	Mortality (2/2)
Treon et al. 1949	Mouse		1	23	240	3	Mortality (10/10)
Treon et al. 1949	Rabbit		1	15	270	1	
Treon et al. 1949	Mouse		1	15	270	2	
Treon et al. 1949	Rat		1	15	270	2	
Treon et al. 1949	Cat		1	23	390	1	
Treon et al. 1949	Rat		1	23	390	3	Mortality (2/2)
Treon et al. 1949	Rabbit		1	23	390	SL	Mortality (1/4)
Treon et al. 1949	Cat		1	1	420	0	
Treon et al. 1949	Cat		1	1	420	0	
Treon et al. 1949	Monkey		1	1	420	0	

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