Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 14

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 fourteenth volume in that series. AEGL documents for BZ (2-quinuclidinyl benzilate), ethyl

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

phosphorodichloridate, hexane, methanesulfonyl chloride, nitric acid, propargyl alcohol, and vinyl acetate monomer 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 BZ (interim reports 19a, 20a, and 21a), ethyl phosphorodichloridate (interim reports 20a and 21a), hexane (interim reports 17 and 21a), methanesulfonyl chloride (interim reports 20a and 21a), nitric acid (interim reports 15, 18, and 21a), propargyl alcohol (interim reports 16 and 19a), and vinyl acetate monomer (interim reports 18 and 21a): Harvey Clewell (The Hamner Institutes for Health Sciences), Jeffrey Fisher (U.S. Food and Drug Administration), 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, Occupational Toxicology Associates, Joyce Tsuji (Exponent, Inc.), 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 15-21 was overseen by Robert Goyer (University of Western Ontario [retired]). Appointed by the NRC, he was responsible for making certain that an independent examination of the interim 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.

Donald E. Gardner, *Chair*
Committee on Acute Exposure
Guideline Levels

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

This report is the fourteenth 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 extrap-

olation 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 Syracuse Research Corporation. 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 recommenda-

tions 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 for the accuracy and completeness of the toxicity data cited in the AEGL reports. Thus far, the committee has prepared thirteen 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). This report is the fourteenth volume in that series. AEGL documents for BZ (2-quinuclidinyl benzilate), ethyl phosphorodichloridate, hexane, methanesulfonyl chloride, nitric acid, propargyl alcohol, and vinyl acetate monomer 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

1

Agent BZ (3-Quinuclidinyl Benzilate)[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 Robert Young (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 (U.S. Environmental Protection Agency). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993, 2001).

effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

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

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

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

SUMMARY

Agent BZ (3-quinuclidinyl benzilate) is an odorless, environmentally stable, white crystalline powder with anticholinergic activity. Once considered a potential incapacitating agent for military applications, it is currently used as a pharmacological tool (a muscarinic antagonist known as QNB). It produces anticholinergic delirium, a non-specific syndrome of cognitive dysfunction, hallucinations, and inability to perform tasks. Inhalation exposure would likely involve an aerosolized solid.

No data on the lethality of BZ in humans after inhalation exposure were available. Lethal doses to humans were estimated by Ketchum (1963) using several methods, including extrapolation of data from animals on the basis of body weight, extrapolation of the lethality ratio of BZ and atropine in animals to humans, and extrapolation of the ratio of physiologic effectiveness (parasympatholytic effects) between BZ and atropine in humans. LD_{50} (lethal dose, 50% lethality) values estimated by these methods were 2-5 mg/kg, 0.3-1.4 mg/kg, and 0.2-1.2 mg/kg, respectively. Conversion of these doses to an air concentration of BZ was not provided.

Data on nonlethal effects of BZ in humans after inhalation exposure are from studies conducted by the military. Subjects in these studies were carefully screened, evaluated, and informed human volunteers (male military personnel). The results qualitatively demonstrated that BZ exerts its parasympatholytic effects (behavioral and cognitive dysfunction) regardless of exposure route.

Inhalation exposure experiments were limited to those conducted by Ketchum and colleagues (Ketchum 1963, 2006; Ketchum et al. 1967), in which responses of test subjects were characterized using a scoring system that integrated various cognitive parameters, blood pressure, and heart rate. Exposures were of short duration (minutes) and were expressed as cumulative exposures (mg-min/m^3). An ICt_{50} value (a concentration-time product causing incapacitation in 50% of the test subjects) of 60.1 mg-min/m^3 (95% confidence interval [CI]: 41.3-87.5 mg-min/m^3) was reported by Ketchum et al. (1967). Nonlethal effects of BZ are completely reversible.

Median lethal doses (LCt_{50}) have been reported for several animal species (U.S. Department of the Army 1974). All exposures were of relatively short durations (5-40 min) but the LCt_{50} values ranged from 12,000 to 123,000 mg-min/m^3 with no apparent relationship to body size. Results of animal experiments (Ketchum et al. 1967) showed that monkeys, dogs, and rabbits exhibited qualitatively similar responses to BZ. Mydriasis (excessive or prolonged dilation of the pupil) and cycloplegia (paralysis of the ciliary muscles of the eye) were consistently observed in all test species. Other effects included ataxia, lethargy, sedation, erratic behavior, weakness, and hyperactivity. Exposures were all of short duration (6-8 min).

AEGL-1 values for BZ could not be developed with scientific rigor. Although data on exposures to BZ resulting in no apparent effects in animals are available, the experiments could not assess possible cognitive and behavioral effects characteristic of BZ that are relevant to humans. Human data on BZ that define no-effect levels or that are consistent with the AEGL-1 definition were not available. Therefore, AEGL-1 values for BZ are not recommended.

For AEGL-2 values, a one-third reduction of the ICt_{50} value of 60.1 mg-min/m^3 (60.1 mg-min/m^3 ÷ 3 = 20 mg-min/m^3 or 4 mg/m^3) was considered an estimated threshold for incapacitating effects. The estimated threshold concentration is less than the lower limit of the ICt_{50} (41.3 mg-min/m^3), which was considered too severe to serve as a point of departure because it could result in incapacitation. The threshold estimate is also lower than concentrations associated with clinical signs which may impair the ability to escape (e.g., progressive deterioration of normal gait and uncomfortable paresthesias of lower extremities reported by subjects exposed to BZ at 46.0-84.7 mg-min/m^3 [or 9.2-16.4 mg/m^3] for 5 min) (Ketchum et al. 1967). An interspecies uncertainty factor of 1 was used because the data are from human studies. An uncertainty factor of 10 was used to account for intraindividual variability. Effects in the human studies are likely due to the anticholinergic properties of BZ; structures of muscarinic receptors are highly conserved and, thus, receptor affinity is not likely to vary among individuals. However, individuals with pre-existing conditions may be more sensitive to the anticholinergic effects of BZ. Because of data limitations, particularly the short exposure duration of the critical study (5 min), a modifying factor of 3 was also applied. Data with which to assess the concentration-time relationship for BZ are not available. The concentration-time relationship for many irritant and systemically acting vapors and gases may be

described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived exponent (n) and to obtain protective AEGL values, time scaling was performed using the default of n = 1 to extrapolate to the 10-min, 30-min, and 1-h durations. AEGL-2 values for the 4-h and 8-h durations are not recommended, because data on exposure to BZ for durations longer than a few minutes are lacking and the effects of longer exposures are uncertain.

No human data are available with which to develop AEGL-3 values for BZ. Several of the human exposures reported by Ketchum (1963) and Ketchum et al. (1967) were associated with high total response index (TRI) scores indicative of notable cognitive and behavioral effects and some motor-function effects but no apparent serious physiologic responses. Effects observed at all exposures were reversed 7-days post-exposure with no medical intervention. Other human studies have uncertainties inherent in the exposure-route extrapolations that would be required if using human LC_{50} estimates (Ketchum 1963) or if using the non-verifiable LCt_{50} of 200,000 mg-min/m^3 estimated by Hoenig (2007). Thus, animal studies were used as the basis for deriving AEGL-3 values.

AEGL-3 values for BZ were derived using 3,700 mg-min/m^3 as the point of departure. That value was determined by reducing the LCt_{50} for monkeys (37,000 mg-min/m^3 for 6-25 min) 10-fold (U.S. Department of the Army 1974). The LCt_{50} for the monkey is neither the highest nor lowest value of the six species tested, but the monkey was considered a better model for aerosol inhalation exposure in humans than the other species. Although a one-third reduction of the LC_{50} is often considered an appropriate estimate of the lethality threshold for chemicals with steep concentration-response relationships (NRC 2001), little is known about the concentration-response curve for BZ. An intraspecies uncertainty factor of 10 was used to account for individual variability. A factor of 10 was applied for interspecies variability because no human lethality data were available and LCt_{50} values for five animal species varied 10-fold. A modifying factor of 3 was applied because of data deficiencies. Time scaling was performed as described for the AEGL-2 values. AEGL-3 values for the 4-h and 8-h durations are not recommended, because data on longer exposure durations are lacking.

AEGL values for BZ are presented in Table 1-1.

1. INTRODUCTION

Agent BZ (3-quinuclidinyl benzilate) is an odorless, environmentally stable, white crystalline powder with anticholinergic activity. It was investigated as a potential incapacitating agent for military applications (Ketchum 1963, 2006; Ketchum et al. 1967; USACHPPM 1996), and is currently used as a pharmacological tool (a muscarinic antagonist known as QNB) (Yamamura and Snyder 1974). In general terms, its activity (by any route of exposure) is that of producing anticholinergic delirium, a non-specific syndrome of cognitive dys-

function, hallucinations, and inability to perform tasks. Most physiologic response data in humans exposed to BZ are for parenteral (intravenous and subcutaneous) or oral routes of administration, although some data on aerosol inhalation are available. Inhalation exposure would likely involve an aerosolized solid.

Chemical and physical data on BZ are presented in Table 1-2.

TABLE 1-1 AEGL Values for Agent BZ

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)[a]	NR	NR	NR	NR	NR	Insufficient data.
AEGL-2 (disabling)	0.067 mg/m^3	0.022 mg/m^3	0.011 mg/m^3	NR	NR	Estimated threshold (20 $mg\text{-}min/m^3$) for incapacitation in human volunteers (Ketchum et al. 1967).
AEGL-3 (lethal)	1.2 mg/m^3	0.41 mg/m^3	0.21 mg/m^3	NR	NR	Estimated lethality threshold (3,700 $mg\text{-}min/m^3$) in monkeys (U.S. Department of the Army 1974)

Abbreviations: NR, not recommended.
[a]Absence of AEGL-1 values does not imply that exposure to concentrations less than the AEGL-2 values is without effect.

TABLE 1-2 Chemical and Physical Data for Agent BZ

Parameter	Value	Reference
Synonyms	QNB; benzilic acid, 3-quinuclidinyl benzilate; EA2277; 3-quinuclindinyl ester; 3-hydroxyquinuclidine benzilate; agent buzz; 3-(2,2-diphenyl-2-hydroxyethanoyloxy)-quinuclidine	USACHPPM 1996; HSDB 2008; NIST 2011
CAS registry no.	6581-06-2	Hoenig 2007
Chemical formula	$C_{21}H_{23}NO_3$	Hoenig 2007
Molecular weight	337.4	Hoenig 2007
Physical state	Solid (white crystalline powder)	Hoenig 2007
Melting point	167.5°C	Hoenig 2007
Boiling point	320°C	Hoenig 2007
Relative vapor density	11.6	Hoenig 2007
Solubility	Slightly soluble in water; soluble in most organic solvents	Hoenig 2007
Vapor pressure	0.03 mm Hg at 70°C	Hoenig 2007
Conversion factors in air	1 ppm = 13.8 mg/m^3 1 mg/m^3 = 0.07 ppm	

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No data regarding lethality in humans following inhalation exposure to BZ are available. Lethal exposures for humans were estimated by Ketchum (1963) using several methods, including extrapolation from animals on the basis of body weight, extrapolation of the lethality ratio of BZ and atropine in animals to humans, and extrapolation from the ratio of physiologic effectiveness (para-sympatholytic effects) between BZ and atropine in humans. Estimated LD_{50} values for BZ were 2-5 mg/kg (by species weight), 0.3-1.4 mg/kg (by atropine lethality ratio), and 0.2-1.2 mg/kg (by relative effectiveness ratio of atropine and BZ). Conversion to a concentration of BZ in air was not provided. An estimated median lethal dose (LCt_{50}) for BZ of 200,000 mg-min/m^3 was reported by Hoenig (2007), but the basis for that value was not described.

2.2. Nonlethal Toxicity

Ketchum (1963) conducted research on the effects of BZ in male volunteers. Subjects were informed military personnel who underwent medical and psychological evaluations as a prerequisite for participation. Test candidates were also selected on the basis of their evaluation by the Minnesota Multiphasic Personality Inventory and results of psychological interviews. Experiments were conducted under continuous medical supervision. Severity of BZ-induced effects (criterion for incapacitation) was evaluated using a total response index (TRI), which was calculated using the equation: ([2 × performance index] + [2 × heart rate index] + blood pressure index) ÷ 5. Cognitive function was assessed by the performance index, which was based on serial performance scores in numerical facility and speed of closure tests. Physiologic effects were assessed by blood pressure and heart rate measurements. TRI levels were:

- TRI 4.0 (mild): subjects show peak heart rate of 80-85 beats/min, systolic blood pressure elevation <10 mm Hg, moderate pupillary dilatation, slight blurring of vision and dryness of mouth, some mental slowing, minimal loss of coordination, no loss of contact with reality, lowest performance score of 60% at 7 h; recovery at approximately 48 h.
- TRI 5.0 (moderate): subjects show peak heart rate of 80-95 beats/min, systolic blood pressure elevation <20 mm Hg, sedation might be marked at 4-16 h, transient illusions/hallucinations/confusion and lapses in concentration, some metal slowing, lowest performance score of 40% at 8 h; recovery complete at approximately 72 h.
- TRI 6.0 (severe): subjects show peak heart rate of 95-110 beats/min, hallucinations/confusion, hyperactive disorganized behavior, incoherent speech, memory and attention deficit, deep sleep/stupor, performance at zero within 6 h; recovery complete at approximately 96 h.

- TRI 7.0 (maximal): peak heart rate of 110-140 beats/min within 3 h, systolic blood pressure increase of 20-60 mm Hg, onset of stupor within 3 h and performance decrement to zero within 4 h followed by protracted sleepiness, disorganized behavior, continual hallucinations, possible outbursts of fear and anger, delirium subsides within 72 h; complete recovery by120 h.

Air concentrations were established to attain estimated doses of BZ ranging from 1.4 to 26 μg/kg. Doses were estimated based on body weight and on the difference between the amount of BZ presented to the subject and the amount remaining in the exposure system. Cumulative concentration values were reported as 24-397 mg-min/m^3. Aerosol size mass median aerodynamic diameter (MMAD) ranged from <0.5 to 4.0 μm. The experiments were conducted using a series of suspensions and solutions of BZ, including an acetone solution, Freon 11 suspension, methylene chloride solution, pyrotechnic mix, and water solution. For the pyrotechnic mix (eight volunteers), breathing was regulated by reference to a visual feedback system that resulted in more uniform (± 10%) ventilation rates and tidal volumes. Cumulative exposures (CT; mg-min/m^3) to BZ ranged from 155-261 mg-min/m^3 and produced TRI values of 4.5 to 8.5.

Probit analysis for exposures associated with various TRI indices was reported by Ketchum (1963). The analysis provided an ED_{50} (a concentration-time product causing a specific TRI score in 50% of the test subjects) with 95% confidence limits for aerosol exposures (see Table 1-3) for groups of 36 volunteers. The exposure duration was not specified but was assumed to be of very short duration (<5 min) on the basis of other experiments and summaries provided in the report (U.S. Department of the Army 1974).

Ketchum et al. (1967) also reported the results of field-condition assessments (project DORK) for exposure to BZ aerosols. The assessments appeared to be an extension of the pyrotechnic exposures mentioned above. Two groups of eight volunteers (enlisted U.S. Army personnel under no coercion or enticement) participated with stringent medical safeguards in place. Subjects were evaluated using the number facility test (simple mathematics speed-accuracy test), speed of closure tests (ability to recognize words in a pseudo random array of letters), hand-eye coordination evaluations, and evaluations of ability to perform tasks typical of military situations (e.g., use of field glasses, sequential reporting of general activities, or completing tasks in routine military scenarios). Subjects were exposed to BZ aerosol generated by a Mars generator, and an ICt_{50} (concentration that will incapacitate 50% of exposed subjects) was estimated to be 60.1 mg-min/m^3 (95% CI: 41.3-87.5 mg-min/m^3) for a 165-pound man with a minute volume of 15 L (see Table 1-4). Incapacitation was determined by inability to perform at better than 10% on two consecutive tests of number facility. Neurologic signs were observed in seven of the eight subjects. Signs included symmetrical increase in deep tendon reflexes in the

TABLE 1-3 Probit Analysis for Response Criteria for Inhalation Exposure to Agent BZ

Response Criteria (TRI score)	Sample Size	ED_{50} (mg-min/m^3)	95% Confidence Limits (mg-min/m^3)
4.0	36	90.5	66.2-123.6
5.0	36	124.8	102.8-151.5
6.0	36	134.8	110.3-164.7
7.0	36	183.1	132.9-252.0

Source: Ketchum 1963.

TABLE 1-4 Cumulative Exposures and TRI Scores for Male Volunteers Exposed to Agent BZ

Subject Number	Minute Volume (L)	Body Weight	TRI Score	BZ (CT, mg-min/m^3)
1	12.4	160	4.4	64.8
2	16.8	165	7.1	84.7
3	13.8	145	6.3	68.3
4	11.9	190	4.2	46.0
5	13.8	145	4.6	71.2
6	18.8	200	5.4	82.2
7	14.8	160	6.3	54.0
8	23.1	190	6.8	72.9

Source: Ketchum et al. 1967.

lower extremities that progressed to ankle clonus and progressive deterioration of normal gait. Subjects also reported uncomfortable paresthesias of the lower extremities and diffuse, nonspecific weakness of all extremities which manifested as an unsteady gait, truncal weakness when sitting, and slow response to rebound testing. Additionally dysarthria (slow, slurred, and difficult to produce speech) was also noted in the subjects.

A maximum no-effect dose of 0.5-1.0 µg/kg for BZ in humans after intramuscular injection was reported by NRC (1982), and estimated median incapacitating inhalation concentrations of 101 mg-min/m^3 (base) and 112 mg-min/m^3 (hydrochloride) were reported by the U.S. Department of the Army (1974) for humans breathing rate at a rate of of 15 L/min.

2.3. Developmental and Reproductive Effects

No human developmental or reproductive toxicity data on BZ were available.

2.4. Genotoxicity

No human genotoxicity data on BZ were available.

2.5. Carcinogenicity

No data were found regarding the carcinogenic potential of BZ in humans.

2.6. Summary

Data regarding the health effects of BZ in humans following inhalation exposure are limited to military application studies. No lethality data are available. Results of experiments using carefully screened and evaluated informed human volunteers (male military personnel) qualitatively demonstrated that BZ would exert parasympatholytic effects (behavioral and cognitive dysfunction). Inhalation exposure experiments are limited to those conducted by Ketchum and colleagues (Ketchum 1963, 2006; Ketchum et al. 1967) in which responses of test subjects were characterized using a scoring system expressed as a TRI value on the basis of various cognitive parameters, blood pressure, and heart rate. Exposures were of short duration (minutes) and expressed as cumulative exposures (mg-min/m^3). An ICt_{50} of 60.1 mg-min/m^3 (95% CI: 41.3-87.5 mg-min/m^3) was reported by Ketchum et al. (1967).

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Monkeys

An LCt_{50} of 37,000 mg-min/m^3 for monkeys has been reported for BZ (U.S. Department of the Army 1974). The value was reportedly based on exposure durations of 6-25 min. No additional information is available.

3.1.2. Dogs

An LCt_{50} of 25,000 mg-min/m^3 for dogs has been reported for BZ (U.S. Department of the Army 1974). The value was reportedly based on exposure durations of 6-16 min. No additional information is available.

3.1.3. Rats

An LCt_{50} of 64,000 mg-min/m^3 for rats has been reported for BZ (U.S. Department of the Army 1974). The value was reportedly based on exposure durations of 5-30 min. No additional information is available.

3.1.4. Mice

An LCt_{50} of 12,000 mg-min/m^3 for mice has been reported for BZ (U.S. Department of the Army 1974). The value was reportedly based on exposure durations of 5-19 min. No additional information is available.

3.1.5. Rabbits

An LCt_{50} of 32,000 mg-min/m^3 for rabbits has been reported for BZ (U.S. Department of the Army 1974). The value was reportedly based on exposure durations of 15-40 min. No additional information is available.

3.1.6. Guinea Pigs

An LCt_{50} of 123,000 mg-min/m^3 for guinea pigs has been reported for BZ (U.S. Department of the Army 1974). The value was reportedly based on exposure durations of 5-30 min. No additional information is available.

3.1.7. Summary of Animal Lethality Data

LCt_{50} values have been reported for several species (U.S. Department of the Army 1974). Details of the experimental protocol and results are not available. All exposures were of relatively short durations (5-40 min), but the LCt_{50} values ranged from 12,000 to 123,000 mg-min/m^3 with no apparent relationship to body size. The mouse and guinea pig were at the low end and high end, respectively, of the range of lethality values.

3.2. Nonlethal Toxicity

The only animal data on the effects of inhalation exposure to BZ are from a study by Ketchum et al. (1967). Studies of the effects of aerosol exposure of monkeys, dogs, rabbits, and rats were conducted prior to involvement of human volunteers. All species were exposed simultaneously, so exposure parameters were identical across species.

3.2.1. Monkeys

Five monkeys were exposed head only to aerosols of BZ at concentrations of 575 mg-min/m^3 for 6 min and 10 seconds or at 164, 70, or 40 mg-min/m^3 for 8 min (Ketchum et al. 1967). Information about the monkeys' species, sex, and body weight were not reported. Effects were assessed at 4, 8, 16, 24, 32, 40, 48, 56, 64, and 72 h and at 7-days post-exposure (see Table 1-5). Aerosols were generated by a Mars generator as was done for the human experiments. A BZ concentration of 40 mg-min/m^3 at 500 yards (equivalent to 5 mg/m^3 for the 8-

min duration) was without detectable effect. Although qualitatively similar, the effects observed at 575 mg-min/m^3 (equivalent to 93 mg/m^3) tended to persist for longer periods (up to 7 days) compared with the lower exposures (40-164 mg-min/m^3) where effects started to resolve by 72 h.

An RCt_{50} (response dose for 50% of animals tested) of less than 1,000 mg-min/m^3 was reported by McNamara (1963; cited in Rosenblatt et al. 1977) on the basis of conditioned avoidance response testing. Exposure duration was not specified.

3.2.2. Dogs

Groups of six dogs (breed, sex, and body weight were not reported) were tested as described for the monkeys (Ketchum et al. 1967). Results of the experiments are summarized in Table 1-6.

McNamara (1963; cited in Rosenblatt et al. 1977) reported RCt_{50} values for BZ of <130 mg-min/m^3 on the basis of mydriasis, 200 mg-min/m^3 on the basis of sustained physical exercise, 250 mg-min/m^3 on the basis of conditioned avoidance response, 25 mg-min/m^3 on the basis of increased heart rate, and ~500 mg-min/m^3 on the basis of weakness in dogs. Exposure durations and details regarding the experimental protocol were not available.

3.2.3. Rabbits

Ketchum et al. (1967) also tested groups of six rabbits (strain, sex, and body weight were not reported) using the same protocol as for the monkeys and dogs. Effects were similar to those observed in those species (see Table 1-7).

TABLE 1-5 Effects of Agent BZ on Monkeys

Concentration (mg-min/m^3)	Duration	Conditions	Distance (yards)	Effects[a]
575	6 min, 10 sec	41°F, 67% relative humidity	100	Mydriasis, cycloplegia, tranquility, erratic behavior, lethargy, hyperactivity, sedation, ataxia.
No data[b]			500	Mydriasis, cycloplegia.
No data[b]			1,000	Mydriasis, cycloplegia.
164			100	Mydriasis, cycloplegia.
70	8 min	32°F, 63% relative humidity	300	Mydriasis, cycloplegia.
40			500	No effects.

[a]All effects occurring in monkeys at any time during the post-exposure observation period are noted, although not all monkeys exhibited all effects.
[b]Study report indicated "no samples".
Source: Ketchum et al. 1967.

McNamara (1963; cited in Rosenblatt et al. 1977) reported RCt_{50} values of 10-50 mg-min/m^3 on the basis of mydriasis in rabbits. Details of the experimental protocol were not provided.

TABLE 1-6 Effects of Agent BZ on Dogs

Concentration (mg-min/m^3)	Duration	Conditions	Distance (yards)	Effects[a]
575	6 min, 10 sec	41°F, 67% relative humidity	100	Mydriasis, cycloplegia, tranquility, erratic behavior, lethargy, hyperactivity, sedation, ataxia, increased heart rate.
No data[b]			500	Mydriasis, cycloplegia, tranquility, erratic behavior, lethargy, hyperactivity, sedation, ataxia, increased heart rate.
No data[b]			1,000	Mydriasis, cycloplegia, increased heart rate.
164	8 min	32°F, 63% relative humidity	100	Mydriasis, cycloplegia, tranquility, erratic behavior, lethargy, hyperactivity, sedation, ataxia, increased heart rate, apprehension.
70			300	Mydriasis, cycloplegia, ataxia, lethargy, hyperactivity, increased heart rate.
40			500	No effects.

[a]All effects occurring in dogs at any time during the post-exposure observation period are noted, although not all dogs exhibited all effects.
[b]Study report indicated "no samples".
Source: Ketchum et al. 1967.

TABLE 1-7 Effects of Agent BZ on Rabbits

Concentration (mg-min/m^3)	Duration	Conditions	Distance (yards)	Effects[a]
575	6 min, 10 sec	41°F, 67% relative humidity	100	Mydriasis, cycloplegia.
No data[b]			500	Mydriasis, cycloplegia, salivation.
No data[b]			1,000	Mydriasis, cycloplegia.
164			100	Mydriasis, cycloplegia, respiratory distress, ataxia.
70	8 min	32°F, 63% relative humidity	300	Mydriasis, cycloplegia, hyperpnea, ataxia.
40			500	Mydriasis, cycloplegia.

[a]All effects occurring in rabbits at any time during the post-exposure observation period are noted, although not all rabbits exhibited all effects.
[b]Study report indicated "no samples".
Source: Ketchum et al. 1967.

3.2.4. Rats

Groups of 20 rats (strain, sex, and body weight were not reported) were exposed simultaneously with the monkeys, dogs, and rabbits in the Ketchum et al. (1967) study. With the exception of dyspnea (4/20 rats) and ataxia (1/20 rats) at 4 h post-exposure, no effects were observed in any of the rats at any exposure.

3.2.5. Summary of Nonlethal Toxicity in Animals

Information on the nonlethal toxicity of BZ in animals is limited to data from Ketchum et al. (1967) and McNamara (1963). Results of the Ketchum et al. (1967) study showed that monkeys, dogs, and rabbits exhibited qualitatively similar responses to BZ. Mydriasis and cycloplegia were consistently observed in all species. Other effects varied and included ataxia, lethargy, sedation, erratic behavior, weakness, and hyperactivity. Generally, the effects were most pronounced at 4- and 8-h post-exposure and, with the exception of cycloplegia, tended to resolve within 24-48 h. Cycloplegia was frequently observed in all species through the 7-day post-exposure observation period. Exposures to BZ were all of short duration (6-8 min). McNamara (1963) reported that dogs, rabbits, and monkeys exhibited similar responses along with some behavioral modifications at cumulative exposures of 10 to ~1,000 mg-min/m^3.

3.3. Developmental and Reproductive Effects

Data regarding the developmental and reproductive toxicity of BZ following inhalation exposures were not available.

3.4. Genotoxicity

No information regarding the genotoxicity of BZ was available.

3.5. Carcinogenicity

No data with which to evaluate the carcinogenic potential of BZ were available.

3.6. Summary

Toxicity data on BZ are extremely limited. Both the human and animal data are from experiments with short exposure durations (minutes). The only available inhalation exposure data are expressed in cumulative exposure terms (mg-min/m^3) and are not precisely characterized. Qualitatively, the effects of BZ

appear to be similar across species. The ability to detect, interpret, and quantify behavioral and cognitive dysfunction characteristic of BZ exposure in laboratory animals is difficult. On the basis of tests with human volunteers, Ketchum et al. (1967) estimated an ICt_{50} of 60.1 mg-min/m^3 (95% CI: 41.3-87.5 mg-min/m^3).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

BZ hydrolyzes in aqueous environments to benzilic acid and 3-quinuclidinol. It is reportedly excreted primarily in the urine (Byrd et al. 1992). In rats, about 3% of a dose (route not specified) is excreted unchanged in the urine.

4.2. Mechanism of Toxicity

BZ is an anticholinergic agent similar in its pharmacologic action to atropine and scopolamine although more potent than both (Ketchum and Sidell 1997). It exhibits a preferential affinity for muscarinc cholinergic receptors in the brain, heart, and smooth muscle, resulting in inhibition of functions mediated through acetylcholine activation of these receptors. For both humans and animals, there is a latency period of about 30 min to several hours or more regardless of exposure route. Longer latency periods are associated with percutaneous exposures.

4.3. Structure-Activity Relationships

No data regarding structure-activity relationships that would be instrumental in developing AEGL values for BZ were available.

4.4. Species Variability

Ketchum et al. (1967) tested monkeys, dogs, rabbits, and rats in their studies. Results of their preliminary tests suggested that rats are less sensitive than the other species tested. The U.S. Department of the Army (1974) found that guinea pigs were even less sensitive than rats.

4.5. Concurrent Exposure Issues

No relevant data regarding concurrent exposure issues were available.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

No quantitative data on BZ relevant to AEGL-1 effects in humans were available.

5.2. Animal Data Relevant to AEGL-1

No animal data on BZ relevant to AEGL-1 effects in humans were available. No-effect levels in animals were reported, but assessment of cognitive and behavioral effects (major effects of BZ) were not possible.

5.3. Derivation of AEGL-1 Values

It is not possible to develop AEGL-1 values for BZ with scientific rigor. Although data on exposures resulting in no apparent effects in animals are available, the experiments could not assess possible cognitive and behavioral effects characteristic of BZ that are relevant to humans. Human data on BZ that define no-effect levels or that are consistent with the AEGL-1 definition are not available. Thus, AEGL-1 values for BZ are not recommended.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

Studies by Ketchum and colleagues (Ketchum 1963, 2006; Ketchum et al. 1967) are relevant to developing AEGL-2 values. Effects of BZ were characterized in these studies by a scoring system expressed as TRI values, which were based on cognitive parameters, blood pressure, and heart rate. All exposures were of short duration (about 20 min) and were expressed as cumulative exposures (CT; mg-min/m^3). An ICt_{50} of 60.1 mg-min/m^3 (95% CI: 41.3-87.5 mg-min/m^3) was reported by Ketchum et al. (1967). CT products of 46-261 mg-min/m^3 were associated with high TRI scores, which are indicative of effects well exceeding the severity of an AEGL-2 threshold (see Section 2.2). No human lethality data are available, but lethal exposures to humans were estimated by Ketchum (1963). Estimates were made by extrapolation of animal data on the basis of body weight, extrapolation of the lethality ratio of BZ and atropine in animals to humans, and extrapolation of the ratio of physiologic effectiveness (parasympatholytic effects) between BZ and atropine in humans. LD_{50} values were estimated to be 2-5 mg/kg (on the basis of species weight), 0.3-1.4 mg/kg

(on the basis of atropine lethality ratio), and 0.2-1.2 mg/kg (on the basis of the relative effectiveness ratio of atropine and BZ). Conversion of the doses to concentrations of BZ in air was not provided.

6.2. Animal Data Relevant to AEGL-2

Results of studies with laboratory animals (monkeys, dogs, rabbits, and rats) showed that exposure to BZ at 40-575 mg-min/m^3 for very short durations (6 and 8 min) generally produced nonlethal effects (mydriasis, cycloplegia, and salivation) consistent with exposure to a parasympatholytic agent. Rats appeared to be especially resistant, because none of the exposures resulted in notable effects. Monkeys and dogs also showed no effect when exposed to BZ at 40 mg-min/m^3. Studies in animals could not assess cognitive and behavioral effects as evaluated for human volunteer subjects. No animal lethality data are available.

6.3. Derivation of AEGL-2 Values

On the basis of tests with human volunteers, Ketchum et al. (1967) estimated an ICt_{50} of 60.1 mg-min/m^3 for a 165-pound human with a breathing rate of 15 L/min. A one-third reduction of the ICt_{50} (60.1 mg-min/m^3 ÷ 3 = 20 mg-min/m^3 or 4 mg/m^3) was considered an estimated threshold for incapacitating effects. A one-third reduction is often used to estimate a no-effect level (in this case, the highest concentration that is not expected to cause incapacitation) from an effect level (in this case, a concentration that incapacitates 50% of exposed persons). Comparison of the estimated threshold level and other possible point of departures for AEGL-2 values suggests that this estimate is likely to be protective. The point of departure of 20 mg-min/m^3 is less than the lower limit of the ICt_{50} (41.3 mg-min/m^3), which was considered too severe to serve as a point of departure because it could result in incapacitation. The threshold level is also lower than the one associated with clinical signs that might impair the ability to escape (e.g., progressive deterioration of normal gait and uncomfortable paresthesias of lower extremities reported by subjects exposed to BZ at 46.0-84.7 mg-min/m^3 [or 9.2-16.9 mg/m^3] for 5 min) (Ketchum et al. 1967) and the median incapacitation concentration of 101 mg-min/m^3 for humans breathing at a rate of 15 L/min (U.S. Department of the Army 1974). Additionally, experiments with four animal species indicated that 40 mg-min/m^3 was a no-effect level in monkeys, dogs, and rats (Ketchum et al. 1967); cycloplegia and mydriasis were observed in rabbits exposed at that concentration. Applying an inter-species uncertainty factor of 3 to the animal no-effect levels results in a CT product of 13.3 mg-min/m^3, which is similar but somewhat lower than the aforementioned point of departure of 20 mg-min/m^3. In the absence of definitive concentration-response data, this comparison supports the point of departure for development of AEGL-2 values.

Data with which to assess the concentration-time relationship for BZ are not available. Experiments conducted by Ketchum and colleagues were of short durations; 6-8 min in animal studies and possibly no more than 5 min in tests with human volunteers. The concentration-time relationship for many irritant and systemically acting vapors and gases may be described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived exponent (n) and to obtain protective AEGL values, time scaling was performed using the default of n = 1 to extrapolate to the longer AEGL-specific exposure durations. Nonlethal effects of BZ are totally reversible. Because of the paucity of data for longer-term exposures, AEGL-2 values for the 4-h and 8-h durations were not developed and are not recommended. Effects observed in the human studies are likely due to the anticholinergic properties of BZ; structures of muscarinic receptors are highly conserved in humans and, thus, receptor affinity is not likely to vary among individuals. For example, very few polymorphisms in the M1 receptor (associated with learning and memory) have been detected and polymorphisms at highly conserved sites that might disrupt function of the receptor are rare (Lucas et al. 2001). However, individuals with pre-existing conditions may be more sensitive to the anticholinergic properties of BZ than the healthy men tested in the Ketchum studies. An intraspecies uncertainty factor of 10 accounts for possible pharmacokinetic differences and possible increased sensitivity between individuals. A modifying factor of 3 was applied to account for uncertainties in the overall database, particularly the short exposure duration (5 min) of the critical study.

AEGL-2 values for BZ are presented in Table 1-8 and their derivation is summarized in Appendix A.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No data regarding lethality in humans resulting from inhalation exposure to BZ are available. Ketchum and colleagues estimated human LD_{50} values of 2-5 mg/kg (extrapolation by species weight), 0.3-1.4 mg/kg (extrapolation by atropine lethality ratio), and 0.2-1.2 mg/kg (extrapolation by relative effectiveness ratio of atropine and BZ). Conversion of these doses to a concentration of BZ in air was not provided.

TABLE 1-8 AEGL-2 Values for Agent BZ

10 min	30 min	1 h	4 h	8 h
0.067 mg/m^3	0.022 mg/m^3	0.011 mg/m^3	Not recommended	Not recommended

7.2. Animal Data Relevant to AEGL-3

Lethality data for several laboratory species have been reported in the form of LCt_{50} values (U.S. Department of the Army 1974). These values had little or no accompanying information. The LCt_{50} was 37,000 mg-min/m^3 in monkeys exposed for 6-25 min, 25,000 mg-min/m^3 in dogs exposed for 6-16 min, 64,000 mg-min/m^3 in rats exposed for 5-30 min, 12,000 mg-min/m^3 in mice exposed for 5-19 min, 32,000 mg-min/m^3 in rabbits exposed for 15-40 min, and 123,000 mg-min/m^3 in guinea pigs exposed for 5-30 min. No information is available regarding the concentration-response relationship for inhaled BZ. In the Ketchum et al. (1967) study, even the highest concentration (575 mg-min/m^3 for 8-min duration) was without serious effect.

7.3. Derivation of AEGL-3 Values

No human data with which to develop AEGL-3 values for BZ are available. Several of the human exposures reported by Ketchum (1963) and Ketchum et al. (1967) were associated with high TRI scores indicative of notable cognitive and behavioral effects and some motor function effects but no apparent serious physiologic responses. Effects were reversed 7-days post-exposure with no medical intervention. Other human studies have uncertainties inherent in the exposure-route extrapolations that would be required if using human LC_{50} estimates (Ketchum 1963) or if using the non-verifiable LCt_{50} of 200,000 mg-min/m^3 estimated by Hoenig (2007). Thus, animal studies were used as the basis for deriving AEGL-3 values.

LCt_{50} values for animals are based on relatively short exposure durations (5-40 min). The LCt_{50} for the monkey (37,000 mg-min/m^3) is neither the highest nor lowest value of the six species tested, but the monkey is a better model for aerosol inhalation exposure in humans than the other species. The monkey LCt_{50} was decreased 10-fold to 3,700 mg-min/m^3, as an estimate of the lethality threshold and a point of departure for AEGL-3 derivation. Although a one-third reduction of the LC_{50} is often considered an appropriate estimate of the lethality threshold for chemicals with steep concentration-response relationships (NRC 2001), little is known about the concentration-response curve for BZ. Therefore, the 10-fold reduction is considered more defensible. Time scaling was performed using the equation $C^n \times t = k$, with $n = 1$ to extrapolate to the longer AEGL-specific exposure durations. A factor of 10 was applied for interspecies differences because no lethality data are available for humans and LCt_{50} values for five animal species varied 10-fold. An intraspecies uncertainty factor of 10 was applied to account for possible pharmacokinetic differences and possible increased sensitivity between individuals. Effects observed in humans are likely due to the anticholinergic properties of BZ; structures of muscarinic receptors are highly conserved in humans and, thus, receptor affinity (and, therefore, toxicodynamics) is not likely to vary among individuals. For example, very few

polymorphisms in the M1 receptor (associated with learning and memory) have been detected and polymorphisms at highly conserved sites that might disrupt function of the receptor are rare (Lucas et al. 2001). However, individuals with pre-existing conditions may be sensitive to the anticholinergic effects of BZ. A modifying factor of 3 was applied because of uncertainties in the database, particularly a lack of incidence data (lethality studies only reported LCt_{50} values) which could be used to estimate a LC_{01} and a lack of studies involving longer exposure durations (longest duration was 40 min). AEGL-3 values for the 4- and 8-h durations are not recommended because data on exposure durations longer than 1 h are lacking.

AEGL-3 values for BZ are presented in Table 1-9 and their derivation is summarized in Appendix A.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

AEGL values for BZ are presented in Table 1-10. The available data do not allow for assessing a minimal-effect threshold appropriate for developing AEGL-1 values. For AEGL-2 values, the point of departure was selected on the basis of preventing cognitive, behavioral, or physiologic effects. Cognitive and behavioral effects resulting from the anticholinergic activity of BZ are the most relevant effects (incapacitation) regarding human exposure to this chemical. Data for the AEGL-2 assessment are from extensive experiments using informed, human volunteers who underwent extensive screening prior to participation in the studies. AEGL-3 values were developed on the basis of LCt_{50} values in laboratory animals; the monkey was selected as the best animal model for humans. The anticholinergic (parasympatholytic) effects of BZ exhibit a notable latency (several hours or more) and are long-lasting (several days) following only brief exposure, but are reversible. Estimates of lethality thresholds for humans and lethality data in animals indicate a large margin between induction of incapacitating effects and lethality.

8.2. Comparisons with Other Standards and Guidelines

No guidelines or standards were available for BZ.

8.3. Data Adequacy and Research Needs

Human exposure data from controlled experiments adequately describe the incapacitating effects of BZ. Concentration-response data for inhalation exposures are lacking compared with data on other exposure routes. Data in animals are adequate for assessing lethality, although definitive lethality threshold data are lacking and effects of exposures for several hours are uncertain.

TABLE 1-9 AEGL Values for Agent BZ

10 min	30 min	1 h	4 h	8 h
1.2 mg/m^3	0.41 mg/m^3	0.21 mg/m^3	Not recommended	Not recommended

TABLE 1-10 AEGL Values for Agent BZ

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)[a]	NR	NR	NR	NR	NR
AEGL-2 (disabling)	0.067 mg/m^3	0.022 mg/m^3	0.011 mg/m^3	NR	NR
AEGL-3 (lethal)	1.2 mg/m^3	0.41 mg/m^3	0.21 mg/m^3	NR	NR

NR: not recommended because of data deficiencies.

[a]Absence of AEGL-1 values does not imply that exposure to concentrations less than the AEGL-2 values is without effect.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR AGENT BZ

Derivation of AEGL-1 Values

Although exposures to BZ resulting in no apparent effects in animals were available, the experiments could not assess possible cognitive and behavioral effects characteristic of BZ that are relevant to humans. Human data on BZ that define no-effect levels or that are consistent with the AEGL-1 definition were not available. Thus, AEGL-1 values for BZ are not recommended.

Derivation of AEGL-2 Values

Key study:	Ketchum, J.S., B.R. Tharp, E.B. Crowell, D.L. Sawhill, and M.E. Vancil. 1967. The Human Assessment of BZ Disseminated Under Field Conditions Edgewood Arsenal Technical Report EATR 4140.U.S. Department of the Army, Medical Research Laboratory, Edgewood Arsenal, MD.
Critical effect:	Point of departure is 20 mg-min/m^3. Value was calculated as one-third of the ICt_{50} (a concentration-time product causing incapacitation of 50% of the test subjects) of 60.1 mg-min/m^3 (95% CI: 41.3-87.5 mg-min/m^3), and was considered an estimated threshold for incapacitating effects in humans. The one-third reduction was considered sufficient because it was well below the lower confidence limit of the ICt_{50}, and is lower than concentrations (46.0-84.7 mg-min/m^3) associated with clinical signs that might impair the ability to escape (e.g., progressive deterioration of normal gait and uncomfortable paresthesias of lower extremities).
Time scaling:	Data with which to assess the concentration-time relationship for BZ toxicity are not available. Experiments conducted by Ketchum and colleagues were of short durations; 6-8 min in animal studies and possibly no more than 5 min in tests with human volunteers. The concentration-time relationship for many irritant and systemically acting vapors and gases may be described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten

	Berge et al. 1986). In the absence of an empirically derived exponent (n) and to obtain protective AEGL values, time scaling was performed using a default of n = 1 for extrapolating from shorter exposures to longer duration.
Uncertainty factors:	1 for interspecies differences, because data were from human volunteers. 10 for intraspecies variability. The structures of muscarinic receptors are highly conserved in humans and, thus, receptor affinity is not likely to vary among individuals; however, some individuals with pre-existing conditions may be sensitive to the anticholingeric effects of BZ. Total uncertainty factor of 10
Modifying factor:	3 because of deficiencies in overall data, particularly lack of longer duration studies
Calculation:	
10-min AEGL-2:	$C = 20$ mg-min/m^3 ÷ 10 min = 2 mg/m^3 $C = 2$ mg/m^3 ÷ 30 = 0.067 mg/m^3
30-min AEGL-2:	$C = 20$ mg-min/m^3 ÷ 30 min = 0.667 mg/m^3 $C = 0.667$ mg/m^3 ÷ 30 = 0.022 mg/m^3
1-h AEGL-2:	$C = 20$ mg-min/m^3 ÷ 60 min = 0.33 mg/m^3 $C = 0.33$ mg/m^3 ÷ 30 = 0.011 mg/m^3
4-h AEGL-2:	Not recommended because of uncertainties regarding longer-term exposures.
8-h AEGL-2:	Not recommended because of uncertainties regarding longer-term exposures.

Derivation of AEGL-3 Values

Key study:	U.S. Department of the Army. 1974. Pp. 109-113 in Chemical Agent Data Sheets, Volume 1. Edgewood Arsenal Special Report AD 0030. U.S. Department of the Army, Edgewood Arsenal, Aberdeen Proving Ground, MD.

Critical effect:	Lethality threshold estimated as one-tenth of the LCt_{50} of 37,000 mg-min/m^3 for monkeys exposed to BZ for 6-25 min.
Time scaling:	Data with which to assess the concentration-time relationship for BZ toxicity are not available. The experiments conducted by Ketchum and colleagues were of short durations; 6-8 min in animal studies and possibly no more than 5 min in tests with human volunteers. The concentration-time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived exponent (n) and to obtain protective AEGL values, time scaling was performed using the default of n = 1 for extrapolating from shorter exposures to longer duration.
Uncertainty factors:	10 for interspecies differences; no lethality data are available for humans and LCt_{50} values for five animal species varied 10-fold. 10 for intraspecies variability; BZ toxicity is due to an anticholinergic mechanism and the structures of muscarinic receptors are highly conserved in humans, so receptor affinity (and, therefore, toxicodynamics) is not likely to vary among individuals; however, some individuals with pre-existing conditions may be sensitive to the anticholinergic effects of BZ.
Modifying factor:	3 because of deficiencies in overall data, in particular a lack of incidence data (the available lethality studies only reported LCt_{50} values) which could be used to estimate a LC_{01} and studies involving longer exposure durations (the longest duration exposure was 40 min).
Calculation:	
10-min AEGL-3:	C = 3,700 mg-min/m^3 ÷ 10 min = 370 mg/m^3 C = 370 mg/m^3 ÷ 300 = 1.2 mg/m^3
30-min AEGL-3:	C = 3,700 mg-min/m^3 ÷ 30 min = 123.3 mg/m^3 C = 123.3 mg/m^3 ÷ 300 = 0.41 mg/m^3

1-h AEGL-3:	$C = 3{,}700$ mg-min/m^3 ÷ 60 min = 61.67 mg/m^3 $C = 61.67$ mg/m^3 ÷ 300 = 0.21 mg/m^3
4-h AEGL-3:	Not recommended because of uncertainties regarding longer-term exposures.
8-h AEGL-3:	Not recommended because of uncertainties regarding longer-term exposures.

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR AGENT BZ

Derivation Summary

AEGL-1 VALUES

Data on BZ were insufficient for deriving AEGL-1 values. Absence of AEGL-1 values does not imply that exposure below the AEGL-2 values are without adverse effects.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.067 mg/m^3	0.022 mg/m^3	0.011 mg/m^3	Not recommended	Not recommended

Reference: Ketchum, J.S., B.R. Tharp, E.B. Crowell, D.L. Sawhill, and M.E. Vancil. 1967. The Human Assessment of BZ Disseminated Under Field Conditions. Edgewood Arsenal Technical Report EATR 4140.U.S. Department of the Army, Medical Research Laboratory, Edgewood Arsenal, MD.

Test species/Strain/Sex/Number: Human volunteers, males, n = 8

Exposure route/Concentrations/Durations: Aerosol inhalation

Effects: Cognitive and behavioral effects, mild effects on heart rate and blood pressure. ICt_{50} of 60.1 mg-min/m^3 (95% CI: 41.3-87.5 mg-min/m^3; presumably for 5 min) for a 165-pound human with a breathing rate of 15 L/min. An ICt_{50} is a concentration-time product causing incapacitation of 50% of the test subjects.

End point/Concentration/Rationale: Point of departure is 20 mg-min/m^3 (one-third of the ICt_{50}). One-third of the ICt_{50} was considered an estimated threshold for incapacitating effects in humans. The reduction was considered sufficient because it was well below the lower confidence limit of the ICt_{50} and concentrations associated with clinical signs which might impair the ability to escape (e.g., progressive deterioration of normal gait and uncomfortable paresthesias of lower extremities reported by subjects exposed to BZ at 46.0-84.7 mg-min/m^3). BZ effects are totally reversible.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 1, because data were from human volunteers
Intraspecies: 10, although the anticholinergic mechanism by which BZ operates is not likely to vary between individuals because the structure of muscarinic receptors are highly conserved in humans, individuals with pre-existing conditions may be sensitive to the antimuscarinic effects of BZ.

Modifying factor: 3, incomplete data base.

Animal-to-human dosimetric adjustment: Not applicable
Time scaling: Experimental data on BZ were expressed as CT products (mg-min/m^3). For AEGL-specific exposure durations, all of which involved extrapolating to longer time frames, the concentrations were determined using the default of n = 1.
Data adequacy: Although definitive concentration-response information for inhalation exposure to BZ is lacking, data regarding human response to inhaled BZ aerosol are available and sufficient for developing AEGL-2 values.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
1.2 mg/m^3	0.41 mg/m^3	0.21 mg/m^3	Not recommended	Not recommended
Reference: U.S. Department of the Army. 1974. Pp. 109-113 in Chemical Agent Data Sheets, Volume 1. Edgewood Arsenal Special Report AD 0030. U.S. Department of the Army, Edgewood Arsenal, Aberdeen Proving Ground, MD.				
Test species/Strain/Sex/Number: Monkeys; species, gender, and number not reported.				
Exposure route/Concentrations/Durations: Aerosol inhalation; LCt_{50} of 37,000 mg-min/m^3 based on exposure durations of 6-25 min.				
Effects: LCt_{50} of 37,000 mg-min/m^3 based on exposure durations of 6-25 min.				
End point/Concentration/Rationale: Lethality threshold estimated as one-tenth of LCt_{50}; definitive information regarding the concentration-response relationship for BZ is lacking.				
Uncertainty factors/Rationale: Total uncertainty factor: 100 Interspecies: 10, no lethality data are available for humans and LCt_{50} values for five animal species varied 10-fold. Intraspecies: 10, the anticholinergic mechanism by which BZ operates is not likely to vary between individuals because the structure of muscarinic receptors are highly conserved in humans; however, individuals with pre-existing conditions may be sensitive to the anticholingeric effects of BZ.				
Modifying factor: 3, incomplete data base (e.g., incidence data and studies involving longer exposure durations).				
Animal-to-human dosimetric adjustment: Not applicable				
Time scaling: Experimental data for BZ were consistently expressed as CT products (mg-min/m^3). For AEGL-specific exposure durations, all of which involved extrapolating to longer time frames, the concentrations were determined using the default of n = 1.				
Data adequacy: LCt_{50} values are available for five species but experimental details are lacking. Data are considered sufficient for deriving AEGL-3 values which can be compared with human exposure data.				

APPENDIX C

CATEGORY PLOT FOR AGENT BZ

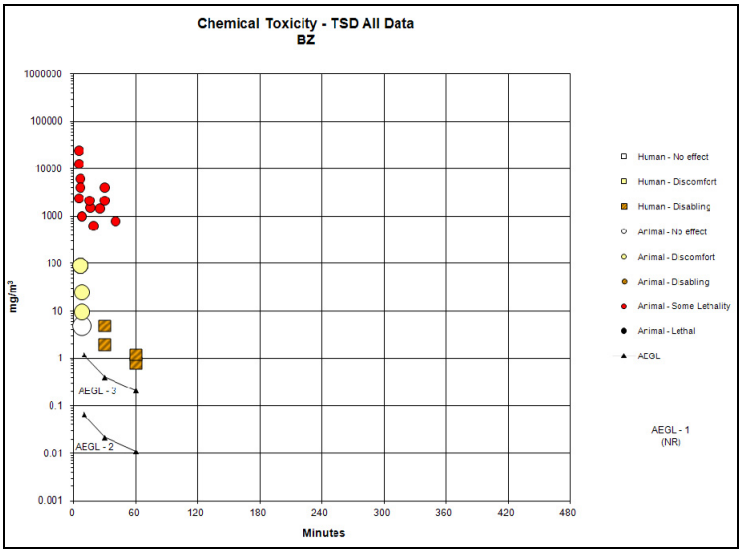

FIGURE C-1 Category plot of animal and human data and AEGL values for Agent BZ. Response data for BZ were routinely expressed as a CT products (concentration × time) of mg-min/m^3. Data points were derived for the lowest and highest exposure durations for which the CT values were determined, as well as for AEGL-specific durations within or near the respective range of the experimental exposure durations.

TABLE C-1 Data Used in Category Plot for Agent BZ

Source	Species	No. Exposures	mg/m^3	Minutes	Category	Comments
NAC/AEGL-1			NR	10	AEGL	
NAC/AEGL-1			NR	30	AEGL	
NAC/AEGL-1			NR	60	AEGL	
NAC/AEGL-1			NR	240	AEGL	
NAC/AEGL-1			NR	480	AEGL	
NAC/AEGL-2			0.067	10	AEGL	
NAC/AEGL-2			0.022	30	AEGL	
NAC/AEGL-2			0.011	60	AEGL	
NAC/AEGL-2			NR	240	AEGL	
NAC/AEGL-2			NR	480	AEGL	
NAC/AEGL-3			1.2	10	AEGL	

(Continued)

TABLE C-1 Continued

Source	Species	No. Exposures	mg/m^3	Minutes	Category	Comments
NAC/AEGL-3			1.2	10	AEGL	
NAC/AEGL-3			0.41	30	AEGL	
NAC/AEGL-3			0.21	60	AEGL	
NAC/AEGL-3			NR	240	AEGL	
NAC/AEGL-3			NR	480	AEGL	
Ketchum 1963	Human	1	2	30	2	
	Human	1	5	30	2	
	Human	1	0.8	60	2	
	Human	1	1.2	60	2	
Department of the Army 1974	Monkey	1	6,167	6	SL	LCt_{50}
	Monkey	1	1,480	25	SL	LCt_{50}
	Dog	1	4,167	6	SL	LCt_{50}
	Dog	1	1,563	16	SL	LCt_{50}
	Rat	1	12,800	5	SL	LCt_{50}
	Rat	1	2,133	30	SL	LCt_{50}
	Mouse	1	2,400	5	SL	LCt_{50}
	Mouse	1	632	19	SL	LCt_{50}
	Rabbit	1	2,133	15	SL	LCt_{50}
	Rabbit	1	800	40	SL	LCt_{50}
	Guinea pig	1	24,600	5	SL	LCt_{50}
	Guinea pig	1	4,100	30	SL	LCt_{50}
Ketchum et al. 1967	Monkey	1	93	6.17	1	Mydriasis, cycloplegia, tranquility, erratic behavior, lethargy, hyperactivity, sedation, ataxia
	Dog	1	93	6.17	1	Mydriasis, cycloplegia, tranquility, erratic behavior, lethargy, hyperactivity, sedation, ataxia, increased heart rate
	Dog	1	5	8	0	
	Rabbit	1	93	6.17	1	Mydriasis, cycloplegia
	Dog	1	1,000	8	SL	RCt_{50}
	Dog	1	25	8	1	
	Rabbit	1	10	8	1	RCt_{50}
	Rabbit	1	1,000	8	SL	

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