Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 19

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VOLUME 19

Committee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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Preface

Extremely hazardous substances (EHSs)[1] can be released accidentally as a result of chemical spills, industrial explosions, fires, or accidents involving railroad cars and trucks transporting EHSs. Workers and residents in communities surrounding industrial facilities where EHSs are manufactured, used, or stored and in communities along the nation's railways and highways are potentially at risk of being exposed to airborne EHSs during accidental releases or intentional releases by terrorists. Pursuant to the Superfund Amendments and Reauthorization Act of 1986, the U.S. Environmental Protection Agency (EPA) has identified approximately 400 EHSs on the basis of acute lethality data in rodents.

As part of its efforts to develop acute exposure guideline levels for EHSs, EPA and the Agency for Toxic Substances and Disease Registry (ATSDR) in 1991 requested that the National Research Council (NRC) develop guidelines for establishing such levels. In response to that request, the NRC published *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* in 1993. Subsequently, *Standard Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Substances* was published in 2001, providing updated procedures, methodologies, and other guidelines used by the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances and the Committee on Acute Exposure Guideline Levels (AEGLs) in developing the AEGL values.

Using the 1993 and 2001 NRC guidelines reports, the NAC—consisting of members from EPA, the Department of Defense (DOD), the Department of Energy (DOE), the Department of Transportation (DOT), other federal and state governments, the chemical industry, academia, and other organizations from the private sector—has developed AEGLs for more than 270 EHSs.

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

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

series. AEGL documents for the cyanide salts, diketene, methacrylaldehyde, pentaborane, tellurium hexafluoride, and tetrafluoroethylene are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports.

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

The interim report of the committee that led to this report was reviewed in draft form by individuals selected for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of the committee interim report, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents A. Wallace Hayes (Harvard School of Public Health), Sam Kacew (University of Ottawa), and Judith Zelikoff (New York University).

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

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

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

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

DEDICATION

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

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 19

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

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

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

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

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

but of short duration, usually less than 1 hour (h), and only once in a lifetime for the general population, which includes infants (from birth to 3 years of age), children, the elderly, and persons with diseases, such as asthma or heart disease.

The National Research Council (NRC) Committee on Toxicology (COT) has published many reports on emergency exposure guidance levels and spacecraft maximum allowable concentrations for chemicals used by the U.S. Department of Defense (DOD) and the National Aeronautics and Space Administration (NASA) (NRC 1968, 1972, 1984a,b,c,d, 1985a,b, 1986a, 1987, 1988, 1994, 1996a,b, 2000a, 2002a, 2007a, 2008a). COT has also published guidelines for developing emergency exposure guidance levels for military personnel and for astronauts (NRC 1986b, 1992, 2000b). Because of COT's experience in recommending emergency exposure levels for short-term exposures, in 1991 EPA and ATSDR requested that COT develop criteria and methods for developing emergency exposure levels for EHSs for the general population. In response to that request, the NRC assigned this project to the COT Subcommittee on Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. The report of that subcommittee, *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993), provides step-by-step guidance for setting emergency exposure levels for EHSs. Guidance is given on what data are needed, what data are available, how to evaluate the data, and how to present the results.

In November 1995, the National Advisory Committee (NAC)[1] for Acute Exposure Guideline Levels for Hazardous Substances was established to identify, review, and interpret relevant toxicologic and other scientific data and to develop acute exposure guideline levels (AEGLs) for high-priority, acutely toxic chemicals. The NRC's previous name for acute exposure levels—community emergency exposure levels (CEELs)—was replaced by the term AEGLs to reflect the broad application of these values to planning, response, and prevention in the community, the workplace, transportation, the military, and the remediation of Superfund sites.

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

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

AEGL-1 is the airborne concentration (expressed as ppm [parts per million] or mg/m^3 [milligrams per cubic meter]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

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

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

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

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

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

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

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

REVIEW OF AEGL REPORTS

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

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

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

Because of the enormous amount of data presented in AEGL reports, the NRC committee cannot verify all of the data used by NAC. The NRC committee relies on NAC and the contractors for the accuracy and completeness of the toxicity data cited in the AEGL reports. Thus far, the committee has prepared eighteen reports in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2001b, 2002b, 2003, 2004, 2007b, 2008b, 2009, 2010a,b, 2011, 2012a,b,c, 2013a,b, 2014a,b,c). This report is the nineteenth volume in that series. AEGL documents for the cyanide salts, diketene, methacrylaldehyde, pentaborane, tellurium hexafluoride, and tetrafluoroethylene are each published as an appendix in this report. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports.

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Appendixes

2

Diketene[1]

Acute Exposure Guideline Levels

PREFACE

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

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min and 1, 4, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

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

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

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

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

SUMMARY

Diketene is a non-hygroscopic, light-colored or colorless liquid that is polymerized on standing. It is flammable and has a moderate fire risk. Diketene has a pungent odor. It is an irritant, causing mild irritation of the eyes, nose, and throat after occupational exposure at 0.58 ppm for 1 min. Inhalation of diketene was not lethal to rats at 250 ppm for 1 h or to rabbits at 194 ppm for 10 min, but deaths occurred in rats exposed at 500 or 750 ppm for 1 h. Rats exposed to diketene at 250-750 ppm for 1 h showed signs of ocular and respiratory-tract irritation. Deaths occurred in mice exposed to diketene at 870 ppm for 10 min and in guinea pigs exposed at 194 ppm for 10 min. Pulmonary edema was found in the animals that died. The 1-h LC_{50} (lethal concentration, 50% lethality) values for rats were 548 ppm for males, 689 ppm for females, and 612 ppm for both sexes combined.

Data were insufficient for deriving AEGL-1 values for diketene. Therefore, AEGL-1 values are not recommended.

Data were also insufficient for deriving AEGL-2 values for diketene. The standing operating procedures for deriving AEGL values specify that AEGL-2 values for chemicals with steep concentration-response curves may be estimated by dividing the AEGL-3 values by a factor of 3. The steepness of the lethality concentration-response curve for diketene indicates that a factor of 3 should be adequate for reducing the AEGL-3 values to a level consistent with the definition of AEGL-2.

AEGL-3 values were derived on the basis of an acute inhalation study in which rats were exposed to diketene at 250, 500, or 750 ppm for 1 h (Katz

1987). The point-of-departure was the lethality $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response) of 181 ppm, which was calculated using a log-probit model. A total uncertainty factor of 30 was applied; a factor of 10 for interspecies differences and a factor of 3 for intraspecies variability. Diketene is irritating and much of its toxicity is likely caused by a direct chemical effect on the tissue; that type of portal-of-entry effect is not expected to vary greatly among individuals. The intraspecies uncertainty factor of 3 is further supported by the similarity in mortality incidence and clinical signs between male and female rats exposed to diketene (Katz 1987). A modifying factor of 2 was also applied because of the limited database on diketene. Time scaling was performed using the equation $C^n \times t = k$. Data on diketene were insufficient for determining an empirical value for the exponent n, so default values of n = 3 for extrapolating to shorter durations (10 and 30 min) and n = 1 for extrapolating to longer durations (4 and 8 h) were used.

The AEGL values for diketene are presented in Table 2-1.

1. INTRODUCTION

Diketene is a light-colored or colorless non-hygroscopic liquid that polymerizes on standing (AIHA 2000; Lewis 2007). It is flammable and has a moderate fire risk. Diketene is used in the production of pigments and toners, pesticides, food preservatives, and pharmaceutical intermediates (HSDB 2003; Lewis 2007). The odor of diketene has been described as pungent (Lewis 2007).

The chemical and physical properties of diketene are presented in Table 2-2.

2. HUMAN TOXICITY DATA

2.1. Human Lethality

No data regarding exposure of humans to lethal concentrations of diketene were found.

TABLE 2-1 AEGL Values for Diketene

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)	1.8 ppm (6.2 mg/m^3)	1.3 ppm (4.5 mg/m^3)	1.0 ppm (3.4 mg/m^3)	0.25 ppm (0.86 mg/m^3)	0.13 ppm (0.45 mg/m^3)	One-third of the AEGL-3 values.
AEGL-3 (lethal)	5.5ppm (19 mg/m^3)	3.8 ppm (13 mg/m^3)	3.0 ppm (10 mg/m^3)	0.75 ppm (2.6 mg/m^3)	0.38 ppm (1.3 mg/m^3)	$BMCL_{05}$ for lethality (Katz 1987)

[a]Not recommended. Absence of AEGL-1 values does not imply that exposures at concentrations below the AEGL-2 values are without effect.

TABLE 2-2 Chemical and Physical Properties of Diketene

Parameter	Value	Reference
Synonyms	3-Butenoic acid, 3-hydroxy-, beta-lacone; ethenone, dimer; ketene, dimer; 4-methylene-2-oxetanone; vinylaceto-beta-lactone	HSDB 2003
CAS registry no.	674-82-8	HSDB 2003
Chemical formula	$C_4H_4O_2$	HSDB 2003
Molecular weight	84.08	HSDB 2003
Physical state	Light-colored or colorless liquid	AIHA 2000; Lewis 2007
Melting point	-6.5°C	HSDB 2003
Boiling point	127.4°C	HSDB 2003
Density/Specific gravity (water = 1)	1.096 (20/20°C) 1.0897	Lewis 2007 HSDB 2003
Vapor density (air = 1)	2.9	HSDB 2003
Solubility	Soluble in common organic solvents; soluble in water	Lewis 2007
Vapor pressure	10 mm Hg at 24.3°C 1.07 kPa at 20°C	AIHA 2000 HSDB 2003
Flash point (tagged closed cup)	34°C	AIHA 2000
Autoignition temperature	310°C	AIHA 2000
Conversion factors	1 mg/m^3 = 0.29 ppm; 1 ppm = 3.44 mg/m^3	AIHA 2000

2.2. Nonlethal Toxicity

Occupational exposure to diketene at a concentration of 2 mg/m^3 (0.58 ppm) for 1 min caused mild irritation of the conjunctiva and mucosa of the nose and throat (Danishevskii 1948,1951; Feldman 1967).

2.3. Summary

No studies were found on human exposure to lethal concentrations of diketene. A concentration of 0.58 ppm caused mild ocular, nasal, and throat irritation.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rat

Groups of five male and five female CRL:CD®(SD)BR rats were exposed to diketene at concentrations of 0, 250, 500, or 750 ppm for 1 h and observed for 14 days after exposure (Katz 1987). The analytic concentrations were 271 ± 2.4, 466 ± 13.7, and 778 ± 16.9 ppm, respectively. The rats were exposed in a 420-L

stainless steel and glass chamber with 10-13 air changes per hour. The chamber atmosphere was analyzed four or five times using an infrared analyzer; the nominal concentration was calculated on the basis of the amount of diketene used and the air flow rate. All rats were subjected to gross examination, but no tissues were collected for microscopic examination.

Mortality and clinical signs are summarized in Table 2-3. The mortality rate was 0/10, 3/10, and 7/10 rats (sexes combined) in the 250-, 500-, and 750-ppm groups, respectively. All deaths occurred within 48 h after exposure, except for one male rat exposed at 750 ppm that died on day 6. The LC_{50} values were 548 ppm for male rats, 689 ppm for female rats, and 612 ppm for both sexes combined. LC_{10} values calculated by the investigators were 346 ppm for males, 410 ppm for females, and 370 ppm for both sexes combined. All rats exposed to diketene exhibited excessive tearing (lacrimation) during exposure and for a few hours after exposure. Porphyrin discharge from the nose was observed in male and female rats for up to 48 h after exposure at 500 and 750 ppm. Effects on the respiratory tract consisted of gasping in all rats at all concentrations and wheezing in one or two rats per group. Rales were observed in one male rat in each exposure group and one female in the 500-ppm group, but the effect might not have been due to diketene, because no increase in the incidence of rales occurred with a 15-fold increase in the exposure concentration. No gross lesions were found in any rats exposed to diketene.

3.1.2. Mice

Wooster et al. (1947) exposed groups of 4, 30, and 20 mice to diketene at concentrations of 194, 580, or 870 ppm, respectively, for 10 min. Diketene was prepared at a known concentration in acetone and sprayed into the chamber from a glass atomizer; the concentration of diketene in inhaled air was 0.67 mg/L (194 ppm). The animals were observed for up to 15 days after exposure. No additional details on the experimental protocol were provided. One mouse died

TABLE 2-3 Mortality and Clinical Signs in Rats Exposed to Diketene

	Exposure Concentration							
	0	250	500	750	0	250	500	750
Parameter	No. males				No. females			
No. exposed	0	5	5	5	0	5	5	5
Mortality	0	0	2	4	0	0	1	3
Excessive tearing	0	5	5	5	0	5	5	5
Porphyrin discharge	0	0	2	2	0	0	2	3
Gasping	0	5	5	5	0	5	5	5
Rales	0	1	1	1	0	0	1	0
Wheezing	0	1	0	0	0	0	1	2
Poor condition	0	0	0	4	0	0	0	1

Source: Katz 1987.

after exposure at 870 ppm, but no deaths occurred in mice exposed at 580 or 194 ppm. No specific clinical signs or pathologic findings were described. The investigators noted that the findings in the animals that died were similar to those described for animals (particularly the cat) exposed to ketene. Microscopically, animals that died after ketene exposure had proteinaceous edematous fluid in the alveoli of the lungs and in the perivascular connective tissue of the bronchial and bronchiolar vessels. After describing the microscopic lesions in animals that died after ketene exposure, Wooster et al. (1947) stated that "the findings in the few animals dying after diketene poisoning were similar." That suggests that the mice that died after exposure to diketene had alveolar and bronchial edema (pulmonary edema).

3.1.3. Other Species

All three guinea pigs died after exposure to diketene at 194 ppm under the same conditions as described for mice (see Section 3.1.2) (Wooster et al. 1947). No clinical signs or pathologic effects were described. From the investigators' description that the findings in the dead animals were similar to those of animals that died from ketene exposure, it was implied that the guinea pigs also had pulmonary edema.

3.2. Nonlethal Toxicity

Wooster et al. (1947) exposed four rats and three rabbits to diketene at 0.67 mg/L (194 ppm) for 10 min under the same conditions as described for mice (see Section 3.1.2). All of the animals survived to the end of the study. No clinical signs or pathologic lesions were described.

3.3. Other End Points of Toxicity

No data were found on the neurotoxicity, developmental toxicity, reproductive toxicity, genetic toxicity, or carcinogenicity of inhaled diketene in experimental animals.

3.4. Summary

Table 2-4 summarizes the lethal effects of acute inhalation exposure to diketene in several species. The LC_{50} for a 1-h exposure of rats to diketene ranged from 548 to 689 ppm. Rats died after exposure to diketene at concentrations 500 or 750 ppm for 1 h, guinea pigs died after exposure at 194 ppm for 10 min, and mice died after exposure at 870 ppm for 10 min. No deaths occurred in rats and rabbits after exposure to diketene at 194 ppm for 10 min. Ocular and respiratory-tract irritation were observed in rats exposed at lethal and nonlethal concentrations

of diketene greater than 250 ppm. The primary findings in mice and guinea pigs exposed to diketene were the same as those found in the cat that died after exposure to ketene (alveolar and bronchial edema or pulmonary edema).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No data on the uptake, metabolism, disposition, or excretion of inhaled diketene were found.

4.2. Mechanism of Toxicity

Diketene is an irritant (Lewis 2007). Wooster et al. (1947) noted that the pathologic changes caused by ketene were similar to those of phosgene.

4.3. Structure-Activity Relationships

Diketene is the dimeric form of ketene, and is similar to but less toxic than ketene. At high temperatures (510-603°K), diketene undergoes thermal decomposition to form ketene, cyclobuta-1,3-dione, and cyclobuta-1,2-dione (Bui et al. 2007). Wooster et al. (1947) exposed rats, cats, guinea pigs, and rabbits to ketene for 10 min and observed the survivors for up to 15 days. Ketene exposure caused severe damage to the respiratory tract (pulmonary edema), but the pathologic effects were described only for cats. The lowest concentrations associated

TABLE 2-4 Summary of Acute Lethality Data from Studies of Laboratory Animals Exposed to Diketene by Inhalation

Species (sex)	Concentration	Exposure Time	Effect (% lethality)	Reference
Rat	194	10 min	0%	Wooster et al. 1947
Rat (females)	689	1 h	LC_{50}	Katz 1987
Rat (males and females)	612	1 h	LC_{50}	Katz 1987
Rat (males)	548	1 h	LC_{50}	Katz 1987
Rat (females)	410	1 h	LC_{10}	Katz 1987
Rat (males and females)	370	1 h	LC_{10}	Katz 1987
Rat (males)	346	1 h	LC_{10}	Katz 1987
Mouse	870	10 min	5%	Wooster et al. 1947
Mouse	194-580	10 min	0%	Wooster et al. 1947
Guinea pig	194	10 min	100%[a]	Wooster et al. 1947
Rabbit	194	10 min	0%	Wooster et al. 1947

[a]Only three animals exposed.

with mortality were 35 ppm for the mouse, 125 ppm for the rat, 183 ppm for the cat and guinea pig, and 325 ppm for the rabbit. In contrast, no deaths were observed in mice exposed to diketene at 194-580 ppm for 10 min, and 100% mortality occurred in rabbits exposed to diketene at 194 ppm for 10 min (Wooster et al. 1947).

4.4. Species Variability

According to Wooster et al. (1947), guinea pigs died after exposure to diketene at 194 ppm for 10 min, but mice, rats, and rabbits survived a 10-min exposure at 194 ppm. Thus, the guinea pig appears to be more sensitive than other species to diketene.

4.5. Susceptible Populations

No data are available on populations that might be susceptible to diketene.

4.6. Concentration-Exposure Duration Relationship

Lethality data from the study by Katz (1987) was used to create Figure 2-1, which shows a steep concentration-response curve. See Section 3.1.1. for a description of the study.

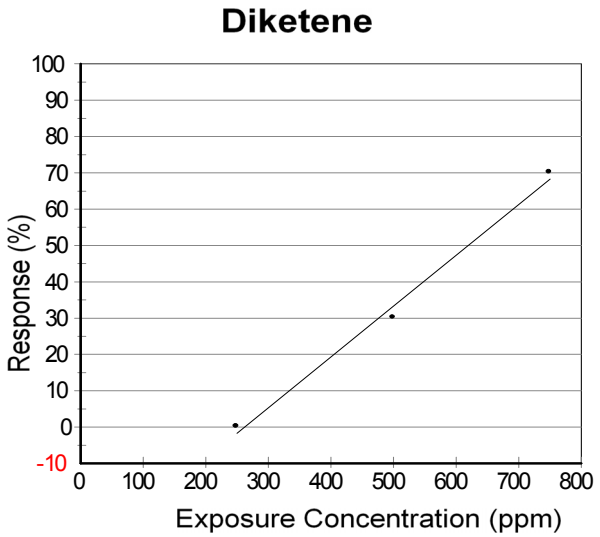

FIGURE 2-1 Concentration-response relationship between diketene and lethality in rats.

4.7. Concurrent Exposure Issues

No concurrent exposure issues for diketene were found.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Humans occupationally exposed to diketene at 0.58 ppm for 1 min experienced mild irritation of the eyes, nose, and throat (Danishevskii 1948, 1951).

5.2. Animal Data Relevant to AEGL-1

No animal data relevant to deriving AEGL-1 values for diketene were found.

5.3. Derivation of AEGL-1 Values

No AEGL-1 values were derived for diketene. The only data available for deriving AEGL-1 values are from a study in which workers exposed to diketene at 0.58 ppm were reported to experience mild irritation of the eyes, nose, and throat. That information is from a secondary source and could not be verified, so the data are considered insufficient for deriving AEGL-1 values. Absence of AEGL-1 values does not imply that exposures at concentrations below the AEGL-2 values are without adverse effects.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

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

6.2. Animal Data Relevant to AEGL-2

Lacrimation and gasping were observed in rats exposed to diketene at 250 ppm for 1 h, and none of the animals died (Katz 1987). No deaths occurred among groups of mice exposed to diketene at 194-580 ppm for 10 min (Wooster et al. 1947).

6.3. Derivation of AEGL-2 Values

The experimental data from animal studies were not appropriate for deriving AEGL-2 values for diketene. Although rats exposed at 250 ppm for 1 h

showed clinical signs indicative of ocular and respiratory-tract irritation and no deaths occurred (Katz 1987), the $BMCL_{05}$ for lethality (used as the point-of-departure for deriving AEGL-3 values) was lower than the highest concentration causing no lethality in rats. Therefore, the rat study should not be used to derive AEGL-2 values. The standing operating procedures for deriving AEGL values specify that AEGL-2 values for chemicals with steep concentration-response curves may be estimated by dividing the AEGL-3 values by 3 (NRC 2001). Because diketene is judged to have a steep concentration-response relationship for lethality, that approach was used to determine AEGL-2 values for diketene. The AEGL-2 values for diketene are presented in Table 2-5.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

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

7.2. Animal Data Relevant to AEGL-3

In an acute inhalation study using rats exposed to diketene vapor (250, 500, and 750 ppm) for 1 h (Katz 1987), deaths occurred at the two highest concentrations. The exposure conditions and results of the study were well documented. Wooster et al. (1947) reported that one of 20 mice died after exposure to diketene at 870 ppm for 10 min and all three guinea pigs exposed to diketene at 194 ppm for 10 min died. These data show that the guinea pig is the more sensitive species to diketene.

7.3. Derivation of AEGL-3 Values

The AEGL-3 values were derived on the basis of the mortality study of rats exposed to diketene at 250, 500, or 750 ppm for 1 h (Katz 1987). A $BMCL_{05}$ of 181 ppm was calculated using the log-probit model in EPA's Benchmark Dose Software (v. 1.3.2), and an LC_{01} (lethality threshold, 1% lethality) of 276 ppm was calculated by probit regression analysis. The $BMCL_{05}$ of 181 ppm was used as point-of-departure for deriving AEGL-3 values. A total uncertainty factor of 30 was applied; a factor of 10 for interspecies differences and a factor of 3 for intraspecies variability. The factor of 3 was applied because diketene is

TABLE 2-5 AEGL-2 Values for Diketene

10 min	30 min	1 h	4 h	8 h
1.8 ppm (6.2 mg/m^3)	1.3 ppm (4.5 mg/m^3)	1.0 ppm (3.4 mg/m^3)	0.25 ppm (0.86 mg/m^3)	0.13 ppm (0.45 mg/m^3)

irritating and much of its toxicity is likely caused by a direct chemical effect on the tissue. That type of portal-of-entry effect is not expected to vary greatly among individuals. A factor of 3 is further supported by the fact that mortality incidences and clinical signs were similar between male and female rats exposed to diketene (Katz 1987). A modifying factor of 2 was also applied because of the limited database on diketene. Time scaling was performed using the equation $C^n \times t = k$. The data on diketene were inadequate to determine an empirical value for the exponent n, so default values of n = 3 when extrapolating to shorter durations (10 and 30 min) and n = 1 when extrapolating to longer durations (4 and 8 h) were used. The AEGL-3 values for diketene are presented in Table 2-6.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

The AEGL values for diketene are presented in Table 2-7. AEGL-1 values are not recommended because of insufficient data. AEGL-2 values were estimated by reducing the AEGL-3 values by a factor of 3. AEGL-3 values were derived from the $BMCL_{05}$ for lethality calculated from an acute inhalation study in rats.

8.2. Other Standards and Guidelines

The Russian occupational exposure limit for diketene is 1 mg/m^3 (0.29 ppm) (RTECS 2006). The AEGL-2 and AEGL-3 values for 1-h exposures are similar to the emergency response planning guidelines (ERPG-2 and ERPG-3) of the American Industrial Hygiene Association (AIHA 2000) (Table 2-8). No other standards or guidelines for diketene were found.

TABLE 2-6 AEGL-3 Values for Diketene

10 min	30 min	1 h	4 h	8 h
5.5 ppm (19 mg/m^3)	3.8 ppm (13 mg/m^3)	3.0 ppm (10 mg/m^3)	0.75 ppm (2.6 mg/m^3)	0.38 ppm (1.3 mg/m^3)

TABLE 2-7 AEGL Values for Diketene

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)	1.8 ppm (6.2 mg/m^3)	1.3 ppm (4.5 mg/m^3)	1.0 ppm (3.4 mg/m^3)	0.25 ppm (0.86 mg/m^3)	0.13 ppm (0.45 mg/m^3)
AEGL-3 (lethal)	5.5 ppm (19 mg/m^3)	3.8 ppm (13 mg/m^3)	3.0 ppm (10 mg/m^3)	0.75 ppm (2.6 mg/m^3)	0.38 ppm (1.3 mg/m^3)

[a]Not recommended. Absence of AEGL-1 values does not imply that exposures at concentrations below the AEGL-2 values are without effect.

TABLE 2-8 Standards and Guidelines for Diketene

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	1.8 ppm	1.3 ppm	1.0 ppm	0.25 ppm	0.13 ppm
AEGL-3	5.5ppm	3.8 ppm	3.0 ppm	0.75 ppm	0.38 ppm
ERPG-1 (AIHA)[a]	–	–	1 ppm	–	–
ERPG-2 (AIHA)	–	–	5 ppm	–	–
ERPG-3 (AIHA)	–	–	20 ppm	–	–

[a]ERPG (emergency response planning guideline, American Industrial Hygiene Association) (AIHA 2000).
The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. The ERPG-1 for diketene is based on the threshold-limit value for ketene.
The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action. The ERPG-2 for diketene is based on clinical signs from a 1-h rat lethality study.
The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing life-threatening health effects. The ERPG-3 is based on 1-h lethality data (LC_{50} of 612 ppm) in the rat.

8.3. Data Adequacy and Research Needs

Additional animal studies with exposure durations relevant to the AEGL durations other than 1 h and with at least one species other than rat are needed to better characterize the acute inhalation toxicity of diketene. The diketene concentrations tested should encompass the entire spectrum of AEGL end points, ranging from 90-100% lethality to no lethality and no-effect-levels for clinical signs and pathologic findings.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR DIKETENE

Derivation of AEGL-1 Values

Insufficient data were available for deriving AEGL-1 values for diketene. Therefore, AEGL-1 values are not recommended. Absence of AEGL-1 values does not imply that exposures below the AEGL-2 values are without effect.

Derivation of AEGL-2 Values

The AEGL-2 values for diketene were estimated by dividing the respective AEGL-3 values by 3. That procedure is in accordance with the standing operating procedures for deriving AEGL values for chemicals with steep concentration-response curves (NRC 2001).

Calculations:

10-min AEGL-2:	5.5 ppm ÷ 3 = 1.8 ppm
30-min AEGL-2:	3.8 ppm ÷ 3 = 1.3 ppm
1-h AEGL-2:	3.0 ppm ÷ 3 = 1.0 ppm
4-h AEGL-2:	0.75 ppm ÷ 3 = 0.25 ppm
8-h AEGL-2;	0.38 ppm ÷ 3 = 0.13 ppm

Derivation of AEGL-3 Values

Key study:	Katz, G.V. 1987. Acute Inhalation Toxicity and One-Hour LC10 Value of Diketene in the Rat. Study No. TX-86-265, February 4, 1967. Toxicological Sciences Section, Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY.
Toxicity end point:	Lethality (1-h $BMCL_{05}$ of 181 ppm)
Time scaling:	$C^n \times t = k$; default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations $(181 \text{ ppm} \div 60)^3 \times 60 \text{ min} = 1{,}647 \text{ ppm-min}$ $(181 \text{ ppm} \div 60)^1 \times 60 \text{ min} = 181 \text{ ppm-min}$
Uncertainty factors:	10 for interspecies differences 3 for intraspecies variability

Modifying factor:	2 for limited database
Calculations:	
10-min AEGL-3:	C^3 = (1,647 ppm-min ÷ 10 min) C = 5.5 ppm
30-min AEGL-3:	C^3 = (1,647 ppm-min ÷ 30 min) C = 3.8 ppm
1-h AEGL-3:	C = (181 ppm-min ÷ 60 min) C = 3.0 ppm
4-h AEGL-3:	C^1 = 181 ppm-min ÷ 240 min C = 0.75 ppm
8-h AEGL-3:	C^1 = 181 ppm-min ÷ 480 min C = 0.38 ppm

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR DIKETENE

AEGL-1 VALUES

Insufficient data were available for deriving AEGL-1 values for diketene. Therefore, AEGL-1 values are not recommended. Absence of AEGL-1 values does not imply that exposures below the AEGL-2 values are without effect.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
1.8 ppm	1.3 ppm	1.0 ppm	0.25 ppm	0.13 ppm

Data adequacy: No adequate studies were available for deriving AEGL-2 values for diketene. The AEGL-2 values were estimated by dividing the respective AEGL-3 values by 3. That procedure is in accordance with the standing operating procedures for deriving AEGL values for chemicals with steep concentration-response curves (NRC 2001).

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
5.5 ppm	3.8 ppm	3.0 ppm	0.75 ppm	0.38 ppm

Key reference: Katz, G.V. 1987. Acute Inhalation Toxicity and One-Hour LC10 Value of Diketene in the Rat. Study No. TX-86-265, February 4, 1967. Toxicological Sciences Section, Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY.

Test species/Strain/Number: Rat; CRL:CD®(SD)BR; 5 males and 5 females per group

Exposure route/Concentrations/Durations: Inhalation; 250, 500, and 750 ppm for 1 h

Effects:
250 ppm: Signs of ocular (lacrimation) and respiratory tract irritation (gasping and rales).
500 ppm: Three rats died (2 male, 1 female); clinical signs were the same as those observed at 250 ppm, plus porphyrin discharge from the nose.
750 ppm: Seven rats died (4 male, 3 female); clinical signs were same as those observed at 500 ppm.

End point/Concentration/Rationale: Lethality, 1-h $BMCL_{05}$ of 181 ppm

Uncertainty factors/Rationale:
Total uncertainty factor: 30
Interspecies: 10
Intraspecies: 3, because diketene is irritating and much of its toxicity is likely caused by a direct chemical effect on the tissue. That type of portal-of-entry effect is not expected to vary greatly among individuals. A factor of 3 is further supported by the fact that mortality incidences and clinical signs were similar between male and female rats exposed to diketene (Katz 1987).

Modifying factor: 2 for limited database

Animal-to-human dosimetric adjustment: None

(Continued)

AEGL-3 VALUES Continued

Time scaling: $C^n \times t = k$; default values of n = 3 when extrapolating to shorter durations and n = 1 when extrapolating to longer durations.
Data adequacy: Only one adequate animal study was available for evaluating the acute inhalation toxicity of diketene. Additional studies in rats exposed for other durations and studies in at least one other species are needed to better characterize the acute inhalation toxicity of diketene.

APPENDIX C

CATEGORY PLOT FOR DIKETENE

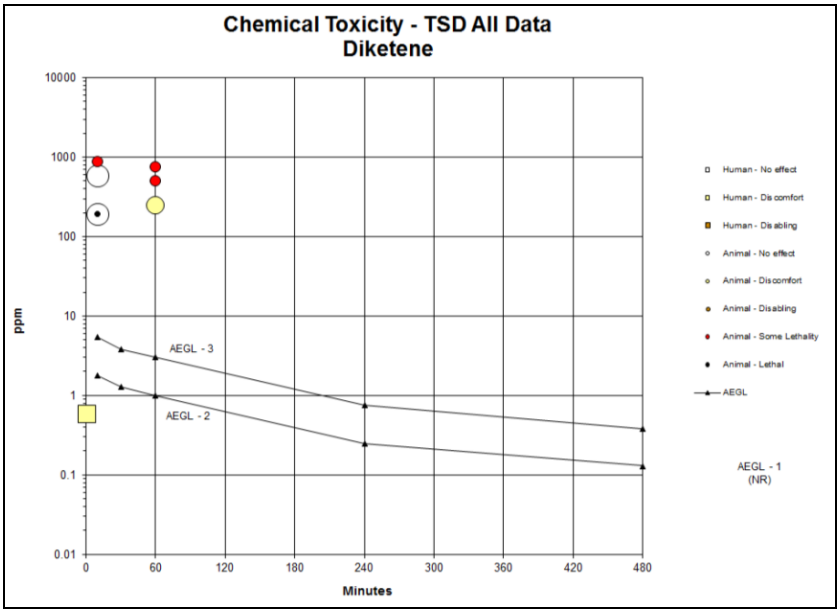

FIGURE C-1 Category plot of toxicity data and AEGL values for diketene.

TABLE C-1 Data Used in Category Plot for Diketene

Source	Species	ppm	Minutes	Category	Comments
AEGL-2		1.8	10	AEGL	
AEGL-2		1.3	30	AEGL	
AEGL-2		1.0	60	AEGL	
AEGL-2		0.25	240	AEGL	
AEGL-2		0.13	480	AEGL	
AEGL-3		5.5	10	AEGL	
AEGL-3		3.8	30	AEGL	
AEGL-3		3.0	60	AEGL	
AEGL-3		0.75	240	AEGL	
AEGL-3		0.38	480	AEGL	
Danishevskii 1948, 1951; Feldman 1967	Human	0.58	1	1	Mild irritation of the conjunctiva and mucosa of nose and throat

(Continued)

TABLE C-1 Continued

Source	Species	ppm	Minutes	Category	Comments
Katz 1987	Rat	250	60	1	No mortality, lacrimation
Katz 1987	Rat	500	60	SL	30% mortality
Katz 1987	Rat	750	60	SL	70% mortality
Wooster et al. 1947	Mouse	194	10	0	No mortality
Wooster et al. 1947	Mouse	580	10	0	No mortality
Wooster et al. 1947	Mouse	870	10	SL	1/20 died
Wooster et al. 1947	Guinea pig	194	10	3	3/3 died

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

APPENDIX D

BENCHMARK CONCENTRATION CALCULATION

Probit Model. (Version: 2.8; Date: 02/20/2007)
Input Data File: C:\BMDS\DATA\DIKETENE.(d)
Gnuplot Plotting File: C:\BMDS\DATA\DIKETENE.plt
Mon Apr 09 09:49:14 2007

BMDS MODEL RUN

The form of the probability function is:
P[response] = Background
+ (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),
where CumNorm(.) is the cumulative normal distribution function

Dependent variable = COLUMN3
Independent variable = COLUMN1
Slope parameter is not restricted

Total number of observations = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
background = 0
intercept = -13.4507
slope = 2.10082

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) – background have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix)

	intercept	slope
intercept	1	-1
slope	-1	1

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
Background	0	NA		
Intercept	-16.3675	5.52762	-27.2014	-5.53353
Slope	2.55065	0.87102	0.843482	4.25782

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Analysis of Deviance Table

Model	Log (likelihood)	# Parameters	Deviance	Test d.f.	P-value
Full model	-12.2173	4			
Fitted model	-12.5124	2	0.590315	2	0.7444
Reduced model	-22.4934	1	20.5522	3	0.0001304

AIC: 29.0249

Goodness of Fit

Dose	Est. Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	10	0.000
271.0000	0.0188	0.188	0	10	-0.438
466.0000	0.2433	2.433	3	10	0.418
778.0000	0.7296	7.296	7	10	-0.211

Chi-square = 0.41 d.f. = 2 P-value = 0.8142

Benchmark Dose Computation
Specified effect = 0.05
Risk type = Extra risk
Confidence level = 0.95

BMD = 321.212
BMDL = 180.893