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.

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Appendixes

7

Tear Gas (CS)[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 Cheryl Bast (Oak Ridge National Laboratory), Lisa Ingerman (SRC, Inc.), Chemical Manager Glenn Leach (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances), and Ernest V. Falke (US 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

Tear gas is a white crystalline powder with a pepper-like odor. It was first synthesized by Corson and Stoughton in 1928 and is, thus, abbreviated as CS (Corson and Stoughton 1928; US Army Chemical School 2005). CS was developed in the 1950s as a replacement for the chemical incapacitant, 1-chloroacetophenone (CN), because CS was a much more potent irritant than CN, but was significantly less toxic (WHO 1970; Colgrave and Creasey 1975; Hu et al. 1989). It was adopted for use by the military, and was widely used in the Vietnam War (WHO 1970; Hu et al. 1989). It is currently used as an incapacitating agent both by military and law enforcement personnel (HSDB 2005). Upshall (1973) reported that an aerosol concentration of CS at 4 mg/m^3 will disperse the majority of rioters within 1 min, and at 10 mg/m^3 will deter trained troops. With the exception of more severe cutaneous reactions, recovery from exposure is generally rapid upon exposure to fresh air, generally within 30 min after exposure (Ballantyne 1977). CS may be manufactured through carbonyl condensation by combining *o*-chlorobenzaldehyde and malononitrile (HSDB 2005). Recent production data on CS were not found.

Human studies did not identify a no-effect level for CS or effects of CS that would be consistent with the definition of AEGL-1. The severity of the effects observed at the lowest tested concentrations in humans (ocular stinging and watering, and nasal, throat, and mouth irritation) exceeded those defined by AEGL-1. Therefore, AEGL-1 values for CS are not recommended. AEGL-2

values were based on human exposure to CS at an average concentration of 0.75 mg/m^3 for 60 min (Beswick et al. 1972). All five subjects tolerated the exposure, but reported ocular stinging and watering, increased salivation, cough, and face stinging. Some subjects also reported throat irritation (4 subjects), nasal stinging and running (3 subjects), mouth stinging (2 subjects), chest burning (2 subjects), nausea (2 subjects), and headache (2 subjects). An intraspecies uncertainty factor of 3 was applied because contact irritation is a portal-of-entry effect and is not expected to vary widely among individuals. Furthermore, the responses of volunteers with jaundice, hepatitis, or peptic ulcer or who were 50-60 years old were similar to those of "normal" volunteers when exposed at a highly irritating concentration of CS for short durations. The ability to tolerate CS at 14-73 mg/m^3 and the recovery time in volunteers with a history of drug allergies, seasonal allergies, asthma, or drug sensitivity were similar to normal volunteers; although more severe chest symptoms were reported in the people with pre-existing conditions (Gutentag et al. 1960; Punte et al. 1963). An interspecies uncertainty factor of 1 was applied because the study was conducted in humans. A modifying factor of 3 was also used because the effects observed at 0.75 mg/m^3 were considered AEGL-2 effects. Time scaling was not performed because irritation is a function of direct contact with CS and is unlikely to increase with duration of exposure at this level of severity (NRC 2001).

AEGL-3 values were based on calculated lethality thresholds for CS at each exposure duration. Rat data from the studies by McNamara et al. (1969), Ballantyne and Callaway (1972), and Ballantyne and Swanston (1978) were used calculate LC_{01} (lethal concentrations, 1% lethality) values for CS. Calculations were performed using the probit analysis-based dose-response program of ten Berge (2006). Time scaling was performed using the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). An empirical value for n of 0.70 was determined on the basis of the rat data. The 4-h AEGL-3 value was adopted as the 8-h AEGL-3 value because time scaling yielded an 8-h value inconsistent with the AEGL-2 values, which were derived from robust human data. A total uncertainty factor of 10 was applied. A factor of 3 was used to account for interspecies differences, because clinical signs are likely caused by a direct chemical effect on the tissues and this type of portal-of-entry effect is unlikely to vary greatly between species. Furthermore, calculated LCt_{50} values for different species were all well within a factor of 2 of each other (88,480 mg-min/m^3 for rats, 67,200 mg-min/m^3 for guinea pigs, 54,090 mg-min/m^3 for rabbits, and 50,010 mg-min/m^3 for mice) (Ballantyne and Swanston 1978). An uncertainty factor of 3 was used to account for intraindividual variability because contact irritation is a portal-of-entry effect and is not expected to vary widely among individuals. As noted above in support of the AEGL-2 values, a factor of 3 is also supported by the results of studies by Punte et al. (1963) and Gutentag et al. (1960) in subjects with pre-existing conditions.

AEGL values for CS are presented in Table 7-1.

TABLE 7-1 AEGL Values for Tear Gas

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)	0.083 mg/m^3	0.083 mg/m^3	0.083 mg/m^3	0.083 mg/m^3	0.083 mg/m^3	Ocular, nasal, and throat irritation in humans (Beswick et al. 1972)
AEGL-3 (lethal)	140 mg/m^3	29 mg/m^3	11 mg/m^3	1.5 mg/m^3	1.5 mg/m^3	Threshold for lethality (LC_{01}) in rats (McNamara et al. 1969; Ballantyne and Callaway 1972; Ballantyne and Swanston 1978)

[a]Not recommended. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 value is without adverse effects. The severity of effects observed at the lowest tested concentrations exceeded those defined by AEGL-1.

1. INTRODUCTION

CS is a white crystalline powder with a pepper-like odor. It was first synthesized by Corson and Stoughton in 1928 (thus, the abbreviation CS) (Corson and Stoughton 1928; US Army Chemical School 2005). It was developed in the 1950s as a replacement for the chemical incapacitant, 1-chloroacetophenone (CN), because CS was a much more potent irritant than CN, but was significantly less toxic (WHO 1970; Colgrave and Creasey 1975; Hu et al. 1989). CS was adopted for use by the military, and was widely used during the Vietnam War (WHO 1970; Hu et al. 1989; Smith and Greaves 2002). It is currently used as an incapacitating agent by military and law enforcement personnel (HSDB 2005). It is reported that an aerosol concentration of 4 mg/m^3 will disperse the majority of rioters within 1 min, and 10 mg/m^3 will deter trained troops (Upshall 1973). With the exception of more severe cutaneous reactions, recovery from exposure is generally rapid upon exposure to fresh air, usually within 30 min after exposure (Ballantyne 1977).

Because CS is stable when heated and has a low vapor pressure, it requires a means of dispersement (Blain 2003). Different forms of dispersement include the combination of CS with a pyrotechnic compound in a grenade or canister, generating a smoke or fog, and dispersement of a fine powder as an aerosol (WHO 1970; Smith and Greaves 2002). CS1 is a micronized powder formulation of CS containing 5% silica gel for dissemination by an explosive burst or dusting apparatus, and CS2 is the same as CS1 except that the CS1 is microencapsulated with silicone to improve its weather resistance and flow properties (WHO 1970).

In controlled studies investigating the toxicologic properties of CS aerosol, CS was disseminated as a 2-10% solution in methylene chloride or acetone by means of a pneumatic atomizing nozzle assembly (Gutentag et al. 1960; Owens and Punte 1963; Punte et al. 1963) or by thermal dispersion by spraying the molten chemical (Gutentag et al. 1960; Punte et al. 1962, 1963).

CS may be manufactured through carbonyl condensation by combining *o*-chlorobenzaldehyde and malononitrile (HSDB 2005). Recent production data of CS were not available.

Hydrolysis of CS produces malononitrile and *o*-chlorobenzaldehyde (NTP 1990). Hydrolysis of CS is relatively rapid, with a half-life of about 15 min at a pH 7, but CS reacts faster with an alkaline solution, having a half-life of about 1 min at a pH of 9 (Blain 2003).

CS has a vapor pressure of 3.4×10^{-5} mm Hg; thus, at concentrations greater than 0.35 mg/m^3, it will exist in vapor and aerosol forms. CS in the vapor phase will be degraded by reaction with photochemically produced hydroxyl radicals, with an estimated half-life of 110 h. CS in the particulate phase will be removed by wet and dry deposition.

The chemical and physical properties of CS are presented in Table 7-2.

TABLE 7-2 Chemical and Physical Properties of Tear Gas

Parameter	Value	Reference
Common name	Tear gas	
Synonyms	CS; *o*-chlorobenzylidenemalonitrile; 2-chlorobenzalmalononitrile; (2-chloro-phenyl)methylene) propanenitrile; 2-chlorobmn; beta, beta-dicyano-o-chlorostyrene	HSDB 2005; O'Neil et al. 2006
CAS registry no.	2698-41-1	O'Neil et al. 2006
Chemical formula	$C_{10}H_5ClN_2$	O'Neil et al. 2006
Molecular weight	188.6	O'Neil et al. 2006
Physical state	White crystalline solid	O'Neil et al. 2006
Melting point	95-96°C	ACGIH 1991
Boiling point	310-315°C	US Army Chemical School 2005
Density (solid)	Bulk: 0.24-0.26 g/mL; crystal: 1.04 g/mL	US Army Chemical School 2005
Solubility in water (g/L)	Sparingly soluble; 2.0×10^{-4} M	ACGIH 1991; O'Neil et al. 2006
Vapor density (air =1)	6.5	US Army Chemical School 2005
Vapor pressure	3.4×10^{-5} mm Hg at 20°C	US Army Chemical School 2005
Henry's Law Constant	1.0×10^{-8} atm-m^3/mol	HSDB 2005
Volatility	0.71 mg/m^3 at 25°C	US Army Chemical School 2005
Stability/reactivity	Combustible material; may burn but does not ignite readily	US Army Chemical School 2005
Conversion factors	1 ppm = 7.71 mg/m^3 1 mg/m^3 = 0.13 ppm	Calculated

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No human acute lethality data on CS were found.

2.2. Nonlethal Acute Toxicity

2.2.1. Experimental Studies

In a review article, Blain (2003) reported a TC_{50} (concentration that caused a perceptible effect on 50% of the population exposed for 1 min) of 0.004 mg/m^3 for ocular irritation and 0.023 mg/m^3 for airway irritation. An ICT_{50} (concentration intolerable to 50% of the population exposed for 1 min) was also reported. No further details were presented.

A group of male volunteers was exposed to CS aerosol with a mass median diameter (MMD) of 0.9 microns (94 ± 15 mg/m^3; 4% larger than 10 microns) or up to 60 microns (85 ± 16 mg/m^3; 4% smaller than 20 microns) to assess differences in ocular and respiratory responses to different particle sizes of CS (Owens and Punte 1963). Six volunteers who had the best ability to tolerate CS were chosen from a group of approximately 50. Subjects wore tightly fitted goggles and a nose and mouth respirator designed to protect against particle sizes less than one micron, and were exposed individually in a wind tunnel with a constant air speed of 5 mph. The exposure protocol was designed to restrict exposure to either the small or large particles to the eyes, to the respiratory system, or to both the eyes and respiratory system. The wind tunnel was elevated to a height of 5 feet, and a rubber-lined port was installed in the bottom of the duct enabling the subject to insert his head into the airstream of the tunnel and remove it quickly after the exposure. CS was disseminated from a 2% solution in methylene chloride by means of a pneumatic atomizing nozzle assembly. CS concentrations were determined from air samples collected using filter paper placed on air sampling probes located around the head area (one on top and one on each side at eye level), followed by extraction with ethanol and measurement with ultraviolet spectrophotometry. A modified cascade impactor was used to measure the CS aerosol containing the small particles, while the larger particles were sized microscopically, measuring and counting the various particles in the pre-ground material before dissemination. Tolerance time was defined as the time at which a subject could no longer remain in the atmosphere containing the compound and left the exposure chamber, and recovery time was defined as the time after the exposure when the subjects were able to sort and arrange a series of 24 playing cards from which the corner numbers were removed. Control values were determined before each test. The results indicate that small particles are more effective in rapidly producing ocular irritation (see Table 7-3). The onset of ocular response is hypothesized to be faster with small particles because

TABLE 7-3 Tolerance and Recovery Time in Humans Exposed to Tear Gas Particles (1-60 microns)

	Subjects Tolerating 60-sec Exposure (%)		Recovery Time (sec)	
Exposure	Small Particles[a]	Large Particles[b]	Small Particles[a]	Large Particles[b]
Eyes	40	100	91	280
Respiratory system	0	67	51	9[c]
Eyes and respiratory system	16	85	52	188

[a]Measured concentration of 94 ± 15 mg/m^3.
[b]Measured concentration of 85 ± 16 mg/m^3.
[c]4/6 subjects were able to perform task immediately after exposure.
Source: Adapted from Owens and Punte 1963.

of they are more soluble than larger particles in ocular fluid. Once begun, however, the irritation process would continue for a longer period with the large particles compared with the small particles. Respiratory effects were more severe with small particles (no volunteers could withstand exposure for more than 30 seconds [sec]) and required more time for recovery than the large particles. The difference in response is due to the ability of smaller-sized particles to penetrate more deeply into the respiratory tract. When both the eyes and the respiratory system were exposed to CS, the respiratory response predominated with exposure to the small particles, whereas the ocular response predominated with exposure to the large particles.

A group of 4-6 volunteers was exposed to CS aerosol in a wind tunnel (8 × 8 × 8 feet; fixed wind speed of 5 mph) (Gutentag et al. 1960; Punte et al. 1963). Volunteers were both military and civilian personnel. Each volunteer's medical history was recorded, and each was given pre-exposure and post-exposure physical examinations. Volunteers were classified as "normal" or were placed in one of four special categories: those with hypertension (diastolic pressure of 80-110 mm Hg or normal blood pressure reading with a history of hypertension; pre-exposure tests included electrocardiogram, chest X-ray, liver function, and urinalysis); those with hay fever, drug sensitivity, or bronchial asthma (volunteers with asthma had normal chest X-ray before exposure); those with a history of jaundice, hepatitis, or peptic ulcers without gastrointestinal bleeding; and those that were 50-60 years of age. Subjects classified as normal were further categorized into untrained men with or without protective masks or trained men with or without protective masks. The trained men had previous exposure to CS, whereas the untrained men did not. CS was dispersed as a 10% solution in acetone or methylene dichloride with a spray nozzle (MMD 3.0 or 1.0 micron, respectively) or by thermal dispersion (spraying the molten chemical; MMD 0.5 micron). Airborne samples of the aerosol were collected at various points in the wind tunnel. Particle size was characterized using a 6-stage modified cascade impactor, and exposure concentrations were measured using ultraviolet spectrophotometry. The subjects did not report any noticeable difference in symptoms from the different dispersion methods.

Groups of 3-6 untrained men without masks were exposed to CS in acetone, and tolerance times were recorded. Times ranged from 53 to >120 sec at 5 mg/m^3, 19-43 sec at 12 mg/m^3, and up to 5 sec at 442 mg/m^3. When groups of 1-7 trained men were exposed, tolerance times ranged from 37 to >120 sec at 4 mg/m^3, 18-41 sec at 10 mg/m^3, and up to 12-25 sec at 141 mg/m^3. To compare the effects of hyperventilation on symptoms, untrained subjects ran for approximately 100 yards before exposure. Exercising subjects could not tolerate CS as well as normally breathing subjects; groups of three subjects exposed at 10, 13, or 39 mg/m^3 could tolerate CS for up to 13, 13, and 9 sec, respectively. While ocular irritation was minimal, chest symptoms were more pronounced and recovery time was slightly prolonged (by 1-2 min). The reactions of subjects with jaundice, hepatitis, or peptic ulcer or those that were 50-60 years old were similar to those of normal subjects. Subjects with a history of drug allergies or sensitivities, hay fever, or asthma also tolerated exposure to CS at concentrations comparable to those tolerated by normal subjects, but the group with preexisting conditions had a higher percentage of individuals with more severe chest symptoms, with many of them laying prostrate on the ground for several minutes. However, no wheezing or rhonchi were heard, and recovery was as rapid as that seen in other exposure groups. When subjects were exposed to CS at temperatures ranging from 0-95°F, tolerance to the chemical was slightly reduced at the high temperature of 95°F. Whether the decrease in tolerance was an actual effect of the exposure, the uncomfortable climate, or a combination of both was unclear. An increase in skin-burning symptoms with increased temperature was attributed to an increase in perspiration.

As part of the study described above, the potential for developing tolerance to CS was investigated by exposing a group of four subjects to CS at 1.5 mg/m^3 for 90 min in a 20,000-L chamber (Punte et al. 1963). No data were provided about the monitoring of the CS aerosol. During exposure, subjects were allowed to smoke, read, and play cards. Only one subject reported nasal irritation (after 2 min), three subjects reported headaches (after 45, 50, and 83 min), and all four subjects reported ocular irritation (after 20, 24, 70, and 75 min). In the second part of the experiment, the four subjects were exposed to CS at 1.5 mg/m^3 for 40 min, and then additional CS aerosol was added to the chamber to achieve an airborne concentration of 11 mg/m^3 in about 10 min. Although the subjects had not been told of the increase in concentration, they all left within 2 min due to respiratory irritation. The exposure concentration was estimated to be 4.3-6.7 mg/m^3 when the subjects left the chamber. In the third part of the experiment, the subjects were exposed to CS at 6 mg/m^3, which was attained over 10 min. Symptoms reported by the subjects included nasal and throat irritation, chest burning, sneezing, ocular irritation and lacrimation, headache, and dermal irritation. Three of the four subjects reported that the exposure was unbearable after 18, 20, and 29 min, with chest symptoms being the reason the subjects left the chamber. The remaining subject was able to tolerate the agent, and the exposure was terminated after 40 min. The investigators attempted to enter the chamber without the benefit of the gradual increase in exposure concentration,

and were unable to remain in the chamber. In the fourth experiment, a concentration of 6.6 mg/m^3 was attained over 30 min. The usual signs and symptoms of CS exposure developed, but to a lesser degree. One of the subjects had to leave after 2 min because of a violent cough, but he returned to the exposure chamber after his cough had ceased upon exposure to fresh air. He remained in the exposure chamber for the duration of the 60-min exposure.

To assess the potential effect of CS exposure on ventilation, cardiac frequency, and breathing pattern, a group of 11 healthy soldier volunteers was exposed to CS aerosol (particle diameter of 1 micron) at a concentration that was progressively increased from 0.2 mg/m^3 to 1.3 mg/m^3 (Cotes et al. 1972; Cole et al. 1977). The exposure duration was not specified, but appeared to be approximately 80 min. CS aerosol was produced by saturating the exposure chamber the evening before the exposure, followed by flushing with air to remove all of the gas except that adsorbed onto the walls and equipment. During exposure, pyrotechnic generators were ignited to progressively raise the concentration of CS throughout the exposure session. Subjects wore woolen or denim battle dress covered with cotton coveralls, boots, and gaiters. Electrocardiogram electrodes were applied to the chest, and subjects wore a full respirator into the chamber. For the commencement of exposure, each subject removed his own respirator. During each exposure, each subject completed two 8-min periods of exercise, which consisted of cycling at 20W up to 120W. During exercise, the subjects breathed through an oral-nasal mask and three-way valve box. Inspiration was from the chamber and expiration was through a 6-L capacity mixing bottle into a low resistance gas meter. Cardiac frequency was measured by electrocardiograph, while a thermister in the valve box recorded respiratory frequency. A control exposure including exercise was conducted the day before and the day after exposure to CS. A major difference between the control and CS exposures was that ventilation was continued throughout the control session but not the CS-exposure session; therefore, the temperature was much higher during the CS-exposure sessions than the control session (~24° vs. 20.5°C for controls).

All subjects experienced intense discomfort, including cough, lacrimation, and substernal pain, when first exposed to the CS aerosol. Discomfort was severe enough that two subjects withdrew (one before and one after the first period of exercise), and two additional subjects were unable to complete the first period of exercise due to coughing. Coughing coincided with ignition of the CS generators. The discomfort disappeared with continuing exposure. Although cardiac frequency increased during exposure to CS compared with control air, the difference was eliminated when the cardiac frequency was corrected for the increased ambient temperature (corrected to the arbitrary temperature of 20°C). The ventilation minute volume was reduced from exposure to CS compared with controls. The reduction appeared to be due to a decrease in respiratory frequency. The exposure was repeated using 17 volunteers (Cole et al. 1975, 1977). Exposure conditions were the same with the following exceptions: the CS candles were ignited between and not during periods of exercise, CS concentrations were slightly higher (0.92-2.15 mg/m^3), and the subjects were seen on five con-

secutive half-day sessions (the first, third, and fifth sessions were for control observations and the other two sessions were allocated one each for exposure to ammonia and to CS [the order of exposure changed between the different weeks of the study]). Results were generally the same as those observed in the first study. The only difference was that the reduction in the ventilation minute volume was the result of a diminution in tidal volume and occurred despite an increase in respiratory frequency.

To investigate the potential for developing tolerance to CS, 35 healthy male volunteers were exposed for 60 min to increasing concentrations of CS aerosol (Beswick et al. 1972). Exposures were conducted in a 100-m^3 chamber. The chamber was generally saturated an hour before the exposure, followed by air being blown through the chamber to remove the CS not absorbed on the walls and equipment. A number of parameters were assessed before and after exposure, including chest radiograph results, hematology and clinical-chemistry analysis, and respiratory-function tests to assess peak flow, tidal volume, and vital capacity. A total of 10 exposure trials were conducted, with no volunteers exposed more than once. Exposure concentrations were kept relatively constant in the first three trials: 0.53-0.86 mg/m^3 in trial 1 (three subjects), 0.71-0.78 mg/m^3 in trial 2 (five subjects), and 0.31-0.74 mg/m^3 in trial 3 (six subjects). For the seven remaining trials, exposure concentrations were increased by a factor of 2, 3, or 4 during the exposure period: 0.8-1.4 mg/m^3 in trial 4 (five subjects), 0.84-2.3 mg/m^3 in trial 5 (four subjects), 0.7-2 mg/m^3 in trial 6 (four subjects), 0.63-2.3 mg/m^3 in trial 7 (two subjects), 0.57-2.1 mg/m^3 in trial 8 (two subjects); 0.42-1.8 mg/m^3 in trial 9 (two subjects), and 0.45-1.7 mg/m^3 in trial 10 (two subjects). Chamber concentrations were measured at 10-min intervals. Volunteers entered the chamber wearing full respirators and protective coveralls. CS was generated and allowed to mix for 3 min before removal of the respirator. Symptoms from all volunteers were reported during individual interviews after exposure. The results of the 10 trials were consolidated into five groups: group I included trial 2 (five subjects), group II included trials 1 and 3 (nine subjects), group III included trial 4 (five subjects), group IV included trials 5 and 6 (eight subjects), and group V included trials 7, 8, 9, and 10 (eight subjects). One of the six subjects in trial 3 left the exposure chamber after 8 min of exposure with complaints of severe stinging of the eyes, throat irritation, cough and dyspnea, salivation, and nausea, and one subject in group IV left after 55 min due to vomiting. All other subjects remained in the chamber for the entire 60-min exposure period. A summary of the symptoms of the exposed individuals is presented in Table 7-4. The predominant symptoms included excess production of mucus and saliva (34/34 subjects), ocular irritation (stinging in 32/34 subjects and lacrimation in 32/34 subjects), runny nose (28/34 subjects), and face stinging (32/34 subjects). Symptoms generally resolved within 10 min of leaving the chamber. Nausea was reported by 11/34 subjects and two vomited, which appeared to follow swallowing of large amounts of saliva. The development of tolerance was assessed in two of the trials (group IV in Table 7-4); in these trials, half of the subjects removed the respirator at the start of the exposure (with the CS concen-

tration increasing with time), while the remaining subjects did not remove their respirators until the last 5 min of exposure. The subjects that were exposed to CS throughout the entire exposure period were able to withstand the entire 60-min exposure (concentrations increasing from 0.84 to 2.30 mg/m^3 and 0.70 to 2.00 mg/m^3) except for the one individual that had to leave the chamber at 55 min because of vomiting. Of the subjects that removed their respirators for the last 5 min of exposure, only one of eight subjects could remain in the chamber for more than 1 min; five left within 30 sec of removing their respirators. No exposure-related changes were observed in hematology or clinical chemistry parameters. Decreases in heart rate after exposure ceased were ascribed to the sense of relief each volunteer felt at the end of an uncomfortable experience, and the increase in systolic blood pressure observed in individuals when exposure commenced was due to the abrupt onset of discomfort; continued exposure resulted in normal blood pressure readings. No abnormalities were noted in measurements of respiratory function, but the investigator noted that the sample size was small and, thus, may not be representative. It was concluded that the main effects of CS are due to local irritation of exposed nerve endings, and systemic changes noted are due to stress.

Three groups of volunteers were exposed to CS aerosol at various concentrations to investigate potential effects on visual acuity (Rengstorff 1969). The first group was composed of 10 male volunteers exposed to CS2 aerosol (CS treated with Cab-o-Sil® 5 and hexamethyldisilaxane) at concentrations of 0.1 to 1.7 mg/m^3. The exposure was conducted in a wind tunnel suspended 4.5 feet above the floor; the volunteer sat on a chair at the end of the wind tunnel and put his head through a rubber aperture in the tunnel until he could no longer tolerate the exposure or for a maximum of 10 min. A powder dispenser disseminated specific concentrations of CS2 (MMD of 0.8 microns) into the air at a wind speed of 4.5 mph. An Orthorater was used to measure the binocular far and near visual acuity of the subjects before and after exposure. The second and third groups were exposed to CS aerosol in a circular steel chamber. CS aerosol (MMD of 0.9 micron) in a methylene dichloride solution was disseminated using a thermal generator, and introduced into the chamber as a uniform cloud. Subjects wore protective masks for the first 5 min in the chamber, and then removed their masks for the commencement of exposure. The second group was composed of 34 volunteers, and an Orthorater was again used to measure the binocular far and near visual acuity before and after exposure. A summary of the amount of time volunteers from this group could tolerate exposure to CS is presented in Table 7-5. The third exposure involved 22 volunteers who had a baseline visual acuity of 20/20 and who could remain in the exposure chamber for 10 min. Binocular acuity was measured using a Snellen visual acuity projector before, during, and a few minutes after exposure. The Snellen chart contained a row of 20/30, 20/25, and 20/20 letters. No exposure-related changes in visual acuity were noted except those due to the inability of some subjects to keep their eyes open because of intense ocular irritation. Visual acuity returned to normal in all subjects several minutes after exposure to CS ended.

TABLE 7-4 Symptoms of Volunteers Exposed to Tear Gas for 60 Minutes

	Exposure Group (nominal-fold increase in concentration during exposure)						
Symptoms	I (steady)	II (× 2)	III (× 2)	IV (× 3)	V (× 4)	Total	Observations
Number exposed	5[a]	8[b]	5[c]	8[d]	8[e]	34	–
Eyes:							
Stinging	5	8	4	7	8	32	No connection between severity and concentration, but duration of symptoms may be less with steady concentration.
Watering	5	8	5	7	7	32	
Nose:							
Stinging	3	4	1	6	4	18	Effects diminished in subjects exposed at steady concentrations or at concentrations that were doubled during the exposure duration.
Running	3	7	3	8	7	28	
Peppery feeling	2	4	2	4	5	17	
Blocked	1	3	2	3	2	11	
Mouth							
Irritation	2	4	–	6	3	15	Copious saliva production; subjects spitting appeared to be vomiting.
Salivation	5	8	5	8	8	34	
Throat:							
Irritation	4	5	3	6	5	23	–
Dry	–	1	–	6	1	8	
Chest:							
Burning	2	2	–	3	1	8	More severe effects appeared to be due to deep breaths taken after holding breath; coughing was sporadic.
Tight	1	3	2	2	3	11	
Dyspnea	–	2	2	2	3	9	
Cough	5	2	4	3	4	18	

Nausea	2	3	1	3	2	11	–
Vomiting (during exposure)	–	–	–	1	1	2	Likely due to swallowing large quantity of saliva. Subject in Group V vomited within first 5 min and left chamber, but returned for duration of exposure. Subject in Group IV vomited after 55 min.
Face stinging	5	7	5	7	8	32	Effects appeared to be of shorter duration in subjects exposed at steady concentrations. Stinging most unpleasant in shaved regions.
Headache	2	1	2	1	–	6	Persisted in 3 subjects throughout exposure; three cases reported post-exposure. Appeared to be due to irritation of the frontal sinuses.

[a]Five subjects exposed at 0.71-0.78 mg/m^3.
[b]Three subjects exposed at 0.56-0.86 mg/m^3, and five subjects exposed at 0.31-0.74 mg/m^3 (one subject excluded because he left the exposure chamber after 8 min).
[c]Five subjects exposed at 0.8-1.4 mg/m^3.
[d]Four subjects exposed at 0.84-2.3 mg/m^3, and four exposed at 0.7-2.0 mg/m^3. To assess the development of tolerance, four subjects removed respirators at start of exposure, while the other four removed respirators 5-min before the end of exposure; the subjects that removed respirators at beginning of exposure were able to withstand the entire 60-min exposure, except for one individual that had to leave the chamber after 55 min because of vomiting. Of the subjects that removed their respirators during the last 5 min of exposure, only one of eight could remain in the chamber for more than 1 min and five left within 30 sec of removing their respirators.
[e]Two subjects exposed at 0.63-2.3 mg/m^3, two exposed at 0.57-2.1 mg/m^3, two exposed at 0.42-1.8 mg/m^3, and two exposed at 0.45-1.7 mg/m^3.
Source: Adapted from Beswick et al. 1972.

TABLE 7-5 Tolerance of Humans Subjects Exposed to Tear Gas for Up to 10 Minutes in Study Evaluating Visual Acuity

Concentration (mg/m^3)	Number of Subjects	Exposure Duration (sec)
0.4	1	135
	1	420
	1	435
	4	600
0.6	1	30
	2	35
	1	38
	1	40
	1	65
	1	68
	1	102
	1	105
	1	135
	7	600
0.9	6	600
1.0	1	35
	1	40
	1	45
	1	50

Source: Adapted from Rengstorff 1969.

To assess the effect of CS exposure on respiration, a group of six volunteers (four with previous exposure to CS) were exposed to various concentrations of CS (3 micron) in a wind tunnel while a portable breathing device monitored respiration (Craig et al. 1960). Subjects remained in the tunnel until the exposure became intolerable (see Table 7-6). Notable coughing was observed in subjects exposed at 15 mg/m^3 for 61 sec or at 150 mg/m^3 for 12 sec. On the basis of the recordings made during exposure, it was concluded that although the breathing pattern of the volunteers was disrupted, adequate ventilation was maintained. Therefore, the incapacitation of CS is attributed to the unpleasant sensations of exposure rather than to any degree of respiratory failure.

A group of 38 US Marines was exposed to a cloud of CS dispersed by a thermal canister as part of a training exercise to test the ability and speed of the trainees in donning their gas masks (Thomas et al. 2002). The exposure occurred after 6 days of strenuous training with minimal sleep and reduced food consumption, and was followed by a 1.5-mile run. Temperature and relative humidity at the time of exposure were approximately 24°C and 91%, respectively. Clinical signs and symptoms began to develop 36-84 h post-exposure during and

TABLE 7-6 Tolerance of Human Subjects Exposed to Tear Gas in Study Evaluating Respiratory Effects

Concentration (mg/m^3)	Exposure Duration (sec)
5	110 +
12	24
15	61 +
64	15 +
80	12
150	12 +

+ Previous exposure to CS.
Source: Craig et al. 1960.

after periods of strenuous exercise (one subject became symptomatic after a 1,000-meter pool swim at 36 h post-exposure; seven became symptomatic after a second swim consisting of a 1,000-meter open ocean swim 60 h post-exposure; and one became symptomatic after a third swimming event consisting of a 1,500-meter open ocean swim 84 h post-exposure). A total of nine subjects were affected, with four requiring admission into intensive care. Effects of exposure included dyspnea upon exertion, hemopytosis (ranging from frank blood to blood-tinged sputum), cough, rales, reduced arterial blood gas (range of 60-68), and infiltrates visible on chest radiograph. Signs and symptoms resolved by 72 h, and lung function before and after exercise challenge returned to normal within 1 week post-exposure. When the exposure in this study was recreated (without test subjects) and air sampling was performed, CS concentrations were found to range from less than quantifiable to approximately 17 mg/m^3.

McDonald and Mahon (2002) proposed that the pulmonary symptoms in the Marines described in the study by Thomas et al. (2002) were not the result of CS exposure, but were rather the result of water aspiration or swimming-induced pulmonary edema (SIPE). Their conclusions were based on the observations that all subjects became symptomatic immediately after swimming, that there was a rapid resolution of symptoms, and that there was no evidence of airway dysfunction. Delayed pulmonary effects of CS exposure are unusual, and there were no other reports of such symptoms even though approximately 200,000 Marines have been exposed to CS since 1996 under similar field conditions.

2.2.2. Case Reports

The effects of exposure to CS are generally of an acute nature. However, reactive airways dysfunction syndrome was reported in two individuals exposed to CS. One case involved a healthy 21-year-old female exposed to CS smoke at a nightclub for 5-10 min (Hu and Christiani 1992). She exhibited the typical signs and symptoms of CS exposure, including tightness and burning in her chest and coughing. Results of a physical examination and chest radiography were normal,

and she was released from the hospital. She continued to experience coughing and shortness of breath, and had reduced measurements of forced expiratory volume in 1 sec (68% of predicted) and forced vital capacity (78%) 4 weeks after exposure. Cough and shortness of breath were still present at the 2-year follow-up exam, and were made worse by exertion, cold air, and some environmental pollutants. The second case report involved exposure to a riot-control agent containing 1% CS and 1% oleo resin capsicum (Roth and Franzblau 1996). A healthy 53-year-old male was exposed for at least 30 sec, and immediately experienced symptoms of mucous membrane irritation, cough, and chest tightness. Wheezing and shortness of breath continued for months after exposure, and were severe enough to require hospitalization. Pulmonary function test results indicated reversible and fixed obstructive pulmonary disease. Effects of exposure to the capsicum cannot be excluded.

A 4-month-old infant exposed to CS for 2-3 h developed pneumonitis and persistent leukocytosis (Park and Giammona 1972). The infant was exposed when a CS canister was fired into a house to subdue an adult. Upon hospitalization, the infant had copious nasal and oral secretions and was sneezing and coughing. A chest X-ray demonstrated that the lungs were clear, but laboratory testing revealed leukocytosis. The infant developed severe respiratory distress by the second day of hospitalization, with pulmonary infiltrates evident on X-ray by day 7. Pulmonary infiltration began to decrease on day 15, and the lungs were clear on day 17. White blood cell counts were elevated throughout hospitalization, and finally decreased when the infant was discharged from the hospital.

CS is a common riot-control agent in Britain; consequently, typical symptoms following exposure to CS have been described following its use in confined spaces, such as a night club (Breakell and Bodiwala 1998) or bus (Karagama et al. 2003), use by police on individuals for self-defense (Euripidou et al. 2004), or under conditions of large-scale riot control (Himsworth 1969; Anderson et al. 1996). Symptoms of exposure included but were not limited to ocular irritation, lacrimation, blurred vision, burning sensations sometimes accompanied by first degree burns, cough, headache, shortness of breath, chest pain, sore throat, retching, vomiting, and salivation (Himsworth 1969; Anderson et al. 1996; Breakell and Bodiwala 1998; Karagama et al. 2003; Euripidou et al. 2004). In general, the symptoms resolved rapidly; however, there were reports of effects lasting longer that that predicted. The hand-held spray canisters used by police contain CS dissolved in methyl isobutyl ketone, an industrial solvent and denaturant (Gray 2000; Euripiou et al. 2004). It has, therefore, been proposed that the ketone combined with the CS may result in longer lasting adverse effects than CS preparations without the solvent.

2.3. Developmental and Reproductive Toxicity

The National Teratology Information Service collected outcome data on 30 pregnant women who were exposed to CS gas: 12 women during the first

trimester, 11 during the second trimester, and seven during the third trimester (McElhatton et al. 2004). Acute maternal toxicity (transient symptoms of ear, nasal, and throat irritation) was reported by 50, 82, and 57% of the exposed women, respectively. Pregnancy outcome was not adversely affected by exposure to CS. Birth weight was within the normal range except for one female baby weighing less than 2,500 g. One infant had a congenital anomaly (hypospadia), and this anomaly has a background incidence of 1 in 1,000 live born male infants. No concentration or duration exposure parameters were described.

2.4. Genotoxicity

No data on the genotoxicity of CS in humans were found.

2.5. Summary

CS is a potent irritant, with symptoms of exposure including lacrimation, blepharospasm, erythema of the eyelids, chest tightness, coughing, nasal irritation and discharge, salivation, throat irritation, nausea, vomiting (from swallowing excess saliva), and cutaneous irritation (ranging from stinging to contact irritation or allergic dermatitis). Upshall (1973) reported that an aerosol concentration of CS at 4 mg/m^3 will disperse the majority of rioters within 1 min, and 10 mg/m^3 will deter trained troops. With the exception of more severe cutaneous reactions, recovery from exposure is generally rapid upon exposure to fresh air, generally within 30 min after exposure (Ballantyne 1977).

Data on human tolerance to CS are summarized in Table 7-7. Many studies investigated the amount of time that elapsed before subjects could no longer remain in an atmosphere containing CS. Gutentag et al. (1960) and Punte et al. (1963) reported tolerances of 5 sec at 442 mg/m^3, 12-25 sec at 141 mg/m^3, 9 sec at 39 mg/m^3, and more than 90 min at 1.5 mg/m^3. Tolerance to low concentrations of CS could be increased when exposure concentration was increased over time (Punte et al. 1963; Beswick et al. 1972). A study investigating the differences in respiratory and ocular responses to different particles sizes of CS found that small particles are more effective than larger particles in producing ocular and respiratory irritation. Recovery time for ocular irritation took longer for large particles, because the onset of irritation was delayed due to the lower solubility of large particles. Recovery time for respiratory irritation took longer for small particles, because the smaller sized particles penetrated further into the respiratory tract (Owens and Punte 1963).

Pregnancy outcomes were not affected in a prospective case study of 30 pregnant women who were exposed to CS gas and experienced transient symptoms of ear, nasal, and throat irritation (McElhatton et al. 2004). No other reproductive or developmental toxicity data of CS in humans were available. No human data on the toxicity of repeated exposures to CS or on the genotoxicity or carcinogenicity of CS were found.

TABLE 7-7 Summary of Selected Human Toxicity Data on Tear Gas

Concentration (mg/m^3)	Tolerance Duration[a]	Notes	Reference
94[b]	<60 sec	6 subjects chosen for ability to tolerate CS.	Owens and Punte 1963
85[c]	<60 sec		
5	53 to ≥120 sec	Untrained subjects; maximum exposure duration of 2 min.	Punte et al. 1963;
12	19-43 sec		Gutentag et al. 1960
442	5 sec		
4	37 to ≥120 sec	Trained subjects (previous exposure to CS); maximum exposure	Punte et al. 1963;
10	18-41 sec	duration of 2 min.	Gutentag et al. 1960
141	12-25 sec		
10	13 sec	Untrained subjects; exercised before exposure.	Punte et al. 1963;
13	13 sec		Gutentag et al. 1960
39	9 sec		
0.4	135-600 sec[d]	4/7 tolerated 10 min.	Rengstorff 1969
0.6	30-600 sec[d]	7/17 tolerated 10 min.	
0.9	600 sec[d]	6/6 tolerated 10 min.	
1	35-50 sec		
6 (attained over 10 min)	18 min	1 subject	Punte et al. 1963
	20 min	1 subject	
	29 min	1 subject	
0.75 (average)[e]	60 min[f]	5 subjects; all remained in chamber for duration of exposure; ocular, nasal, mouth, and throat irritation, nausea, chest discomfort, headache, and stinging of the face.	Beswick et al. 1972
0.56-0.86	8 min	9 subjects; concentration increased during exposure;	
0.31-0.74	60 min[f]	1 subject in 0.31–0.74-mg/m^3 group left after 8 min because of irritation; 8 subjects tolerated 60-min exposure with same signs as 0.75-mg/m^3 group.	

0.8-1.4	60 min[f]	5 subjects; all tolerated exposure with same signs as 0.75-mg/m^3 group.	
0.84-2.3 0.7-2.0 0.63-2.3 0.57-2.1 0.42-1.8 0.45-1.7	60 min[f]	16 subjects; 1 subject vomited after 5 min, left chamber but returned for duration of exposure; 1 subject vomited after 55 min; 14 subjects tolerated 60-min exposure with same signs as 0.75-mg/m^3 group.	
1.5	90 min[g]	4 subjects; 1 developed nasal irritation (at 2 min); 3 developed headache (at 45, 50, and 83 min); 4 had ocular irritation (at 20, 24, 70, and 75 min)	Punte et al. 1963

[a]Time at which the subject could no longer tolerate exposure.
[b]Mass median diameter of 0.9 microns.
[c]Mass median diameter of 60 microns.
[d]Exposure was for a maximum of 10 min.
[e]Average concentration calculated using the six interval concentrations.
[f]Exposure was for a maximum of 60 min.
[g]Exposure was for a maximum of 90 min.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Monkeys

Groups of eight immature male and female *Macaca mulatta* monkeys (3-4 kg) were exposed to a cloud of CS dispersed via an M7A3 CS grenade in a 20,000-L chamber at an average CS concentration of 900 mg/m^3 for 3 min, 1,700 mg/m^3 for 5 min, 2,850 mg/m^3 for 10 min, or 2,500 mg/m^3 for 32 min (Striker et al. 1967). The report stated that the cloud was sampled and measured at various times, but details were not provided. A group of eight monkeys served as controls; they were treated similarly to the exposed monkeys except they were not put into an exposure chamber. Monkeys were observed frequently for clinical signs during the first 72 h after exposure. Chest radiographs were taken before exposure and after 2, 6, or 12 h or 1, 3, 7, or 30 days post-exposure. Monkeys were killed after 12 h or after 3, 7, or 30 days. Clinical signs in monkeys exposed to CS at 900 mg/m^3 for 3 min or at 1,700 mg/m^3 for 5 min included blinking and a "fright reaction" observed immediately after removal from the exposure chamber, which disappeared within a few minutes after the monkeys were moved to fresh air. Monkeys exposed at 2,850 mg/m^3 for 10 min exhibited frequent blinking, labored respiration, coughing, oral and nasal discharge, occasional vomiting, and decreased activity and response to external stimuli. One monkey also had copious ocular discharge. Clinical signs were most severe at 12 h and were generally resolved within 72 h. Clinical signs in monkeys exposed to CS at 2,500 mg/m^3 for 30 min were severe and included prostration, dyspnea, copious oral and nasal discharge, and scleral congestion after removal from the exposure chamber. Five monkeys died; four died 3-12 h after exposure and one died on day 4. Dyspnea was most severe at 12 h, while oral and nasal discharge and effects on the eyes were most severe at 24 h. Radiographic findings were present only in this group; infiltrates appeared 3 h after exposure, were most severe after 24 h, and cleared after 3 days.

Pathologic examination of the monkeys 12 h after exposure to CS at 900 or 1,700 mg/m^3 revealed mild pulmonary congestion, bronchorrhea, emphysema, and atelectasis (Striker et al. 1967). These effects disappeared in the monkeys examined on day 3, but recurred in monkeys examined on days 7 and 30. Pathologic lesions were more severe and developed earlier in monkeys exposed at 2,850 mg/m^3 for 10 min. Pulmonary edema and congestion and bronchorrhea were found at 12 h, and progressed to purulent bronchitis and bronchopneumonia at day 3. After 1 week, acute pleuritis and interstitial pneumonitis were seen, and mucosal lesions and bronchopneumonia were resolving. Lesions were still present after 4 weeks, and included emphysema, atelectasis, and focal interstitial pneumonitis. Pathologic findings in monkeys that died after exposed to CS at 2,500 mg/m^3 for 30 min included severe pulmonary edema and congestion. The three surviving monkeys were killed on days 3, 7, or 30. The monkey killed on

day 3 days had considerable edema, but congestion was less prominent. Examination of the monkey killed on day 7 revealed emphysema involving all lobes and bronchiolitis, but most of the edema had cleared. The monkey killed on day 30 had small shrunken lungs, purulent mucoid material filling many small bronchioles, and distinct bronchiolitis.

McNamara et al. (1969) exposed groups of four monkeys (strain and sex not specified) to seven different CS concentration-duration combinations. No further experimental details were available. Mortality data from this study are summarized in Table 7-8.

3.1.2. Rats

Groups of 10 rats were exposed to an aerosol of CS for 25-90 min (Punte et al. 1962). Animals were exposed in a dynamic inhalation chamber containing individual cages on racks. Aerosol was generated by passing dry nitrogen through an aspirator. Molten CS was maintained in a side-armed flask in an oil bath at 140-150°C. The aerosol was easily generated and liquid droplets recrystalized before entering the exposure chamber. Chamber concentrations were measured by drawing chamber air through filter paper for subsequent analysis by spectrophotometry. Samples for particle-size determinations were collected by a Cascade impactor, and MMD was derived by use of stage calibrations based on the density of the compound; the particle size was about 1.5 microns (MMD). Observations for clinical signs were made during and after exposure. Surviving animals were maintained for 14 days, and then killed and examined histopathologically. Immediately after exposure began, the animals became excitable and hyperactive, and lacrimation and salivation occurred within 30 sec. Lethargy and dyspnea occurred after approximately 5-15 min. Dyspnea persisted for approximately an hour after exposure ceased, and all other signs subsided about 5 min after the rats were removed from the chamber. Histopathologic examinations revealed an increase in the number of Goblet cells in the respiratory tract and conjunctiva, necrosis in the respiratory and gastrointestinal tracts only if particles had impacted the surface, and an occasional animal with pulmonary edema and hemorrhage in the adrenal glands. The calculated LCT_{50} was 32,500 mg-min/m^3.

An unpublished report by McNamara et al. (1969) appears to provide data additional to those that were published by Punte et al. (1962). Specific study details are not provided in the unpublished report, but one set of study results is consistent with those published by Punte et al. (1962). The report includes the mortality results from tests with additional animal species exposed by inhalation to CS, as well as mortality data for CS dispersed by different methods. As discussed above, Punte et al. (1962) reported mortality data for rats, but the values were reported only in terms of mg-min/m^3. Specific concentrations of CS (sprayed as molten agent) with corresponding exposure durations for these data are reported in the unpublished study by McNamara et al. (1969) and are presented in Table 7-8.

TABLE 7-8 Mortality Data from Studies by McNamara et al. (1969) in Different Species Exposed to Tear Gas

Species	Concentration (mg/m^3)	Duration (min)	Mortality	Time to Death (days)[a]
Rats[b]	560	25	1/10	1(1)
	543	35	2/10	1(2)
	489	45	3/10	2(1), 3(1), 4(1)
	454	55	5/10	1(3), 3(2)
	500	60	2/10	1(2)
	500	80	6/10	1(1), 2(2), 6(3)
	500	90	8/10	1(1), 3(2), 7(2), 11(3)
Mice[b]	1,200	10	0/20	–
	1,100	20	7/20	7(1), 8(3), 9(3)
	900	30	2/20	7(2)
	800	40	5/20	5(2), 9(3)
	740	50	5/20	5(1), 6(3), 7(1)
	683	60	14/20	5(4), 8(5), 9(4), 13(1)
Guinea pigs[b]	400	5	1/10	7(1)
	400	10	2/10	7(1), 8(1)
	400	15	4/10	1(2), 6(2)
	500	20	3/10	1(1), 6(1), 7(1)
	400	25	7/10	2(5), 7(1), 8(1)
	400	30	7/10	1(4), 5(1). 7(1), 9(1)
	425	40	8/10	1(7), 3(1)
Rabbits[b]	500	30	1/4	6(1)
	250	40	0/4	–
	267	45	0/4	–
	250	80	3/4	1(1), 2(1), 7(1)
	333	90	4/4	1(1), 2(1), 3(1), 8(1)
Dogs[c]	833	20	0/4	–
	649	30	1/4	12(1)
	508	36	2/4	5(1), 10(1)
	899	40	2/4	1(1), 2(1)
	520	45	2/4	1(1), 4(1)
	612	45	2/4	1(2)
	797	60	3/4	1(2), 3(1)
	909	60	2/4	1(2)
Monkeys[c]	469	24	1/4	5(1)
	673	30	2/4	1(2)
	381	45	2/4	1(2)
	612	45	1/4	1(1)
	699	60	1/4	1(1)
	941	60	3/4	1(3)
	1,057	60	2/4	1(2)

[a]Number in parenthesis indicates number of deaths on that day.
[b]Source of CS was the same for rats, mice, guinea pigs, and rabbits.
[c]Source of CS was the same for dogs and monkeys, except CS used in the monkey studies had a mass-median diameter of 2.0-3.2 microns (ultraviolet analysis was conducted at 260 nanometers).
Source: Adapted from McNamara et al. 1969.

Groups of 18 male albino SPF rats were exposed to pyrotechnically-generated CS smoke in a 10-m^3 chamber (Colgrave and Creasey 1975). The rats were exposed to at 5,871 ± 476 mg/m^3 for 15 min, at 6,030 ± 590 mg/m^3 for 10 min, or at 6,800 ± 1,166 mg/m^3 for 5 min (averages and standard deviations were calculated on the basis of the values reported by the investigators as 6,000, 6,000, and 6,400 mg/m^3, respectively). CS was released from four CS cartridges, each containing CS (12.5 g), potassium chlorate (16 g), lactose (15 g), and kaolin (7.5 g). The cloud of CS in the exposure chamber was sampled at approximately 1-min intervals for the 10- and 15-min exposures and at 30-sec intervals during the 5-min exposure. The analytic method used to measure CS concentrations was not described. Survivors were killed at times ranging from 15 min to 2 days post-exposure. All animals were necropsied, and selected tissues were analyzed by both light and electron microscopy. Nonexposed controls were used to establish the typical macroscopic and microscopic appearance of the tissues of the particular strain used. Mortality occurred in four rats exposed at 5,871 mg/m^3 for 15 min (death occurred with 24 h), and in two rats exposed at 6,030 mg/m^3 for 10 min (death occurred within 24 or 36 h). All animals exposed at 6,800 mg/m^3 survived until the study terminated after 2 days. Animals that died after exposure to CS for 15 min developed marked pulmonary congestion with scattered alveolar hemorrhages and patchy edema. Survivors developed less marked pulmonary congestion and only occasional areas of edema and hemorrhaging. Rats that died after exposure to CS for 10 min also developed pulmonary congestion, but the severity was much less than that seen with the 15-min exposures. Hemorrhages and edema were occasionally seen in the lungs of survivors. Examination of rats exposed to CS for 5 min revealed mild pulmonary congestion with occasional hemorrhage up to 6 h post-exposure. Rats killed between 12 h and 2 days post-exposure had no pulmonary findings except for one rat with moderate and extensive pulmonary congestion. Electron microscopic examination of the lungs from all exposed rats revealed changes in the epithelium and interstitium, with accumulation of fluid between the membrane layers and collagen-containing areas of the septum. Degenerative changes of the epithelium and endothelium led to rupture or dissolution of the capillary wall. The investigators stated that the changes were similar in all exposed rats, with the changes varying only in the degree of severity. Damage was evident as early as 15 min after exposure, and became more severe after 30 and 60 min.

Ballantyne and Callaway (1972) exposed groups of male and female Wistar-derived SPF rats to pyrotechnically-generated CS smoke at concentrations of 750 mg/m^3 for 30 min, 480 mg/m^3 for 1 h, or 150 mg/m^3 for 2 h in a 10-m^3 exposure chamber. A group of control animals was also maintained, but no description of the treatment of the controls was provided to determine whether they were exposed under similar conditions to clean air. The grenades used for the exposure contained CS (2 g), potassium chlorate (2.4 g), lactose (2.4 g), and kaolin (1.2 g). Although the report stated that the concentration of CS in the exposure chamber was sampled at the start of the exposure and at 6-min intervals up to and including 57 min, no information was provided about the analytic

technique. Groups of animals were killed after 1, 10, and 28 or 29 days. Some of the animals exposed at 480 or 150 mg/m^3 were retained for up to 32 months to evaluate potential lasting toxicity and pathology (Marrs et al. 1983a). Animals that died or were moribund after 1 month and those killed after 32 months were subjected to gross necropsy, and the heart, lungs, small intestine, liver, pancreas, spleen, kidneys, brain, gonads, and pituitary and adrenal glands were removed and processed for histologic examination.

All animals exposed for 30 min at 750 mg/m^3 survived to the scheduled necropsy, and histopathologic changes were found only on post-exposure day 1 (see Table 7-9). One rat had congestion of alveolar capillaries and a few scattered alveolar hemorrhages, while another rat had a few minute foci of renal tubular necrosis at the inner cortex. No pathologic changes were found in rats at post-exposure day 10 or 28. Exposure to CS at 480 mg/m^3 for 1 h resulted in the mortality of some rats (see Table 7-9), with the majority of the deaths occurring on post-exposure days 1 and 2. Pathologic changes in animals surviving exposure at 480 mg/m^3 were generally confined to post-exposure day 1; lesions were limited to minimal pulmonary congestion and hepatic congestion in one rat, minimal pulmonary hemorrhage and hepatic necrosis in another rat, and mild pulmonary congestion in a third rat. Two rats had mild pulmonary edema. A few rats killed after 10 days had healed lesions, as evidenced by binucleate liver cells around centrilobular veins and immature epithelium in some renal tubules. No abnormal pathologic changes were noted at day 29. Histopathologic findings in rats that died were much more severe and included renal changes (mild-to-moderate necrosis of the cortex, moderate-to-severe necrosis of the medulla, and some mild congestion), pulmonary changes (mild-to-severe congestion, mild hemorrhage, and some mild edema), and hepatic changes (glycogen depletion in all rats and a few cases of mild congestion and mild-to-moderate necrosis).

Exposure to CS at 150 mg/m^3 for 2 h resulted in no mortality. Pathologic examination of the animals revealed lesions only on day 1 post-exposure. Lesions were confined to female animals; one rat had a few scattered alveolar hemorrhages, one had acute mucoid enteritis, and one had pneumonic consolidation of the upper right lung lobe.

Exposure to CS at 480 mg/m^3 for 1 h or at 150 mg/m^3 for 2 h did not affect the lifespan of rats, and no statistically significant increases were found in non-neoplastic lesions in the exposed groups compared with controls (Marrs et al. 1983a). Common non-neoplastic lesions in male and female rats included changes in the lungs (engorgement, congestion, inflammatory changes, and pulmonary edema) and pyelonephritis of the kidneys. Liver congestion was also a common finding. No exposure-related neoplastic lesions were evident in male rats. Female rats in the 150-mg/m^3 group exhibited an increased incidence of pituitary tumors; incidence was 26% in the control group, 29% in the group exposed to CS at 480 mg/m^3 for 1 h, and 47% in the group exposed at 150 mg/m^3 for 2 h. The increases were not statistically significant.

TABLE 7-9 Summary of Acute Toxicity Data from Studies by Ballantyne and Callaway (1972) in Hamsters and Mice Exposed to Tear Gas

						Day 1		Day 10		Day 25 or 29	
						No. killed	No. w/ lesions	No. killed	No. w/ lesions	No. killed	No. w/ lesions
750	30	Hamster	Male	24	0	8	3	8	0	8	0
		Rat	Male	24	0	8	2	8	0	8	0
480	60	Hamster	Male	47	16 (34%)	8	4	2	0	9	0
			Female	59	15 (25%)	7	6	3	0	8	0
		Rat	Male	60	6 (10%)	6	2	2	0	8	0
			Female	60	3 (3%)	7	1	2	0	8	0
150	120	Hamster	Male	58	2 (3%)	8	0	6	0	6	0
			Female	62	0	8	3	10	0	8	0
		Rat	Male	60	0	8	0	8	0	8	0
			Female	60	0	8	2	8	1	8	0

Source: Adapted from Ballantyne and Callaway 1972.

In another experiment, Ballantyne and Callaway (1972) exposed groups of 10 rats for 5 to 20 min to CS at an approximate concentration of 4,000 mg/m^3, followed by a 14-day observation period. An anti-riot grenade containing approximately 50 g of CS was ignited in a 10-m^3 static chamber and allowed to burn to completion. All animals that died and the survivors killed at the end of the 14-day observation period were subjected to gross and histologic examinations. Clinical signs during exposure could not be recorded because the aerosol generated in the chamber resulted in a complete lack of visibility. Upon removal from the chamber, animals exhibited signs of increased buccal and nasal secretions and dyspnea, particularly at the longer exposure durations. Mortality data are summarized in Table 7-10. No animals died during exposure. Necropsy revealed pulmonary edema and congestion, often with multiple, variable sized areas of hemorrhage, and mucus in the trachea and major bronchi. Histopathologic examination of these animals revealed severe congestion of the alveolar capillaries and intrapulmonary veins and alveolar hemorrhage. Mucus was seen in some bronchi and bronchioles, and occasional areas of collapse and hemorrhage were seen distal to a completely occluded bronchiole. Moderate-to-marked pulmonary edema was also observed in several animals. No evidence of acute inflammatory cell infiltrate was observed in any of the lungs examined, suggesting that the CS aerosol produced direct injury to the pulmonary capillary endothelium. Circulatory failure evidenced as congestion of the liver, kidneys, and spleen and dilation of the right ventricle was present in most of the animals that died. Animals that survived to day 14 days did not have any residual pathologic changes at necropsy.

Groups of 20 or 21 male Porton-Wistar rats were exposed by whole body inhalation to various concentrations of CS aerosol for 10-60 min (see Table 7-11) (Ballantyne and Swanston 1978). Animals were exposed in a 1-m^3 dynamic flow chamber. The aerosol was generated by filling a Collision spray with molten CS (heated to 150°C) and passing pure nitrogen into the air stream. The resultant aerosol was fed into the diluting air stream. The chamber atmosphere was sampled for 1 min at 5-min intervals by aspirating air through glass fiber discs held in double cone filters. A bubbler containing hydrochloric acid in ethanol was connected in line to the glass filter to act as an additional trap. The contents of the bubbler were used to elute CS from the filter discs, and the concentration of CS in the resultant extract was measured by absorption spectrophotometry and compared with a prepared standard. Signs of toxicity included increased nasal and buccal secretions and increased rates of respiration when removed from the chamber; effects disappeared within approximately 1 h post-exposure. No animals died during exposure; deaths generally occurred within the first 2 days following exposure. A summary of mortality data is presented in Table 7-11. Necropsy findings in animals dying within 48 h included pulmonary congestion and edema (with some animals also having multiple variable sized hemorrhages) and congestion of the trachea. Moderate amounts of mucus were also seen in the trachea. Histopathologic examination of the lungs from these animals revealed moderate-to-marked congestion, inter- and intra-alveolar hem-

orrhaging, and excess secretions in the bronchioles and intrapulmonary bronchi. Examination of animals dying after 48 h revealed similar findings, as well as evidence of early bronchopneumonia. Congestion of the liver, kidneys, spleen, and small intestines were also frequently seen in animals dying from exposure. No abnormal findings were found in animals surviving the 14-day observation period.

3.1.3. Mice

Groups of 20 mice were exposed to an aerosol of CS for 10-60 min (Punte et al. 1962). Experimental procedures, clinical signs, and necropsy results are similar to those described for the corresponding study in rats (see Section 3.1.2). The calculated LCT_{50} was 43,500 mg-min/m^3. An unpublished report by McNamara et al. (1969) appears to provide data additional to those that were published in this study. Specific study details are not provided in the unpublished report, but one set of study results is consistent with those published by Punte et al. (1962). The report includes the mortality results from tests with additional animal species exposed by inhalation to CS, as well as mortality data for CS dispersed by different methods. Punte et al. (1962) reported mortality data for mice, but the values were reported only in terms of mg-min/m^3. Specific concentrations of CS (sprayed as molten agent) with corresponding exposure durations for these data are reported in the unpublished study by McNamara et al. (1969) and are presented in Table 7-8.

Ballantyne and Callaway (1972) exposed groups of 10 mice for 5-20 min to CS at an approximate concentration of 4,000 mg/m^3, followed by a 14-day observation period. The experimental protocol, clinical signs, and necropsy findings were similar to those described in the corresponding study in rats (see Section 3.1.2). Mortality data are summarized in Table 7-10.

TABLE 7-10 Summary of Mortality Data from Studies by Ballantyne and Callaway (1972) in Different Species Exposed to Tear Gas

	Exposure Duration	Mortality (No. died/No. exposed)			
Concentration (mg/m^3)	(min)	Rat	Mouse	Guinea Pig	Rabbit
3,950	5	0/10	1/10	1/5	0/5
4,760	5	0/10	0/10	0/5	0/5
4,250	10	1/10	0/10	5/5	0/5
4,330	10	1/10	4/10	3/5	2/5
4,150	15	0/10	3/10	3/5	2/5
5,167	15	7/10	3/10	5/5	2/5
4,000	20	9/10	8/10	5/5	4/5
4,300	20	8/10	6/10	5/5	5/5

Source: Adapted from Ballantyne and Callaway 1972.

TABLE 7-11 Summary of Mortality Data from Studies by Ballantyne and Swanston (1978) in Different Species Exposed to Tear Gas

Species	Average Concentration (mg/m^3)	Duration (min)	Mortality (No died/No. exposed)	Mortality (%)	LCT_{50} ($mg\text{-}min/m^3 \pm 95\%$ CI)
Rat (male)	1,802	10	0/20	0	88,480 (77,370-98,520)
	1,806	45	8/20	40	
	1,911	45	9/20	45	
	2,629	60	20/21	95	
	2,699	60	20/20	100	
Mouse (male)	1,432	15	1/40	3	
	2,753	20	17/40	43	50,010 (42,750-60,220)
	2,333	30	10/19	53	
	2,400	30	17/40	43	
	2,550	30	24/36	67	
Guinea pig (female)	2,326	10	2/20	10	67,200 (59,200-78,420)
	2,380	15	2/10	20	
	1,685	25	10/20	50	
	2,310	20	8/20	40	
	1,649	30	11/20	55	
	1,302	45	9/11	82	
	2,041	30	13/20	65	
	2,373	30	10/19	53	

Rabbit (female)	846	5	0/10	0	54,090 (42,630-70,400)
	836	10	0/10	0	
	1,434	10	0/10	0	
	1,802	10	1/5	20	
	2,188	15	2/10	20	
	2,380	15	3/8	38	
	1,407	30	4/10	40	
	1,653	30	2/10	20	
	1,309	45	4/5	80	
	2,118	45	9/10	90	
	2,133	60	7/8	88	
	3,066	60	8/9	89	

Source: Adapted from Ballantyne and Swanston 1978.

Groups of 19-40 male albino mice were exposed by whole body inhalation to various concentrations of CS aerosol for 15-30 min (see Table 7-11) (Ballantyne and Swanston 1978). The experimental protocol, clinical signs, and necropsy findings were similar to those described in the corresponding study in rats (see Section 3.1.2). Mortality data are summarized in Table 7-11.

3.1.4. Guinea Pigs

Groups of ten guinea pigs were exposed to an aerosol of CS for exposure durations of 5-40 min (Punte et al. 1962). Experimental procedures, clinical signs, and necropsy results are similar to those described for rats in Section 3.1. 2. The calculated LCT_{50} is 8,300 mg min/m^3. An unpublished report by McNamara et al. (1969) appears to provide data additional to those that have been published. Specific study details are not provided in this report, but one set of study results is consistent with those published by Punte et al. (1962). The report includes the mortality results of additional animal species exposed by inhalation to CS, as well as mortality data for CS dispersed by various methods. As described above, Punte et al. (1962) reported mortality data for guinea pigs, but the values were reported only in terms of mg min/m^3. Specific concentrations of CS (sprayed as molten agent) with corresponding exposure durations for these data are reported in McNamara et al. (1969) and are presented in Table 7-8.

Ballantyne and Callaway (1972) exposed groups of five guinea pigs for 5 to 20 min to an approximate CS concentration of 4,000 mg/m^3, followed by a 14-day observation period. The experimental protocol, clinical signs, and necropsy findings are similar to those described in the rat study (see Section 3.1.2). Mortality data are summarized in Table 7-10.

Groups of ten to twenty female Dunkin Hartley guinea pigs were exposed by whole body inhalation to various concentrations of CS aerosol for durations of 10 to 45 min (see Table 7-11) (Ballantyne and Swanston 1978). Experimental protocol, clinical signs, and necropsy findings are as described for the rat study in Section 3.1.2. Mortality data are summarized in Table 7-11.

3.1.5. Rabbits

Groups of four rabbits were exposed to an aerosol of CS for exposure durations of 30-90 min (Punte et al. 1962). Experimental procedures, clinical signs, and necropsy results are similar to those described for rats in Section 3.1.2, except that hyperactivity, salivation, and lachrymation were not reported. The calculated LCT_{50} is 17,000 mg min/m^3. An unpublished report by McNamara et al. (1969) appears to provide data additional to those that have been published. Specific study details are not provided in this report, but one set of study results is consistent with those published by Punte et al. (1962). The report includes the mortality results of additional animal species exposed by inhalation to CS, as well as mortality data for CS dispersed by various methods. As described above,

Punte et al. (1962) reported mortality data for guinea pigs, but the values were reported only in terms of mg min/m^3. Specific concentrations of CS (sprayed as molten agent) with corresponding exposure durations for these data are reported in McNamara et al. (1969) and are presented in Table 7-8.

Ballantyne and Callaway (1972) exposed groups of five rabbits for 5 to 20 min to an approximate CS concentration of 4,000 mg/m^3, followed by a 14-day observation period. The experimental protocol, clinical signs, and necropsy findings are similar to those described in the rat study (see Section 3.1.2). Mortality data are summarized in Table 7-10.

Groups of five to ten female New Zealand white rabbits were exposed by whole body inhalation to various concentrations of CS aerosol for durations of 5 to 60 min (see Table 7-11) (Ballantyne and Swanston 1978). Experimental protocol, clinical signs, and necropsy findings are as described for the rat study in Section 3.1.2. Mortality data are summarized in Table 7-11.

3.1.6. Hamsters

Ballantyne and Callaway (1972) exposed groups of male and female golden hamsters to pyrotechnically-generated CS smoke at concentrations of 750 mg/m^3 for 30 min, 480 mg/m^3 for 1 h, or 150 mg/m^3 for 2 h in a 10-m^3 exposure chamber. The experimental protocol is the same as that for the corresponding study in rats (see Section 3.1.2). All animals exposed for 30 min at 750 mg/m^3 survived to the scheduled necropsy, and histopathologic changes were observed only on post-exposure day 1 (see Table 7-11). Three hamsters had a few scattered alveolar hemorrhages, and one also had congestion of the alveolar capillaries. No pathologic changes were found at post-exposure day 10 or 28. Exposure at 480 mg/m^3 for 1 h killed some hamsters (see Table 7-11); the majority of the death occurred after 1-2 days. Pathologic changes in animals surviving exposure at 480 mg/m^3 were generally found only on post-exposure day 1. Eight hamsters had mild pulmonary congestion, and four of them also had mild pulmonary hemorrhage. One hamster with no lung lesions had mild renal congestion and necrosis in the medulla, and another had mild necrosis in the medulla. A few hamsters killed after 10 days had healed lesions, as evidenced by binucleate liver cells around centrilobular veins and immature epithelium in some renal tubules. No abnormal pathologic changes were found at day 29. Histopathologic findings in hamsters that died were generally similar to those in rats (see Section 3.1.2); however, the lesions were less severe in hamsters than in rats.

Exposure to CS at 150 mg/m^3 for 2 h resulted in the mortality of two male hamsters (after 12 or 16 days), and necropsy revealed bronchopneumonia. Pathologic examination of surviving animals revealed lesions only on day 1. Lesions were found only in female hamsters; one had a few scattered alveolar hemorrhages and two had a few scattered foci of acute renal tubular necrosis at the inner cortex.

Exposure to CS at 480 mg/m^3 for 1 h or at 150 mg/m^3 for 2 h did not affect the lifespan of the hamsters, and no statistically significant increases in non-neoplastic lesions were found in the exposed groups compared with controls (Marrs et al. 1983a). Common non-neoplastic lesions in male and female hamsters included changes in the lungs (engorgement, congestion, inflammatory changes, and pulmonary edema) and pyelonephritis of the kidneys. No exposure-related neoplastic lesions were evident in male or female hamsters.

3.1.7. Dogs

McNamara et al. (1969) exposed groups of four dogs (strain and sex not specified) to eight different CS concentration-duration combinations. No further experimental details were available. Mortality data are summarized in Table 7-8.

Following a 30-sec exposure to CS at 25 mg/m^3, one dog exhibited increased blood pressure, an altered respiratory pattern, tachycardia, and increased femoral artery blood flow (Cucinell et al. 1971). In another test, two dogs were exposed for 23 min to CS at 2,600 mg/m^3. One dog survived and the other dog died after 52 h. The investigators noted that dogs recover partially when exposed to a lethal dose of CS but then develop respiratory distress and die within 48-70 h.

3.2. Nonlethal Acute Toxicity

3.2.1. Mice

An RD_{50} (concentration that reduces the respiratory rate by 50%) for CS of 4.0 mg/m^3 (95% confidence interval: 3.3-5.2 mg/m^3) was reported for male Swiss-Webster mice (Kane et al. 1979).

3.2.2. Rabbits

To investigate whether CS exposure can cause diarrhea, four rabbits were exposed to thermally-generated pure CS in a 10-m^3 chamber (Ballantyne and Beswick 1972). The exposures involved the following: one rabbit each was exposed at 58 mg/m^3 for 30 min, 46 mg/m^3 for 20 min, 54 mg/m^3 for 12 min, or 17 mg/m^3 for 17 min. Animals were placed singly in cages with removable trays lined with several layers of filter paper arranged to collect stool samples. The number of stool pellets passed, their total weight, and their water content were recorded for several day before and after exposure. Exposure to CS did not result in an increased incidence of diarrhea.

Two rabbits were exposed in a static chamber to the entire contents of a 3-ounce unit containing 71.5 g of CS (Gaskins et al. 1972). The unit required 20 sec to fully dispense. Both rabbits became unconscious after approximately 2 min of exposure and were moved to fresh air. The rabbits regained their righting

reflex approximately 10-20 min after exposure and were almost completely recovered after 1 h (moderate ocular wetness was the only visible effect). Gross necropsy of the rabbits performed after 2 weeks did not reveal any abnormalities. Two other rabbits were exposed to 23.2 g of CS during dispersion of a CS unit requiring about 10 sec to completely discharge. The dispensed CS formed a cloud in the chamber. The rabbits tried to avoid the spray as it was dispensed, and then sat quietly with their eyes tightly closed for the remainder of the 5-min exposure. No abnormalities were observed in the eyes or skin of the rabbits.

3.3. Repeat-Dose Studies

3.3.1. Rats

Groups of five male and five female F344/N rats were exposed to CS2 at concentrations of 0, 1, 3, 10, 30, or 100 mg/m^3 for 6 h/day, 5 days/week for 2 weeks (NTP 1990). (CS2 contains 94% CS, 1% hexamethyldisilizane, and 5% Cab-o-Sil®). All rats exposed at 30 or 100 mg/m^3 died before the end of the study. Rats from all exposure groups exhibited adverse clinical signs, ranging from erythema and blepharospasm at the lower concentrations to dacryorrhea, mouth breathing, listlessness, and mouth breathing at the higher concentrations. Rats in the 1-mg/m^3 group gained more weight over the exposure period than controls, but at concentrations of 3 mg/m^3 and higher body weight was generally decreased.

Groups of 10 male and 10 female F344/N rats were exposed to CS2 at 0, 0.4, 0.75, 1.5, 3, or 6 mg/m^3 for 6 h/day, 5 days/week for 13 weeks (NTP 1990). One male rat exposed at 6 mg/m^3 died, and all others survived to study termination. Clinical signs of ocular irritation (partial or complete eyelid closure) were noted in all exposure groups, and rats exposed at 6 mg/m^3 developed erythema of the extremities that persisted overnight. Rats exposed to CS2 at 1.5 mg/m^3 or higher gained significantly less weight over the study period than controls; final mean body weight was 17-44% lower than that of controls for males and 10-24% lower for females. An approximate 46% reduction in thymus weight relative to body weight was noted in male and female rats exposed at 6 mg/m^3. Concentration-related histopathologic changes included focal erosion with regenerative hyperplasia and squamous metaplasia of the respiratory epithelium. Acute inflammation and hyperplasia of the respiratory epithelium were also found.

One group of 56 male rats was exposed to a mean CS concentration of 1,470 or 1,770 mg/m^3 for 5 min/day for 5 days and another group of 49 male rats was exposed at a mean concentration of 12.5 or 14.8 mg/m^3 for 80 min/day for 9 days to (Ballantyne and Callaway 1972). Exposures to the thermally-generated CS aerosol (MMD of 1-2 micrometers) were conducted in a 1-m^3 chamber, with chamber air sampled continuously throughout exposure at a rate of 1 L/min using a double cone filter. The samples were analyzed for CS content (details not provided). Groups of three to five survivors were killed after 1, 6,

and 24 h and 2, 3, 4, 5, 7, 10, 14, and 21 days, and gross and microscopic examinations were performed. All animals survived the 5-min exposures. Histopathologic examination revealed minimal congestion of the alveolar capillaries after 1 or 6 h in two of five rats and a few scattered alveolar hemorrhages after 2 days in one of four rats. Scattered patches of bronchopneumonia were found in one of five rats after 7 days, in one of three rats after 8 days, one of three rats after 10 days, and two of five rats after 18 days. Pathologic changes in control rats included scattered alveolar hemorrhages in two of 11 rats and subacute mucoid enteritis in one of 11 rats. Death occurred in five of the 49 rats exposed at 12.5 or 14.8 mg/m^3 for 80 min/day; one died after the seventh exposure, two after the eight exposure, and two died 5 days after the final exposure. Necropsy revealed widespread acute bronchopneumonia. Histopathologic examination of the surviving animals revealed lesions for up to 5 days after exposure and not thereafter.

3.3.2. Mice

Groups of five male and five female B6C3F$_1$ mice were exposed to CS2 at concentrations of 0, 1, 3, 10, 30, or 100 mg/m^3 for 6 h/day, 5 days/week for 2 weeks (NTP 1990). All mice exposed at 10 mg/m^3 and greater died before study termination. Mice from all exposure groups exhibited adverse clinical signs, ranging from erythema and blepharospasm at the lower concentrations to dacryorrhea, mouth breathing, listlessness, and mouth breathing at the higher concentrations. Mice exposed at 1 mg/m^3 gained more weight over the exposure period than controls, but generally lost body weight at exposure concentrations of 3 mg/m^3 and higher.

Groups of 10 male and 10 female B6C3F$_1$ mice were exposed to CS2 at 0, 0.4, 0.75, 1.5, 3, or 6 mg/m^3 for 6 h/day, 5 days/week for 13 weeks (NTP 1990). All mice exposed at 6 mg/m^3 died and one male and one female mouse from the 3-mg/m^3 group died during the second week of exposure. Closed or partially-closed eyes during exposure were observed in mice from all exposure groups through week 6, and in mice exposed at 3 mg/m^3 during weeks 12 and 13. Concentration-related decreases in body weight compared with controls were found in all exposure groups; final mean body weights of mice in the 3-mg/m^3 group were 13% lower for males and 9% lower for females. Exposure-related histopathologic changes were observed in mice exposed at 1.5 mg/m^3 and higher, and included focal inflammation and squamous metaplasia (primarily in the nasal turbinates) and inflammation of the vomeronasal organ.

3.3.3. Rats, Mice, Guinea Pigs, and Rabbits

Groups of five to 10 guinea pigs, five rabbits, 10 rats, and 10-20 mice were exposed to CS at approximate concentrations of 30-40 mg/m^3 for 5 h/day for 1-7 successive days (Ballantyne and Callaway 1972). An anti-riot grenade

containing 0.5 to 0.75 g of CS was ignited every 30 min in a 10-m^3 static chamber to maintain the nominal concentration. The investigators stated that concentrations were determined by continuous sampling throughout the exposure, but no details were provided. Animals were removed to fresh air following each exposure, and were maintained for a 14-day post-exposure period. All animals that died and the survivors killed at the end of the study were given gross and histologic examinations. A summary of the mortality data is presented in Table 7-12. The description of clinical signs was limited to a statement that rabbits and rats exhibited more rhinorrhea and lacrimation than did mice, whereas guinea pigs showed few clinical signs apart from occasional sneezing during the first hour of exposure. Necropsy of animals that died revealed moderate-to-marked congestion of the alveolar capillaries and intrapulmonary veins and inter- and intra-alveolar areas of hemorrhage; many of the animals that died also had congestion of the liver, kidneys, and small intestine. Moderate pulmonary edema was noted in a "few of the animals." No residual pathologic changes were found in animals that survived until the end of the study.

3.4. Developmental and Reproductive Toxicity

Groups of 22-24 pregnant Porton strain rats or 12 pregnant New Zealand white rabbits were exposed to CS aerosol for 5 min/day on gestation days 6-15 or 6-18, respectively (Upshall 1973). CS The aerosol had a particle size of 1-2 micrometers and was generated by melting pure crystalline CS at 120°C using a Collison spray. A preliminary study investigated exposure to CS at 0 or 20 mg/m^3, and was followed by a concentration-response study that evaluated CS at concentrations of 0, 6, 20, or 60 mg/m^3. Control rats were recaged and moved out of their normal environment during the test-group exposure, and control rabbits were exposed to a siliconized silica aerosol at 60 mg/m^3. Additional control groups of pregnant rats were exposed to a particulate aerosol (60 mg/m^3 of Neosil) or to water aerosol to evaluate the stress of aerosol exposure. Rats were killed on gestation day 21 and rabbits on gestation day 30. Cesarean sections were performed, and the fetuses were evaluated for skeletal or visceral abnormalities. In addition, the lungs, liver, kidneys, and adrenal glands from the rabbit dams in the concentration-response study were evaluated histologically. No definitive effects of treatment were noted. In the preliminary rat study, exposed animals exhibited a decrease in maternal weight gain compared with controls (-23%), but a clear concentration-response relationship was not observed in the main study (-23, -12, and 15% for the 6, 20, or 60 mg/m^3 groups, respectively). Fetal weight appeared to decrease with increasing concentration in the main rat study (3.3, 3.2, and 3.1 g, respectively, vs. 3.5 for controls), but the fetal weights were comparable those in other studies. No other statistically significant effects were observed. No exposure-related effects were found in exposed rabbits or their offspring. Although the exposure concentrations were sufficient to cause extreme irritation, clinical signs in exposed rats and rabbits were not reported.

TABLE 7-12 Summary of Mortality Data in Different Species Exposed to Tear Gas for 5 Hours per Day for Up to 7 Days

Species	Duration		Concentration (mg/m^3)	Mortality (No. died/No. exposed)
	Hours/Day	No. Days		
Guinea pig	5	1	44.7	0/5
		3	36.0	2/5
		4	34.2	3/10
		6	35.2	2/5
		7	43.7	10/10
Rabbit	5	3	36.0	1/5
		5	34.2	2/5
Rat	5	1	37.0	1/10
		3	36.0	9/10
		5	34.2	7/10
Mouse	5	1	40.0	0/10
		2	38.8	0/10
		3	36.0	1/10
		4	31.9	10/10
		5	56.4	16/20

Source: Ballantyne and Callaway 1972.

3.5. Genotoxicity

In general, CS was not mutagenic to *Salmonella typhimurium*. Mutations were not induced with or without the presence of S9 at CS concentrations of 12.5-800 µg/plate in strains TA97a, TA98, TA100, TA102, or TA104 (Meshram et al. 1992); of up to 1.5 mg/plate in strains TA98, TA100, TA1535, or TA1537 (Wild et al. 1983); ranging from 10 µg/plate to 2 mg/plate in strains TA98, TA1535, TA1537, or TA1538 (von Däniken et al. 1981); or at CS2 concentrations of 3.3-333 µg/plate in strains TA98, TA100, TA1535, or TA1537 (NTP 1990). Equivocal responses for CS and CS2 were reported in strain TA100 only without S9 (von Däniken et al. 1981; NTP 1990), and for CS2 in strain TA97 but only with 30% S9 (NTP 1990). Cytotoxicity from CS was observed starting at 200 µg/plate, but the presence of 30% S9 generally reduced the cytotoxicity.

Other in vitro genotoxicity testing was generally positive. CS induced sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells both with and without S9 at CS2 concentrations of 6 µg/mL and greater (NTP 1990). Trifluorothymidine resistance in mouse L5178Y lymphoma cells

was induced in the absence of S9 at a CS concentration of 2.5 µg/mL (McGregor et al. 1988; NTP 1990). V79 Chinese hamster cells exposed to CS in culture at 19, 38, or 75 µM for 3 h and evaluated 6 days later showed reduced survival (by about 20, 30, and 80%, respectively; estimated from a graph), and exhibited a concentration-related increase in the frequency of mutants resistant to 6-thioguanine (mutations induced approximately 4- to 5-fold above controls at the highest concentration) (Ziegler-Skylakakis et al. 1989). Exposure to CS also increased the frequency of micronuclei by approximately 2-fold at 19 µM and up to 18-fold at 75 µM (measured 24 h after exposure), but did not induce DNA-repair synthesis as assessed using the BrdUrd density-shift method. A concentration-dependent increase was observed in spindle cell disturbances, particularly C-metaphases (chromosomes completely scattered in cytoplasm and often highly contracted), when cells were exposed to CS at 5, 9, 19, or 38 µM for 3 h (Schmid and Bauchinger 1991). The C-mitotic effect was also reflected in the appearance of a metaphase block and the disappearance of other mitotic figures (prophases and ana-telophases). When a differential staining technique was applied to allow for visualization of the spindle apparatus and chromosomes, a concentration-dependent increase in the number of mitoses with abnormal spindles was again observed, particularly apolar mitoses (mitotic figures without any signs of polar spindle configurations) (Salassidis et al. 1991). Further investigation into the mechanism of CS-induced c-mitotic spindle damage found that exposure of cells to CS at 38 µM for 20 h or 3 h followed by 20 h of recovery resulted in an increase in the number of aneuploid cells and in the polyploid index (Schmid and Bauchinger 1991). The number of aneuploid cells and the polyploid index were increased to a much greater extent by exposure to the metabolite *o*-chlorobenzaldehyde than to CS, suggesting that this metabolite may play a role in the induction of spindle damage. A comparison of the effectiveness of various exposure conditions revealed that cells exposed to CS at concentrations of up to 38 µM for 20 h exhibited a concentration-dependent increase in the number of S-cells and the frequency of chromatid-type aberrations (single breaks, isolocus breaks and exchanges, and gaps). Exposure to CS for 3 h followed by a 20-h recovery period resulted in similar effects but was not as effective. No effects were observed when cells were incubated with the supernatant from the 3 h exposure (Bauchinger and Schmid 1992). The cell cycle time of the V79 cell line is approximately 8-10 h; therefore, the cells had time to run through one or two S-phases.

Genotoxicity testing in vivo was generally negative. CS did not bind to DNA in the liver or kidneys of rats injected intraperitoneally with radiolabeled CS at 13 mg/kg and evaluated 8 or 75 h after dosing, but did bind to nuclear proteins in these organs (von Däniken et al. 1981). CS did not cause an increase in sex-linked recessive mutations in germ cells of male *Drosophila* when administered in the feed at concentrations ranging from 5×10^{-4} M to 2.6×10^{-3} M for 3 days (Wild et al. 1983), and did not increase micronucleated polychromatic erythrocytes in the bone marrow of NMRI mice administered CS by intraperito-

neal injection at 19 or 38 mg/kg or by oral administration at 113 or 226 mg/kg (Wild et al. 1983). The oral dose of 226 mg/kg killed 10 of 13 exposed mice.

3.6. Chronic Toxicity and Carcinogenicity

Groups of 50 male and 50 female $B6C3F_1$ mice and 50 male and 50 female F344/N rats were exposed to CS2 at target concentrations of 0, 0.75, or 1.5 mg/m^3 (mice) or 0, 0.075, 0.25, or 0.75 mg/m^3 (rats) for 6 h/day, 5 days/week for 105 weeks (NTP 1990). Rats exposed at 0.75 mg/m^3 developed histopathologic changes in the respiratory and olfactory epithelium of the nasal passage and inflammation and proliferation of the periosteum of the turbinate bones. No neoplastic effects were present. Lesions seen in the nasal cavity of exposed mice included inflammation in the anterior middle portions of the nasal passage and focal hyperplasia and/or squamous metaplasia of the respiratory epithelium. No other adverse effects were noted. Female mice exhibited a statistically significant, exposure-related reduction in the incidences of hyperplasia and adenomas of the pituitary gland pars distalis (adenoma rates in the 0-, 0.75-, and 1.5-mg/m^3 groups were 16/47, 5/46, and 1/46, respectively). Lymphomas in female mice also occurred with a significant negative trend (21/50, 12/50, and 8/50, respectively).

Groups of 75 male SPF Porton strain mice, 50 male Porton Wistar-derived rats, and 50 Dunkin Hartley guinea pigs were exposed to CS at nominal concentrations of 0, 3, 30, or 300 mg/m^3 (MMD of 3-4 micrometers) for 1 h/day, 5 days/week for up to 55 exposures (11 weeks) in mice and up to 120 exposures (24 weeks) in rats and guinea pigs (Marrs et al. 1983b). Exposure at the high concentration resulted in excessive mortality in mice and guinea pigs within days of exposure; therefore, tests at the high concentration was discontinued after three exposures in mice and after five exposures in rats and guinea pigs (the number of deaths were not provided) (Marrs et al. 1983b). During the first month of the experiment, 17% of the mice and 46% of the guinea pigs in the high-concentration groups died. A significant trend ($p < 0.001$) was found in the incidence of early death in mice with concentration. The investigators also reported a significant trend ($p < 0.001$) in the incidence of early death with concentration in guinea pigs; however, most of the mortality in guinea pigs occurred during the first month. Post-mortem examination of 10 guinea pigs that died during exposure revealed acute alveolitis in seven of the animals, with mild alveolitis present in the other three. The cause of death in mice that died during exposure to CS could not be determined. The investigators reported that toxic signs were not usually observed, and that death occurred suddenly and without warning. No cause of death could be ascribed to animals that died during the observation period. CS exposure did not affect the growth of rats or guinea pigs, but did result in a concentration-related decrease in the growth of mice. No definitive, exposure-related histologic findings were observed in mice, rats, or guinea pigs at the end of the study. No exposure-related neoplasms were found.

3.7. Summary

Clinical signs in the acute and repeated-dose animal studies suggest that CS is highly irritating. The majority of the acute inhalation exposure data in animals focused primarily on lethality, and death was generally caused by pulmonary edema and congestion. Renal damage was also occasionally noted, but may have been secondary to anoxia. Results of genotoxicity tests were mixed. Results in gene mutations tests using *S. typhimurium* were generally negative, as were results of in vivo genotoxicity assays. CS induced trifluorothymidine resistance in mouse L5178/TK lymphoma cells in the absence of S9, and induced both sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells in the presence and absence of S9. No developmental toxicity was found in rats or rabbits, and there was no evidence of carcinogenicity in rats or mice.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

4.1.1. Absorption

One cat with a cannulated trachea was exposed to CS aerosol by an oral-nasal mask to assess absorption of CS by the upper respiratory tract (cannulation prevented access to the lower respiratory tract), while a second cat was exposed via a tracheal tube to assess absorption by the lower respiratory tract (Leadbeater 1973). Blood concentrations of CS and its metabolites after exposure to the upper and lower respiratory tract were about 30 and 80%, respectively, of those measured in intact cats.

4.1.2. Toxicokinetics

The half-lives of CS, 2-chlorobenzylmalonitrile, and 2-chlorobenzaldehyde were measured in cats and rabbits (Leadbeater 1973; Paradowski 1979). The chemicals were administered directly into the femoral artery via a cannula in cats and directly into the ear vein of rabbits. The half-lives of CS, 2-chlorobenzylmalonitrile, and 2-chlorobenzaldehyde in cats were 5.5, 9.5, and 4.5 sec, respectively, and in rabbits they ranged from 19-25, 38-55, and 38-41 sec, respectively. The in vitro half-lives of these chemicals in the blood of cats, humans and rats were also measured. In cat blood, the half-life was 5 sec for CS, 470 sec for 2-chlorobenzylmalonitrile, and 70 sec for 2-chlorobenzaldehyde. The respective half lives in humans were 5, 660, and 15 sec and in rats were 7, 30, and 15 sec (Leadbeater 1973). The in vitro half-life of CS in the blood of rabbits was approximately 60 sec; the investigators postulated that this half-life might be longer than

those of rats, cats, and humans because of the higher concentration of CS tested in rabbits (Paradowski 1979).

CS incubated with rat liver homogenate for 5 min (ethanol-buffer; pH 7.4; 37°C) resulted in a 59% decrease in the initial amount of glutathione, with 26% of the depletion occurring spontaneously (non-enzymatically) (Rietveld et al. 1986). Binding to glutathione in vivo was confirmed by enhanced urinary thioether excretion in rats following intraperitoneal administration of CS (Rietveld et al. 1983, 1986). The thioether was identified as 2-chlorobenzylmercapturic acid.

4.1.3. Metabolism

Metabolism of CS appears to be qualitatively similar in different species. In vivo, CS can be hydrolyzed to 2-chlorobenzaldehyde or malononitrile or can be reduced to 2-chlorobenzyl malononitrile (see Figure 7-1) (Leadbeater 1973; Paradowski 1979). 2-Chlorobenzaldehyde can then be either oxidized to 2-chlorobenzoic acid for subsequent glycine conjugation or reduced to 2-chlorobenzyl alcohol for ultimate excretion as 2-chlorobenzyl acetyl cysteine or 2-chlorobenzyl glucuronic acid. Malononitrile can break down to cyanide, and be excreted as thiocyanate. The reduction of CS to 2-chlorobenzyl malononitrile is a relatively minor pathway; 2-chlorobenzyl malononitrile can be conjugated with glycine or can be hydrolyzed to 2-chlorophenyl 2-cyanoproprionate.

Radiolabeled CS was administered intravenously to rats at 0.08, 0.8, and 80 µmol/kg (^{3}H-ring labeled), 0.8 and 80 µmol/kg (^{14}C-cyanide labeled), or 0.8 and 80 µmol/kg of (^{14}C=C side-chain labeled) (Brewster et al. 1987). Rats were also treated intragastrically with CS at 80, 106, and 159 µmol/kg (^{14}C-cyanide labeled). The major urinary metabolites recovered in rats up to 96 h after intravenous or intragastric administration of CS were 2-chlorohippuric acid (49% of dose), 2-chlorobenzyl glucuronic acid (10%), 2-chlorobenzyl cysteine (8%), and 2-chlorobenzoic acid (8%), and minor metabolites included 2-chlorophenyl acetyl glycine (3%), 2-chlorobenzyl alcohol (1.6%), and 2-chlorophenyl 2-cyano propionate (1.6) (see Figure 7-1).

In another investigation, urinary concentrations of cyanide and thiocyanate were measured over a 24-h period in untreated rats, in rats administered CS intravenously, or in rats exposed to the CS hydrolysis product malononitrile intraperitoneally or intragastrically (Brewster et al. 1987). Following CS and malononitrile administration, urinary cyanide concentrations remained at or below baseline levels, while thiocyanate concentrations generally increased with the CS or malononitrile dose. The percentage molar conversion from CS to thiocyanate was 21.5% at an intraperitoneal dose of 212 µmol/kg and 30% at an intragastric dose of 212 µmol/kg. In tests with malononitrile, the percentage was 60% or more at an intraperitoneal dose of 80 µmol/kg or intragastric dose of 212 µmol/kg.

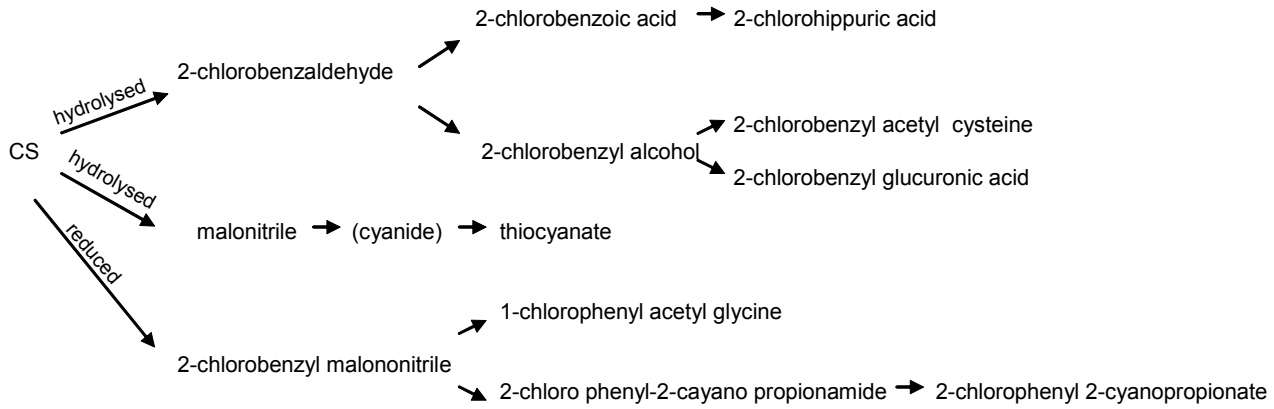

FIGURE 7-1 Predominant metabolic pathways of tear gas in rats proposed by Leadbeater (1973), Paradowsk (1979), and Rietveld et al. (1983).

Metabolism in rabbits is similar to that in rats. The predominant biotransformation pathway in the blood of rabbits administered high doses of CS by intravenous injection (0.5 LD_{50} to the LD_{50}) was hydrolysis of CS to 2-chlorobenzyaldehyde and malononitrile (~30-40%) (Paradowski 1979). A minor pathway involved reduction to 2-chlorobenzyl malononitrile (10%) The investigators indicated that the remaining 50-60% of the administered CS disappeared from the blood by other means; no other explanation was provided. The liver is involved in the metabolism of CS, as demonstrated by an increase in the half-lives of CS and its metabolites in the blood of rabbits when the liver was excluded from the circulation. More of the CS was accounted for after dosing, with approximately 75% of the CS hydrolyzed to 2-chlorobenzyaldehyde and 15% reduced to 2-chlorobenzyl malononitrile. When the kidneys were excluded from the circulation, no changes were observed in CS or metabolites in the blood.

Maximum blood concentrations of CS and its derivatives in cats were attained 30 min after intragastric administration at 40 mg/kg (Leadbeater 1973). After 90 min, blood concentrations of 2-chlorobenzylmalonitrile and 2-chlorobenzaldehyde were still elevated, can CS concentrations had returned to zero. When anesthetized cats were exposed for 60 min via oral-nasal masks to CS aerosol (75 or 750 mg/m^3 of pyrotechnically-generated CS aerosol, 750 mg/m^3 of pure CS aerosol from molten CS, or 62.5 mg/m^3 of CS aerosol generated from an aqueous suspension of micronized CS in acetic acid using a Collison sprayer), concentrations of CS and 2-chlorobenzylmalonitrile rapidly reached steady values, but concentrations of 2-chlorobenzaldehyde continued to increase. Comparison of the blood concentrations resulting from exposure to CS at 750 and 75 mg/m^3 showed that there was not a 10-fold decrease in the concentration of CS and its metabolites 2-chlorobenzylmalonitrile and 2-chlorobenzaldehyde; the concentrations were reduced by 4.5, 7.7, and 5.9, respectively. Exposure of cats to CS at 100 mg/m^3 for 5 min/day for 4 days, followed by exposure to CS at 75 or 750 mg/m^3, resulted in reduced blood concentrations of CS and its derivatives.

Rats receiving a single oral dose of CS at 50-500 mg/kg had lower blood concentrations of CS and its derivatives than cats (Leadbeater 1973). CS was only detected in high-dose group. Blood concentrations of 2-chlorobenzylmalonitrile and 2-chlorobenzaldehyde in rats and cats did not increase in a dose-related manner. Rats exposed by inhalation to CS aerosol at concentrations of 14-245 mg/m^3 for 5 min had measurable amounts of CS and 2-chlorobenzylmalonitrile in their blood immediately after exposure, but 2-chlorobenzaldehyde was detected only in rats exposed at concentrations greater than 100 mg/m^3.

Animal data suggest that CS should be absorbed by the human respiratory tract following inhalation exposure, and that metabolism of CS should proceed via a pathway similar to those found in laboratory animals. However, humans are not able to tolerate concentrations of CS as great as those tolerated by animals. Six healthy human males were exposed by inhalation to CS at 0.5-1.5 mg/m^3 over 90 min, and blood was drawn before and after exposure to measure CS and its derivatives (Leadbeater 1973). Two men left the chamber within 20

min. CS and 2-chlorobenzaldehyde were not detected in the blood of any of the volunteers, and only a trace of 2-chlorobenzylmalonitrile was detected in the blood of one man who remained in the chamber for the entire exposure.

4.1.4. Distribution and Elimination

To evaluate the fate of CS, radiolabeled CS was administered intravenously (^{3}H-ring labeled, ^{14}C-cyanide labeled, or ^{14}C=C side-chain labeled) or intragastrically (^{14}C-cyanide labeled) to rats, and urine, feces, and CO_2 were collected for 96 h (Brewster et al. 1987). The majority of the administered dose was recovered in the urine (44.4 to 100%). Recovery in feces was 1.2-23.4%, and recovery in CO_2 was minimal at 0-2.1%. Comparison of recovery data for the three different radiolabels after intravenous administration showed that more radioactivity was recovered in the feces of rats administered the ^{14}C=C side-chain labeled CS (21-23%) than from rats administered the other two labels (4-8%).

Male mice were administered ^{14}CN-CS by intravenous injection, and were killed at selected intervals to evaluate distribution by autoradiography (Brewster et al. 1987). A significant amount of radioactivity was present in the gastrointestinal tract after 5 min. After 1 h, significant amounts of radioactivity were present in the gastrointestinal tract, urinary bladder, mouth, and esophagus, with lesser amounts in the blood, liver, and salivary glands. At 24 h, most of the residual radioactivity was present in the mouth, salivary glands, gastrointestinal tract, or urinary bladder.

4.2. Mechanism of Toxicity

CS is an SN_2 alkylating agent and, therefore, reacts directly with nucleophilic compounds (Cucinell et al. 1971). Consequently, sulfhydryl-containing enzymes and other biologic compounds are prime targets. Most notably, CS reacts rapidly with the disulfhydryl form of lipoic acid, a coenzyme in the pyruvate decarboxylase pathway. In in vitro studies, CS reacted readily with cysteine, N-acetyl L-cysteine, glutathione, dithiothreitol, and lipoic acid, and had first-order reaction constants of 0.33, 0.42, 0.85, 4.88, and 10.4, respectively. Incubation of rat liver homogenate with CS for 5 min (ethanol-buffer; pH 7.4; 37°C) resulted in a 59% decrease in the initial amount of glutathione, with 26% of the depletion occurring spontaneously (non-enzymatically) (Rietveld et al. 1986). Binding to glutathione in vivo was confirmed by enhanced urinary thioether excretion in rats after intraperitoneal administration of CS; the thioether was identified as 2-chlorobenzylmercapturic acid (Rietveld et al. 1983, 1986). In another study, rats administered CS intraperitoneally at a dose that was 120% of the LD_{50} became moribund approximately 30 min after injection (most likely

due to the relatively slow generation of cyanide from the malononitrile metabolite). The role of cyanide in CS-induced lethality is supported by the observation that administration of thiosulfate intraveneously reduced mortality by 65% compared with control rats (21/32 exposed rats survived vs. 1/11 control rats). Intravenous administration of CS at 8 mg/kg in dogs resulted in a rapid drop in the plasma sulfhydryl concentration, which returned to normal within approximately 3 h (Cucinell et al. 1971).

4.3. Other Relevant Information

4.3.1. Species Variability

CS is a potent acute irritant. Ocular and pulmonary toxicity results from direct contact with CS and its associated alkylating properties; therefore, the mechanism of action is not expected to vary greatly between species. Ballantyne and Swantson (1978) calculated LCT_{50} values of 88,480 mg-min/m^3 for rats, 67,200 mg-min/m^3 for guinea pigs, 54,090 mg-min/m^3 for rabbits, and 50,010 mg-min/m^3 for mice. These values are well within a factor of two of each other.

4.3.2. Susceptible Populations

CS is an irritant and the mechanism of toxicity is a direct contact effect; therefore, the mechanism of action is not expected to vary greatly between individuals. The reactions in people with jaundice, hepatitis, or peptic ulcer or those that were 50-60 years old were similar to those of "normal" volunteers when exposed at highly irritating concentration of CS for short durations (Gutentag et al. 1960; Punte et al. 1963). Subjects with a history of drug allergies or sensitivities, hay fever, or asthma also tolerated exposure to CS and were similar to normal subjects, but the group with pre-existing conditions had a higher percentage of individuals with more severe chest symptoms (many of them laying prostrate on the ground for several minutes). However, no wheezing or rhonchi were heard, and recovery was as rapid as that seen in other exposure groups.

4.3.3. Concentration-Exposure Duration Relationship

The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases can be described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). The value of n for CS was determined on the basis of acute lethality data from studies of rats, mice, rabbits, guinea pigs, dogs, and monkeys (see Table 7-13). The dose-response software of ten Berge (2006) was used in the analyses (see Appendix A for details).

TABLE 7-13 Values of the Exponent n for Tear Gas

Species	n value	95% Confidence Limits
Rat	0.704	0.543–0.865
Mouse	0.701	0.509–0.892
Rabbit	0.658	0.467–0.849
Guinea pig	0.559	0.018–1.099
Dog	0.356	-1.464–0.751
Monkey	0.187	-0.281–0.656

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Several studies describe irritation in humans cause by CS (see Table 7-7); however, the severity of the effects exceeds those defined by AEGL-1.

5.2. Animal Data Relevant to AEGL-1

No animal studies of CS were available for deriving AEGL-1 values.

5.3. Derivation of AEGL-1 Values

AEGL-1 values are not recommended because no studies were available in which toxicity was limited to AEGL-1 effects. Effects observed at the lowest tested concentrations exceeded the severity of those defined by AEGL-1. Absence of AEGL-1 values does not imply that exposure below the AEGL-2 values are without adverse effects.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

Five subjects exposed to CS at 0.71-0.78 mg/m^3 (average concentration 0.75 mg/m^3, calculated from the six interval measurements) tolerated a 60 min exposure (Beswick et al. 1972). All subjects reported ocular stinging and watering, increased salivation, cough, and face stinging. Other effects reported by some of the subjects included throat irritation (4 subjects), nasal stinging and running (3 subjects), mouth stinging (2 subjects), chest burning (2 subjects), nausea (2 subjects), and headache (2 subjects). Nausea was likely due to swallowing large amounts of saliva and the headaches were likely due to frontal sinus irritation (Beswick et al. 1972). In another study, four subjects exposed to CS at 1.5 mg/m^3 tolerated a 90 min exposure, but experienced clinical signs of irritation. One subject developed nasal irritation within 2 min, three subjects

developed headache (at 45, 50, and 83 min), and all four experienced ocular irritation (at 20, 24, 70, and 75 min) (Punte et al. 1963). When the CS concentration was gradually increased over the course of 60 min, most of the 30 subjects were able to tolerate exposure to concentrations ranging from 0.31 to 2.3 mg/m^3; one subject left at 5 min because of vomiting but returned for the duration of the exposure, another vomited at 55 min of exposure, and one subject left after 8 min because of irritation (Beswick et al. 1972). The two cases of vomiting were attributed to swallowing large amounts or saliva. Clinical signs noted during the 60 min exposure included ocular, nasal, mouth, and throat irritation, nausea, chest discomfort, headache, and stinging of the face.

6.2. Animal Data Relevant to AEGL-2

Blinking, mild pulmonary congestion, and emphysema were observed in monkeys exposed to CS at 900 mg/m^3 for 3 min or 1,700 mg/m^3 for 5 min. Monkeys exposed at 2,500 mg/m^3 for 32 min exhibited blinking, labored respiration, coughing, oral and nasal discharge, vomiting, decreased activity, pulmonary edema, and congestion (Striker et al. 1967). Mice exposed to CS at 40 mg/m^3 for 5 h had rhinorrhea and lacrimation, and guinea pigs exposed at 45 mg/m^3 for 5 h showed occasional sneezing during the first hour of exposure.

6.3. Derivation of AEGL-2 Value

AEGL-2 values are based on human exposure to CS at 0.75 mg/m^3 for 60 min (Beswick et al. 1972). All five subjects tolerated the exposure, but experienced ocular irritation, increased salivation, and coughing; some subjects also reported nasal, mouth, and throat irritation, nausea, and headache. An intraspecies uncertainty factor of 3 was applied because contact irritation is a portal-of-entry effect and is not expected to vary widely among individuals. This factor is also supported by the finding that responses of volunteers with jaundice, hepatitis, or peptic ulcer or who were 50-60 years old were similar to those of "normal" volunteers when exposed at a highly irritating concentration of CS for short durations. The ability to tolerate CS at 14-73 mg/m^3 and the recovery time in volunteers with a history of drug allergies, seasonal allergies, asthma, or drug sensitivity were similar to "normal" volunteers; although more severe chest symptoms were reported in the volunteers with pre-existing conditions (Gutentag et al. 1960; Punte et al. 1963). An interspecies uncertainty factor of 1 was applied because the study was conducted in humans. A modifying factor of 3 was also used because the effects observed at 0.75 mg/m^3 were considered AEGL-2 effects (watering eyes could impair escape). Time scaling was not performed because ocular irritation is a function of direct contact with the CS and is unlikely to increase with duration of exposure at this level of severity (NRC 2001). AEGL-2 values for CS are presented in Table 7-14, and the calculations are in Appendix B.

TABLE 7-14 AEGL-2 Values for Tear Gas

10 min	30 min	1 h	4 h	8 h
0.083 mg/m^3	0.083 mg/m^3	0.083 mg/m^3	0.083 mg/m^3	0.083 mg/m^3

These values are supported by the Punte et al. (1963) study in which four subjects tolerated a 90-min exposure at 1.5 mg/m^3 and reported ocular and nasal irritation and headache. The values are also supported by other experiments conducted by Beswick et al. (1972). When an additional 30 subjects were exposed for 60 min to CS at 0.31-2.3 mg/m^3, one subject left at 5 min because of vomiting, but returned for the duration of the exposure, and another vomited at 55 min of exposure. Both cases of vomiting were attributed to swallowing large amounts or saliva. One subject voluntarily left after 8 min because of irritation; this subject was exposed at 0.56-0.86 mg/m^3 (AEGL-2 values are below this range).

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human studies of CS were available for deriving AEGL-3 values.

7.2. Animal Data Relevant to AEGL-3

Animal lethality data are available for rats, mice, rabbits, guinea pigs, dogs, and monkeys exposed to varying concentrations of CS for varying durations (McNamara et al. 1969; Ballantyne and Callaway 1972; Ballantyne and Swanston 1978). Exposure durations ranged from 5 to 300 min and concentrations of CS ranged from 37 to 5,176 mg/m^3. Mortality incidences ranged from 0 to 100%, depending on concentration-duration pairings. The experimental parameters are summarized in Tables 7-8, 7-10, 7-11, and 7-12.

7.3. Derivation of AEGL-3 Values

Using the rat, mouse, rabbit, guinea pig, dog, and monkey data sets of McNamara et al. (1969), Ballantyne and Callaway (1972), and Ballantyne and Swanston (1978), the lethality threshold for CS at each AEGL-3 exposure duration was calculated using the probit analysis-based dose-response program of ten Berge (2006) (see Appendix A). The threshold for lethality was set at the LC_{01}. The rat, mouse, and rabbit data all yielded similar time-scaling values and AEGL-3 values (see Appendix A). Large variances in the dog and monkey data precluded calculation of 95% confidence intervals. The rat data set was used to

derive AEGL-3 values, because it yielded values that were the most consistent with the available human data. Time scaling was performed using the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). An empirical value for n of 0.70 was determined on the basis of the rat data. The 4-h AEGL-3 value was adopted as the 8-h AEGL-3 value because time scaling yielded an 8-h value inconsistent with the AEGL-2 values, which were derived from a rather robust human dataset. A total uncertainty factor of 10 was applied. A factor of 3 was used to account for interspecies differences, because clinical signs are likely caused by a direct chemical effect on the tissues and this type of portal-of-entry effect is unlikely to vary greatly between species. Furthermore, calculated LCt_{50} values for different species are all well within a factor of 2 of each other (88,480 mg-min/m^3 for rats, 67,200 mg-min/m^3 for guinea pigs, 54,090 mg-min/m^3 for rabbits, and 50,010 mg-min/m^3 for mice) (Ballantyne and Swanston 1978). An uncertainty factor of 3 was used to account for intraindividual variability because contact irritation is a portal-of-entry effect and is not expected to vary widely among individuals. As noted above in support of the AEGL-2 values, a factor of 3 is also supported by the results of studies by Punte et al. (1963) and Gutentag et al. (1960) in subjects with pre-existing conditions. AEGL-3 values for CS are presented in Table 7-15, and calculations presented in Appendix B.

The AEGL-3 values are considered protective. No mortality was noted in rats, rabbits, or mice exposed to CS at 1,802, 1,434, or 4,250 mg/m^3 for 10 min, respectively (Ballantyne and Swanston 1978), suggesting that the 10-min AEGL-3 of 140 mg/m^3 is appropriate. Similarly, no deaths were observed in 10 mice or five guinea pigs exposed at 40 or 44.7 mg/m^3, respectively, for 5 h (Ballantyne and Callaway 1972). One of 10 rats died after exposure to CS at 37 mg/m^3 for 5 h (Ballantyne and Callaway 1972). These data support the 4-h AEGL-3 of 1.5 mg/m^3.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

AEGL-1 values were not recommended because effects exceeding the severity of AEGL-1 were detected at the lowest concentrations tested.

AEGL-2 values are based on irritation in humans and AEGL-3 values are based on an estimated threshold for lethality in rats. AEGL values for tear gas are presented in Table 7-16.

TABLE 7-15 AEGL-3 Values for Tear Gas

10 min	30 min	1 h	4 h	8 h
140 mg/m^3	29 mg/m^3	11 mg/m^3	1.5 mg/m^3	1.5 mg/m^3

8.2. Other Standards and Guidelines

Standards and guidelines for CS are presented in Table 7-17. Differences between the emergency response planning guideline 3 (ERPG-3) and the 1-h AEGL-3 value and between the immediately dangerous to life or health and 30-min AEGL-2 values are due to differences in the point of departure and uncertainty factors. The ERPG-3 is based on a 1-h LC_{50} of 1,000 mg/m^3 and undisclosed uncertainty factors (AIHA 2008). The IDLH is based on a Department of Army safety guide, which reported that a 2-min exposure to CS at 2-10 mg/m^3 was considered intolerable by six of 15 people (NIOSH 1996).

TABLE 7-16 AEGL Values for Tear Gas

	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)	0.083 mg/m^3	0.083 mg/m^3	0.083 mg/m^3	0.083 mg/m^3	0.083 mg/m^3
AEGL-3 (lethal)	140 mg/m^3	29 mg/m^3	11 mg/m^3	1.5 mg/m^3	1.5 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. The severity of effects observed at the lowest tested concentrations exceeded those defined by AEGL-1.

TABLE 7-17 Standards and Guidelines for Tear Gas

	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.083 mg/m^3	0.083 mg/m^3	0.083 mg/m^3	0.083 mg/m^3	0.083 mg/m^3
AEGL-3	140 mg/m^3	29 mg/m^3	11 mg/m^3	1.5 mg/m^3	1.5 mg/m^3
ERPG-1 (AIHA)[a]			0.005 mg/m^3		
ERPG-2 (AIHA)[a]			0.1 mg/m^3		
ERPG-3 (AIHA)[a]			25 mg/m^3		
IDLH (NIOSH)[b]		2 mg/m^3			
PEL-TWA (OSHA)[c]					0.4 mg/m^3
REL-TWA (NIOSH)[d]					0.4 mg/m^3
TLV-STEL (ACGIH)[e]	0.005 ppm (0.4 mg/m^3)				
MAC (The Netherlands)[f]					0.4 mg/m^3

[a]ERPG (emergency response planning guidelines, American Industrial Hygiene Association [AIHA 2008]).
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 CS is based on one of 10 individuals reporting a burning or itching sensation at 0.0004 mg/m^3 and a calculated EC_{50} of 0.004 mg/m^3.
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 CS is based on human irritation data.
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 for tear gas is based on animal lethality data (ab approximate 1-h LC_{50}).
[b]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.
[c]PEL-TWA (permissible exposure limit – time-weighted average, Occupational Health and Safety Administration) (29CFR Part1910.1000 [1996]) 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.
[d]REL-TWA (recommended exposure limit – time-weighted average, National Institute for Occupational Safety and Health) (NIOSH 2011) is defined analogous to the OSHA PEL-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 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]MAC (maximaal aanvaarde concentratie [maximal accepted concentration], Dutch Expert Committee for Occupational Standards, The Netherlands) (MSZW 2004) is defined analogous to the OSHA PEL-TWA.

8.3. Data Adequacy and Research Needs

Inadequate data are available to derive AEGL-1 values for CS. Adequate human data are available for deriving AEGL-2 values, and animal data are available for deriving AEGL-3 values. Additional data providing information at exposures that produce minimal irritation would be useful for deriving AEGL-1 values.

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APPENDIX A

TIME-SCALING CALCULATIONS FOR TEAR GAS

The relationship between dose and time for any given chemical is a function of the physical and chemical properties of the substance and the unique toxicologic and pharmacologic properties of the individual substance. Historically, the relationship according to Haber (1924), commonly called Haber's Law or Haber's Rule ($C \times t = k$, where C = exposure concentration, t = exposure duration, and k = a constant), has been used to relate exposure concentration and duration to effect (Rinehart and Hatch 1964). This concept states that exposure concentration and exposure duration may be reciprocally adjusted to maintain a cumulative exposure constant (k) and that this cumulative exposure constant will always reflect a specific quantitative and qualitative response. This inverse relationship of concentration and time may be valid when the toxic response to a chemical is equally dependent on the concentration and the exposure duration. However, an assessment by ten Berge et al. (1986) of LC_{50} data for certain chemicals revealed chemical-specific relationships between exposure concentration and exposure duration that were often exponential. This relationship can be expressed by the equation $C^n \times t = k$, where n represents a chemical-specific (and even a toxic end point-specific) exponent. The relationship described by this equation is basically the form of a linear regression analysis of the log-log transformation of a plot of C vs. t. ten Berge et al. (1986) examined the airborne concentration (C) and short-term exposure duration (t) relationship relative to death for approximately 20 chemicals and found that the empirically derived value of n ranged from 0.8 to 3.5 among this group of chemicals. Hence, the value of the exponent n in the equation $C^n \times t = k$ quantifies the relationship between exposure concentration and exposure duration. Haber's Rule is the special case where n = 1. As the value of n increases, the plot of concentration vs. time yields a progressive decrease in the slope of the curve.

An n of 0.70 mg/m^3 for CS was obtained by analysis of lethality data in rats (McNamara et al. 1969; Ballantyne and Callaway 1972; Ballantyne and Swanston 1978) using the software of ten Berge (2006). This exposure-time relationship for lethality was considered appropriate for deriving AEGL-3 values. The 4-h AEGL-3 value was adopted as the 8-h AEGL-3 value because time scaling yielded an 8-h value inconsistent with the AEGL-2 values that were derived from robust human data.

TABLE A-1 Results of ten Berge Program (1% Lethality)

		LC_{01} Point Estimate, mg/m^3 (95% confidence limits)					
Species	Exponent *n*	10 min	30 min	1 h	4 h	8 h	Reference(s)
Rat	0.704 (0.543–0.865)	1,385 (477–2,500)	290 (97–496)	109 (32–196)	15 (3.1–35)	5.6 (-0.93–15)	McNamara et al. 1969; Ballantyne and Callaway 1972; Ballantyne and Swanston 1978
Mouse	0.701 (0.509–0.892)	998 (208–1,899)	208 (36–404)	77 (11–166)	11 (-0.86–3.2)	4.0 (-0.23–15)	McNamara et al. 1969; Ballantyne and Callaway 1972; Ballantyne and Swanston 1978
Rabbit	0.658 (0.467–0.849)	656 (227–1,136)	124 (28–249)	43 (7.0–103)	5.2 (0.40–19)	1.8 (0.094–8.6)	McNamara et al. 1969; Ballantyne and Callaway 1972; Ballantyne and Swanston 1978
Guinea pig	0.559 (0.018–1.099)	3.65 (0–100)	0.51 (0–25)	0.15 (0–12)	0.012 (0–3.3)	0.0036 (0–1.8)	McNamara et al. 1969; Ballantyne and Callaway 1972; Ballantyne and Swanston 1978
Dog	0.356 (-1.464–0.751)	349[a]	7,604[a]	53,150[a]	2,597,000[a]	18,150,000[a]	McNamara et al. 1969
Monkey	0.187 (-0.281–0.656)	26[a]	0.075[a]	0.0018[a]	0.0000011[a]	0.000000028[a]	McNamara et al. 1969; Striker et al. 1967
Monkey	2.123 (-21–25)	11[a]	6.6[a]	4.7[a]	2.5[a]	1.8[a]	McNamara et al. 1969

[a]Large variances precluded estimating 95% confidence limits.

TABLE A-2 Data in Rats Used in Log Probit Model
Date: 02 October 2008 Time: 09:11:09

Sequence No.	Concentration (mg/m^3)	Minutes	Exposed	Responded
1	560	25	10	1
2	543	35	10	2
3	489	45	10	3
4	454	55	10	5
5	500	60	10	2
6	500	80	10	6
7	500	90	10	8
8	750	30	8	0
9	150	120	8	0
10	3,950	5	10	0
11	4,760	5	10	0
12	4,250	10	10	1
13	4,330	10	10	1
14	4,150	15	10	0
15	5,176	15	10	7
16	4,000	20	10	9
17	4,300	20	10	8
18	1,802	10	20	0
19	1,806	45	20	8
20	1,911	45	20	9
21	2,629	60	21	20
22	2,699	60	20	20
23	37	300	10	1

Used Probit Equation Y = B0 + B1*X1 + B2*X2
X1 = conc mg/m^3, ln-transformed
X2 = minutes, ln-transformed

ChiSquare = 50.11
Degrees of freedom = 20
Probability Model = 2.13E-04

Ln(Likelihood) = -47.54

B 0 = -9.6233E+00 Student t = -3.9484
B 1 = 1.1705E+00 Student t = 5.6748
B 2 = 1.6634E+00 Student t = 5.6382

Variance B 0 0 = 5.9402E+00
Covariance B 0 1 = -4.8485E-01
Covariance B 0 2 = -6.7032E-01
Variance B 1 1 = 4.2542E-02
Covariance B 1 2 = 4.9302E-02
Variance B 2 2 = 8.7045E-02

Estimation ratio between regression coefficients of ln(conc) and ln(minutes)
Point estimate = 0.704
Lower limit (95% CL) = 0.543
Upper limit (95% CL) = 0.865

Estimation of conc mg/m^3 at response of 1%
Minutes = 10
Point estimate conc mg/m^3 = 1.385E+03 for response of 1%
Lower limit (95% CL) conc mg/m^3 = 4.772E+02 for response of 1%
Upper limit (95% CL) conc mg/m^3 = 2.500E+03 for response of 1%

Estimation of conc mg/m^3 at response of 1%
Minutes = 30
Point estimate conc mg/m^3 = 2.906E+02 for response of 1%
Lower limit (95% CL) conc mg/m^3 = 9.659E+01 for response of 1%
Upper limit (95% CL) conc mg/m^3 = 4.963E+02 for response of 1%

Estimation of conc mg/m^3 at response of 1%
Minutes = 60
Point estimate conc mg/m^3 = 1.085E+02 for response of 1%
Lower limit (95% CL) conc mg/m^3 = 3.223E+01 for response of 1%
Upper limit (95% CL) conc mg/m^3 = 1.958E+02 for response of 1%

Estimation of conc mg/m^3 at response of 1%
Minutes = 120
Point estimate conc mg/m^3 = 4.052E+01 for response of 1%
Lower limit (95% CL) conc mg/m^3 = 1.021E+01 for response of 1%
Upper limit (95% CL) conc mg/m^3 = 8.137E+01 for response of 1%

Estimation of conc mg/m^3 at response of 1%
Minutes = 240
Point estimate conc mg/m^3 = 1.513E+01 for response of 1%
Lower limit (95% CL) conc mg/m^3 = 3.122E+00 for response of 1%
Upper limit (95% CL) conc mg/m^3 = 3.501E+01 for response of 1%

Estimation of conc mg/m^3 at response of 1%
Minutes = 480
Point estimate conc mg/m^3 = 5.649E+00 for response of 1%
Lower limit (95% CL) conc mg/m^3 = 9.345E-01 for response of 1%
Upper limit (95% CL) conc mg/m^3 = 1.540E+01 for response of 1%

APPENDIX B

DERIVATION OF AEGL VALUES FOR TEAR GAS

Derivation of AEGL-1 Values

AEGL-1 values are not recommended for CS because the effects observed at the lowest tested concentrations exceeded the severity of AEGL-1 effects.

Derivation of AEGL-2 Values

Key study:	Beswick, F.W., P. Holland, and K.H. Kemp. 1972. Acute effects of exposure to orthochlorobenzilidene malononitrile (CS) and the development of tolerance. Br. J. Ind. Med. 29(3):298-306.
Toxicity end point:	Human exposure to CS at an average concentration of 0.75 mg/m^3 for 60 min. All five subjects tolerated the exposure but reported ocular stinging and watering, increased salivation, coughing, and face stinging. Some subjects also reported throat irritation (4 subjects), nasal stinging and running (3 subjects), mouth stinging (2 subjects), chest burning (2 subjects), nausea (2 subjects), and headache (2 subjects).
Time scaling:	None. Irritation is a function of direct contact with CS and is unlikely to increase with duration of exposure at this level of severity (NRC 2001).
Uncertainty factors:	1 for interspecies differences 3 for intraspecies variability; contact irritation is a portal-of-entry effect and is not expected to vary widely between individuals. Value of 3 is also supported by a study that showed that volunteers with a history of jaundice, hepatitis, or peptic ulcer or those that were 50-60 years old had responses similar to those of "normal" volunteers when exposed at a highly irritating concentration of CS for short durations. The ability to tolerate exposure to CS at 14-73 mg/m^3 and the recovery time in people with a history of drug allergies, seasonal allergies, asthma, or drug sensitivity was similar to normal volunteers; although more severe chest symptoms were reported in the people with pre-existing conditions (Gutentag et al. 1960; Punte et al. 1963).
Modifying factor:	3, because effects observed at 0.75 mg/m^3 were AEGL-2 effects.

Calculations: 0.75 mg/m^3 ÷ 9 = 0.083 mg/m^3 (applied to all AEGL durations)

Derivation of AEGL-3 Values

Key studies: McNamara, B.P., E.J. Owens, J.T. Weimer, T.A. Ballard, and F.J. Vocci. 1969. Toxicology of Riot Control Chemicals CS, CN, and DM. Edgewood Arsenal Technical Report EATR-4309. US Department of the Army, Edgewood Arsenal Medical Research Laboratory, Edgewood Arsenal, MD. November 1969.

Ballantyne, B., and S. Callaway. 1972. Inhalation toxicology and pathology of animals exposed to o chlorobenzylidene malononitrile. Med. Sci. Law 12(1):43-65.

Ballantyne, B., and D.W. Swanston. 1978. The comparative acute mammalian toxicity of 1-chloroacetophenone (CN) and 2-chlorobenzylidene malononitrile (CS). Arch. Toxicol. 40(2):75-95.

Toxicity end point: LC_{01} for rats; calculated using probit analysis-based dose-response program of ten Berge (2006), see Appendix A.

	LC_{01} Point Estimate, mg/m^3 (95% confidence limits)				
Exponent *n*	10 min	30 min	1 h	4 h	8 h
0.704 (0.543-0.865)	1,385 (477–2,500)	290 (97–496)	109 (32–196)	15 (3.1–35)	5.6 (-0.93–15)

Time scaling: $C^n \times t = k$; n = 0.70 (based on rat lethality data). No time scaling was performed for the 8-h AEGL value, because time scaling yielded a value that was inconsistent with the AEGL-2 values that were derived from robust human data.

Uncertainty factors: 3 for interspecies differences. Effects from CS are likely caused by a direct chemical effect on the tissues. This type of portal-of-entry effect is unlikely to vary greatly between species. Value is also supported by calculated LCT_{50} values of 88,480 mg min/m^3 for rats, 67,200 mg min/m^3 for guinea pigs, 54,090 mg min/m^3 for rabbits, and 50,010 mg min/m^3 for mice (Ballantyne and Swanston 1978); values all well within a factor of two of each other.

3 for intraspecies variability. Effects from CS are likely caused by a direct chemical effect on the tissues. This type of portal-of-entry effect is not likely to vary greatly among individuals. Value is also supported by a study that showed that volunteers with a history of jaundice, hepatitis, or peptic ulcer or those that were 50-60 years old had responses similar to those of "normal" volunteers when exposed at a highly irritating concentration of CS for short durations. The ability to tolerate exposure to CS at 14-73 mg/m^3 and the recovery time in people with a history of drug allergies, seasonal allergies, asthma, or drug sensitivity was similar to normal volunteers; although more severe chest symptoms were reported in the people with pre-existing conditions (Gutentag et al. 1960; Punte et al. 1963).

Calculations:

10-min AEGL-3:	1,385 $mg/m^3 \div 10 = 140$ mg/m^3
30-min AEGL-3:	290 $mg/m^3 \div 10 = 29$ mg/m^3
1-h AEGL-3:	109 $mg/m^3 \div 10 = 11$ mg/m^3
4-h AEGL-3:	15 $mg/m^3 \div 10 = 1.5$ mg/m^3
8-h AEGL-3:	Set equal to the 4-h AEGL-3 of 1.5 mg/m^3

APPENDIX C

ACUTE EXPOSURE GUIDELINE LEVELS FOR TEAR GAS

Derivation Summary

AEGL-1 VALUES

AEGL-1 values are not recommended for CS because the effects observed at the lowest tested concentrations exceeded the severity of AEGL-1 effects.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.083 mg/m^3	0.083mg/m^3	0.083 mg/m^3	0.083 mg/m^3	0.083 mg/m^3

Key reference: Beswick, F.W., P. Holland, and K.H. Kemp. 1972. Acute effects of exposure to orthochlorobenzilidene malononitrile (CS) and the development of tolerance. Br. J. Ind. Med. 29(3):298-306.

Test species/Strain/Number: Humans, 5

Exposure route/Concentration/Duration: Inhalation, 0.71-0.78 mg/m^3 (average: 0.75 mg/m^3) for 60 min

Effects: Clinical signs of irritation. Ocular stinging and watering, increased salivation, cough, and face stinging was reported in all subjects. Additional signs of irritation included throat irritation (4 subjects), nasal stinging and running (3 subjects), mouth stinging (2 subjects), chest burning (2 subjects), nausea (2 subjects), and headache (2 subjects).

End point/Concentration/Rationale: Ocular, nasal, mouth, and throat irritation, coughing, nausea, and headache at 0.75 mg/m^3 for 60 min.

Uncertainty factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1, because data were from human volunteers
Intraspecies: 3, contact irritation is a portal-of-entry effect and is not expected to vary widely between individuals. Value is also supported by a study that showed that volunteers with a history of jaundice, hepatitis, or peptic ulcer and those that were 50-60 years old had responses similar to those of "normal" volunteers when exposed at a highly irritating concentration of CS for short durations. The ability to tolerate the exposure to CS at 14-73 mg/m^3 and the recovery time in people with a history of drug allergies, seasonal allergies, asthma, or drug sensitivity was similar to normal volunteers; although more severe chest symptoms were reported in the people with pre-existing conditions (Gutentag et al. 1960; Punte et al. 1963).

Modifying factor: 3, because effects at 0.75 mg/m^3 were considered AEGL-2 effects.

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: Not applied. Irritation is a function of direct contact with the CS and is unlikely to increase with duration of exposure at this level of severity (NRC 2001).

(Continued)

AEGL-2 VALUES Continued

Data adequacy: AEGL-2 values are supported by the data of Punte et al. (1963) and Beswick et al. (1972). Exposure of four subjects at 1.5 mg/m^3 for 90 min resulted in ocular and nasal irritation in all subjects and headache in 3 subjects (Punte et al. 1963). When a total of 30 subjects were exposed for 60 min to gradually increasing CS concentrations ranging from 0.31-2.3 mg/m^3, one subject left at 5 min because of vomiting but returned for the duration of the exposure, and another vomited at 55 min of exposure (vomiting in both cases attributed to swallowing large amounts or saliva). One subject voluntarily left the exposure after 8 min because of irritation; this subject was exposed in the range of 0.56-0.86 mg/m^3, and the AEGL-2 values are below this range.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
140 mg/m^3	29 mg/m^3	11 mg/m^3	1.5 mg/m^3	1.5 mg/m^3

Key references:

McNamara, B.P., E.J. Owens, J.T. Weimer, T.A. Ballard, and F.J. Vocci. 1969. Toxicology of Riot Control Chemicals CS, CN, and DM. Edgewood Arsenal Technical Report EATR-4309. US Department of the Army, Edgewood Arsenal Medical Research Laboratory, Edgewood Arsenal, MD. November.

Ballantyne, B., and S. Callaway. 1972. Inhalation toxicology and pathology of animals exposed to o chlorobenzylidene malononitrile. Med. Sci. Law 12(1):43-65.

Ballantyne, B., and D.W. Swanston. 1978. The comparative acute mammalian toxicity of 1- chloroacetophenone (CN) and 2-chlorobenzylidene malononitrile (CS). Arch. Toxicol. 40(2):75-95.

Test species/Strain/Number: Rat, various strains; 8, 10, 20, or 21 per group

Exposure route/Concentration/Duration: Inhalation, 37-5,175 mg/m^3 for 5-300 min.

Effects: Lethality

End point/Concentration/Rationale: LC_{01} for rats calculated using probit-analysis dose-response program of ten Berge (2006).

	LC_{01} Point Estimate, mg/m^3				
Exponent *n*	10 min	30 min	1 h	4 h	8 h
0.704 (0.543-0.865)	1,385 (477-2,500)	290 (97-496)	109 (32-196)	15 (3.1-35)	5.6 (-0.93-15)

Uncertainty factors/Rationale:

Total uncertainty factor: 10

Interspecies: 3, effects from CS are likely caused by a direct chemical effect on the tissues. This type of portal-of-entry effect is unlikely to vary greatly between species. Value is also supported by calculated LCT_{50} values of 88,480 mg min/m^3 for rats, 67,200 mg min/m^3 for guinea pigs, 54,090 mg min/m^3 for rabbits, and 50,010 mg min/m^3 for mice (Ballantyne and Swanston 1978); values are all well within a factor of two of each other.

Intraspecies: 3, effects from CS are likely caused by a direct chemical effect on the tissues. This type of portal-of-entry effect is not likely to vary greatly among individuals. Value is also supported by a study that showed that volunteers with a history of jaundice, hepatitis, or peptic ulcer or those that were 50-60 years old had responses similar to those

of "normal" volunteers when exposed at a highly irritating concentration of CS for short durations. The ability to tolerate the exposure to CS at 14-73 mg/m^3 and the recovery time in people with a history of drug allergies, seasonal allergies, asthma, or drug sensitivity was similar to normal volunteers; although more severe chest symptoms were reported in the people with pre-existing conditions (Gutentag et al. 1960; Punte et al. 1963).

Modifying factor: None applied

Animal-to-human dosimetric adjustment: Not applicable

Time scaling: $C^n \times t = k$, where n = 0.70 based on rat lethality data. The 4-h AEGL-3 value was adopted as the 8-h AEGL-3 value because time scaling yielded an 8-h value inconsistent with the AEGL-2 values that were derived from robust human data.

Data adequacy: The AEGL-3 values are considered protective. No mortality was noted in rats exposed to CS at 1,802 mg/m^3 for 10 min (Ballantyne and Swanston 1978), in rabbits at 1,434 mg/m^3 for 10 min (Ballantyne and Swanston 1978), or in mice and rabbits at 4,250 mg/m^3 for 10 min (Ballantyne and Callaway 1972). Dividing these concentrations by a total uncertainty factor of 10, yields values ranging from 140-425 mg/m^3, suggesting that the 10-min AEGL-3 is appropriate. No mortality was noted in guinea pigs exposed at 44.7 mg/m^3 for 5 h or in mice exposed at 40 mg/m^3 for 5 h (Ballantyne and Callaway 1972). Applying a total uncertainty factor of 10 to these concentrations yields a value of approximately 4.0 mg/m^3 for 5 h. One of ten rats died when exposed at 37 mg/m^3 for 5 h (Ballantyne and Callaway 1972). Dividing 37 mg/m^3 by 2 to obtain an approximate threshold for lethality, yields 18.5 mg/m^3; application of a total uncertainty factor of 10, yields a value of 1.9 mg/m^3 for 5 h. The values derived from the 5-h data show that the AEGL-3 values are protective.

APPENDIX D

CATEGORY PLOT FOR TEAR GAS

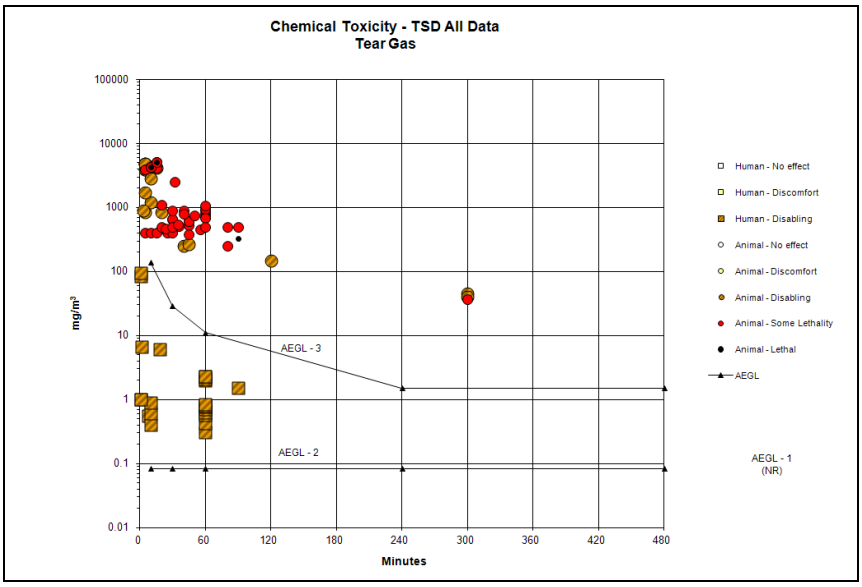

FIGURE D-1 Category plot of toxicity data and AEGL values for tear gas.

TABLE D-1 Data Used in the Category Plot for Tear Gas

Source	Species	Sex	No. Exposures	mg/m^3	Minutes	Category	Comments
AEGL-1				NR	10	AEGL	
AEGL-1				NR	30	AEGL	
AEGL-1				NR	60	AEGL	
AEGL-1				NR	240	AEGL	
AEGL-1				NR	480	AEGL	
AEGL-2				0.083	10	AEGL	
AEGL-2				0.083	30	AEGL	
AEGL-2				0.083	60	AEGL	
AEGL-2				0.083	240	AEGL	
AEGL-2				0.083	480	AEGL	
AEGL-3				140	10	AEGL	
AEGL-3				29	30	AEGL	
AEGL-3				11	60	AEGL	
AEGL-3				1.5	240	AEGL	
AEGL-3				1.5	480	AEGL	
Ballantyne and Calloway 1972	Guinea pig		1	45	300	2	Sneezing
Ballantyne and Calloway 1972	Guinea pig		1	3,950	5	SL	Mortality: 1/5
Ballantyne and Calloway 1972	Guinea pig		1	4,150	15	SL	Mortality: 3/5
Ballantyne and Calloway 1972	Guinea pig		1	4,250	10	3	Mortality: 5/5
Ballantyne and Calloway 1972	Guinea pig		1	4,330	10	SL	Mortality: 3/5
Ballantyne and Calloway 1972	Guinea pig		1	4,760	5	2	Mortality: 0/5
Ballantyne and Calloway 1972	Guinea pig		1	5,167	15	3	Mortality: 5/5

(Continued)

TABLE D-1 Continued

Source	Species	Sex	No. Exposures	mg/m^3	Minutes	Category	Comments
Ballantyne and Calloway 1972	Mouse		1	40	300	2	Rhinorrhea and lacrimation
Ballantyne and Calloway 1972	Mouse		1	3,950	5	SL	Mortality: 1/10
Ballantyne and Calloway 1972	Mouse		1	4,150	15	SL	Mortality: 3/10
Ballantyne and Calloway 1972	Mouse		1	4,250	10	2	Mortality: 0/10
Ballantyne and Calloway 1972	Mouse		1	4,330	10	SL	Mortality: 4/10
Ballantyne and Calloway 1972	Mouse		1	4,760	5	2	Mortality: 0/10
Ballantyne and Calloway 1972	Mouse		1	5,167	15	SL	Mortality: 3/10
Ballantyne and Calloway 1972	Rabbit		1	3,950	5	2	Mortality: 0/5
Ballantyne and Calloway 1972	Rabbit		1	4,150	15	SL	Mortality: 2/5
Ballantyne and Calloway 1972	Rabbit		1	4,250	10	2	Mortality: 0/5
Ballantyne and Calloway 1972	Rabbit		1	4,330	10	SL	Mortality: 2/5
Ballantyne and Calloway 1972	Rabbit		1	4,760	5	2	Mortality: 0/5
Ballantyne and Calloway 1972	Rabbit		1	5,167	15	SL	Mortality: 2/5
Ballantyne and Calloway 1972	Rat		1	37	300	SL	Rhinorrhea, lacrimation, and mortality (1/10)
Ballantyne and Calloway 1972	Rat		1	150	120	2	Mortality: 0/8
Ballantyne and Calloway 1972	Rat		1	3,950	5	2	Mortality: 0/10
Ballantyne and Calloway 1972	Rat		1	4,150	15	2	Mortality: 0/10
Ballantyne and Calloway 1972	Rat		1	4,250	10	SL	Mortality: 1/10
Ballantyne and Calloway 1972	Rat		1	4,330	10	SL	Mortality: 1/10
Ballantyne and Calloway 1972	Rat		1	4,760	5	2	Mortality: 0/10
Ballantyne and Calloway 1972	Rat		1	5,167	15	SL	Mortality: 7/10
Ballantyne and Swanston 1978	Rabbit	Female	1	846	5	2	Mortality: 0/10

Beswick et al. 1972	Human	1	0.31	60	2	Ocular, nasal, throat irritation; nausea, chest discomfort, headaches
Beswick et al. 1972	Human	1	0.42	60	2	Ocular, nasal, throat irritation; nausea, chest discomfort, headaches
Beswick et al. 1972	Human	1	0.56	8	2	Ocular, nasal, throat irritation; nausea, chest discomfort, headaches
Beswick et al. 1972	Human	1	0.57	60	2	Ocular, nasal, throat irritation; nausea, chest discomfort, headaches
Beswick et al. 1972	Human	1	0.63	60	2	Ocular, nasal, throat irritation; nausea, chest discomfort, headaches
Beswick et al. 1972	Human	1	0.7	60	2	Ocular, nasal, throat irritation; nausea, chest discomfort, headaches
Beswick et al. 1972	Human	1	0.78	60	2	Ocular, nasal, throat irritation; nausea, chest discomfort, headaches
Beswick et al. 1972	Human	1	0.8	60	2	Ocular, nasal, throat irritation; nausea, chest discomfort, headaches
Beswick et al. 1972	Human	1	0.84	60	2	Ocular, nasal, throat irritation; nausea, chest discomfort, headaches
Beswick et al. 1972	Human	1	2	60	2	Ocular, nasal, throat irritation; nausea, chest discomfort, headaches
Beswick et al. 1972	Human	1	2.1	60	2	Ocular, nasal, throat irritation; nausea, chest discomfort, headaches
Beswick et al. 1972	Human	1	2.3	60	2	Ocular, nasal, throat irritation; nausea, chest discomfort, headaches
Beswick et al. 1972	Human	1	2.3	60	2	Ocular, nasal, throat irritation; nausea, chest discomfort, headaches
McNamara et al. 1969	Dog	1	508	36	SL	Mortality: 2/4
McNamara et al. 1969	Dog	1	520	45	SL	Mortality: 2/4

(Continued)

TABLE D-1 Continued

Source	Species	Sex	No. Exposures	mg/m^3	Minutes	Category	Comments
McNamara et al. 1969	Dog		1	612	45	SL	Mortality: 2/4
McNamara et al. 1969	Dog		1	649	30	SL	Mortality: 1/4
McNamara et al. 1969	Dog		1	797	60	SL	Mortality: 3/4
McNamara et al. 1969	Dog		1	833	20	2	Mortality: 0/4
McNamara et al. 1969	Dog		1	899	40	SL	Mortality: 2/4
McNamara et al. 1969	Dog		1	909	60	SL	Mortality: 2/4
McNamara et al. 1969	Guinea pig		1	400	5	SL	Mortality: 1/10
McNamara et al. 1969	Guinea pig		1	400	10	SL	Mortality: 2/10
McNamara et al. 1969	Guinea pig		1	400	15	SL	Mortality: 4/10
McNamara et al. 1969	Guinea pig		1	400	25	SL	Mortality: 7/10
McNamara et al. 1969	Guinea pig		1	400	30	SL	Mortality: 7/10
McNamara et al. 1969	Guinea pig		1	500	20	SL	Mortality: 3/10
McNamara et al. 1969	Monkey		1	381	45	SL	Mortality: 2/4
McNamara et al. 1969	Monkey		1	469	24	SL	Mortality: 1/4
McNamara et al. 1969	Monkey		1	612	45	SL	Mortality: 1/4
McNamara et al. 1969	Monkey		1	673	30	SL	Mortality: 2/4
McNamara et al. 1969	Monkey		1	699	60	SL	Mortality: 1/4
McNamara et al. 1969	Monkey		1	941	60	SL	Mortality: 3/4
McNamara et al. 1969	Monkey		1	1,057	60	SL	Mortality: 2/4
McNamara et al. 1969	Mouse		1	683	60	SL	Mortality: 14/20
McNamara et al. 1969	Mouse		1	740	50	SL	Mortality: 5/20
McNamara et al. 1969	Mouse		1	800	40	SL	Mortality: 5/20
McNamara et al. 1969	Mouse		1	900	30	SL	Mortality: 2/20

McNamara et al. 1969	Mouse	1	1,100	20	SL	Mortality: 7/20
McNamara et al. 1969	Mouse	1	1,200	10	2	Mortality: 0/20
McNamara et al. 1969	Rabbit	1	250	40	2	Mortality: 0/4
McNamara et al. 1969	Rabbit	1	250	80	SL	Mortality: 3/4
McNamara et al. 1969	Rabbit	1	267	45	2	Mortality: 0/4
McNamara et al. 1969	Rabbit	1	333	90	3	Mortality: 4/4
McNamara et al. 1969	Rabbit	1	500	30	SL	Mortality: 1/4
McNamara et al. 1969	Rat	1	454	55	SL	Mortality: 5/10
McNamara et al. 1969	Rat	1	500	60	SL	Mortality: 2/10
McNamara et al. 1969	Rat	1	500	80	SL	Mortality: 6/10
McNamara et al. 1969	Rat	1	500	90	SL	Mortality: 8/10
McNamara et al. 1969	Rat	1	543	35	SL	Mortality: 2/10
Owens and Punte 1963	Human	1	1.5	90	2	Nasal and ocular irritation, headache
Owens and Punte, 1963	Human	1	6	18	2	Intolerable irritation; escape possible
Owens and Punte 1963	Human	1	6.7	2	2	Intolerable irritation; escape possible
Owens and Punte 1963	Human	1	85	1	2	Intolerable airway and ocular irritation
Owens and Punte 1963	Human	1	94	1	2	Intolerable airway and ocular irritation
Rengsdorf 1969	Human	1	1	1	2	Intense ocular irritation
Rengsdorf 1969	Human	1	0.4	10	2	Intense ocular irritation
Rengsdorf 1969	Human	1	0.6	10	2	Intense ocular irritation
Rengsdorf 1969	Human	1	0.9	10	2	Intense ocular irritation
Rengsdorf 1969	Human	1	1	1	2	Intense ocular irritation
Striker et al. 1967	Monkey	1	900	3	2	Pulmonary congestion, emphysema

(Continued)

TABLE D-1 Continued

Source	Species	Sex	No. Exposures	mg/m^3	Minutes	Category	Comments
Striker et al. 1967	Monkey		1	1,700	5	2	Pulmonary congestion, emphysema
Striker et al. 1967	Monkey		1	2,500	32	SL	Severe irritation, pulmonary edema, emphysema, mortality (5/8)
Striker et al. 1967	Monkey		1	2,850	10	2	Pulmonary congestion, emphysema, ocular/respiratory irritation

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