Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 19

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VOLUME 19

Committee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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Preface

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

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

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

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

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

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

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

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

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

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

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

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

DEDICATION

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

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Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 19

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

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

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

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

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

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

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

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

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

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

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

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

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

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

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

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

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

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

REVIEW OF AEGL REPORTS

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

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

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

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

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Appendixes

4

Pentaborane[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 Sylvia Milanez (Oak Ridge National Laboratory), Gary Diamond (SRC, Inc.), Lisa Ingerman (SRC, Inc.), Chemical Manager George Woodall (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

Pentaborane is a very flammable, colorless liquid that is insoluble in water, but hydrolyzes over several hours to form boric acid, hydrogen, and heat. It is a strong reducer and reacts with ammonia, organic amines, and unsaturated hydrocarbons. Human and animal studies have shown that pentaborane primarily causes central nervous system (CNS) toxicity. Symptoms in humans include dizziness, drowsiness, headache, hiccups, impaired judgment, incoordination, muscle spasms, and convulsions. Animals experience tremors, salivation, miosis (constriction of pupils), lethargy, aggressiveness, and convulsions.

AEGL-1 values were not developed for pentaborane because no relevant human or animal studies were available. Human studies found either no effects or CNS toxicity that was more severe than those defined by AEGL-1.

The AEGL-2 values are based on a no-effect level for CNS toxicity in dogs. The end point was selected to avoid even minor effects on CNS function, which could impair judgment and result in accidents and injury (Mindrum 1964). Dogs were exposed to pentaborane for 60 min for 5 days, and neurotoxicity was assessed through their performance in a conditioned avoidance response (CAR) test and through behavioral observations (Weir et al. 1964). A single exposure to pentaborane at 1.4 ppm caused no neurologic signs or delays in the CAR test, and was used as the point-of-departure. Dogs exposed at 1.4 ppm a second time (the following day), however, began to exhibit CNS effects, including decreased activity, miosis, and CAR delays, and additional exposures caused irritability and aggres-

siveness. A total uncertainty factor of 10 was applied. An interspecies uncertainty factor of 3 was used because pentaborane causes similar effects (CNS toxicity) in humans and four species of laboratory animals, and acute lethality values varied less than 3-fold among the species. An intraspecies uncertainty factor of 3 was applied because the homogeneous response among species and the steep concentration-response curve for lethality indicate that there would be little variability among humans. Concentrations were scaled across time using the equation $C^n \times t = k$ (ten Berge et al. 1986). An empirical value for n of 1.3 was determined by linear-regression analysis of acute lethality data from studies of rats (Weir et al. 1961, 1964). The AEGL-2 values are supported by studies in monkeys exposed for 2 min and dogs exposed for 5 min (Weeks et al. 1964), which would have yielded similar or higher AEGL-2 values. These studies were not used because the exposure durations were too short, and the monkeys were not subjected to the CAR test.

The AEGL-3 values are based on an acute lethality study in which mice were exposed to pentaborane at 6.9-11.6 ppm for 60 min (Weir et al. 1961, 1964). Mice had tremors, ataxia, convulsions, and red exudate around the mouth and nose, and death occurred within 24 h. Benchmark dose software (EPA Version 2.4.0) was used to calculate LC_{50} (lethal concentration, 50% lethality), $BMCL_{05}$ (benchmark concentration, 95% lower confidence limit with 5% response), and BMC_{01} (benchmark concentration with 1% response) values of 7.75, 5.08, and 6.04 ppm, respectively. The AEGL-3 point-of-departure was the $BMCL_{05}$ of 5.08 ppm, which was considered an estimate of the threshold for lethality in mice. A total uncertainty factor of 10 was applied and concentrations were scaled across time for the same reasons as described for the AEGL-2 values. The AEGL-3 values are supported by the lethality data from mice exposed for 4 h (Feinsilver et al. 1960), rats exposed for 5-60 min (Weir et al. 1961, 1964), monkeys exposed for 2 min (Weeks et al. 1964), and dogs exposed for 2-15 min (Weeks et al. 1964), which would have yielded similar AEGL-3 values.

The AEGL values for pentaborane are presented in Table 4-1.

TABLE 4-1 AEGL Values for Pentaborane

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)	0.56 ppm (1.4 mg/m^3)	0.24 ppm (0.62 mg/m^3)	0.14 ppm (0.36 mg/m^3)	0.048 ppm (0.12 mg/m^3)	0.028 ppm (0.072 mg/m^3)	No-effect level for CNS toxicity in dogs (Weir et al. 1964)
AEGL-3 (lethal)	2.0 ppm (5.2 mg/m^3)	0.87 ppm (2.2 mg/m^3)	0.51 ppm (1.3 mg/m^3)	0.17 ppm (0.44 mg/m^3)	0.10 ppm (0.26 mg/m^3)	Lethality threshold ($BMCL_{05}$) for mice (Weir et al. 1961, 1964)

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

1. INTRODUCTION

Pentaborane is a very flammable liquid and has a pungent odor (HSDB 2006). It is used in catalysts, corrosion inhibitors, and fluxing agents, and as an experimental jet and rocket fuel in air-breathing engines and (HSDB 2006; Lewis 2007). Pentaborane is manufactured by the hydrogenation of diborane. Two US manufacturers of pentaborane are listed in the Hazardous Substances Data Bank (HSDB 2006), but no production volumes are specified. A different source indicates that pentaborane is not commercially available in significant quantities (Schubert 2000).

Pentaborane is not soluble in water, but hydrolyzes over a period of several hours to form boric acid, hydrogen, and heat. It is a member of a class of chemicals known as the boron hydrides or boranes, which are strong reducers and react with ammonia, organic amines, and unsaturated hydrocarbons.

Selected chemical and physical properties of pentaborane are presented in Table 4-2.

TABLE 4-2 Chemical and Physical Properties of Pentaborane

Parameter	Value	References
Synonyms	Pentaboron nonahydride; pentaborane 9; dihydropentaborane	HSDB 2006
CAS registry no.	19624-22-7	HSDB 2006
Chemical formula	B_5H_9	HSDB 2006
Molecular weight	63.17	HSDB 2006
Physical state	Colorless liquid	HSDB 2006
Melting point	-46.6°C	HSDB 2006
Boiling point	60°C; 58°C	HSDB 2006; Lewis 2007
Density/specific gravity	0.61 at 0-4°C	HSDB 2006
Vapor density (air = 1)	2.2	HSDB 2006
Solubility in water	Decomposes at 150°C; hydrolyzes slowly in water	HSDB 2006
Vapor pressure	171 mmHg at 20°C; 66 mmHg at 0°C	HSDB 2006
Flammability limits	Lower limit = 0.42%; upper limit = 98%; flash point = 30°C (closed cup); autoignition at 35°C	HSDB 2006
Conversion factors	1 ppm = 2.58 mg/m^3 1 mg/m^3 = 0.388 ppm	NIOSH 2011

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

2.1.1. Case Reports

During the process of detoxifying old canisters filled with pentaborane gas at an industrial site in Virginia, two workers were seriously injured and one died (Yarbrough et al. 1984). The air concentrations of pentaborane were unknown. The most acutely exposed worker began having convulsions 4 min after dermal contact, and 4 min later had an opisthotonic spasm and went limp. He had erythema and marked congestion of the conjunctiva and oral mucous membranes. An electroencephalogram (EEG) conducted 6 h after the exposure revealed no electrical activity, and the worker died 8 days later. Autopsy revealed severe necrotizing pneumonia, fatty changes with centrilobular degeneration in the liver, brain degeneration, and lack of mature spermatozoa in the testicles. The second worker had similar effects but survived. He was in a coma for 4 months, after which he had muscle weakness, incoordination, limited vision, and severe cortical atrophy and ventricular dilation (detected by a computed tomography [CT] scan). The third worker suffered numerous myoclonic jerks, several grand mal seizures, disorientation, agitation, and hallucinations, and had an abnormal EEG. He was discharged after 11 days with no obvious symptoms. Less serious effects occurred in the emergency medical responders and a bystander to this incident (Hart et al. 1984; Silverman et al. 1985, 1989; see Section 2.2.2.).

2.2. Nonlethal Toxicity

2.2.1. Odor Threshold and Odor Awareness

Using 17 subjects and 40 measurements, Comstock and Oberst (1953) determined that the median detectable odor concentration of pentaborane was 2.5 mg/m^3 (1.0 ppm). The tested concentrations and the corresponding ability to detect the odor were 0.2 ppm (5%), 0.3 ppm (12.5%), 0.6 ppm (32.5%), 1.0 ppm (57.5%), and 2.0 ppm (100%). The subjects described the odor as garlic-like, acetylene-like, and pungent. Pentaborane's odor also has been characterized as unpleasant, sweetish, and like sour milk or sweet penetrating burning rubber (Mindrum 1964; HSDB 2006). Olfactory fatigue was associated with pentaborane exposure (Mindrum 1964).

Several secondary sources cite odor detection thresholds of 1.0 or 0.97 ppm for pentaborane, but provide no experimental data (Krackow 1953; Amoore and Hautala 1983; Ruth 1986). These sources were probably citing the values determined by Comstock and Oberst (1953). Insufficient data were available to calculate a level of distinct odor awareness for pentaborane.

2.2.2. Case Reports

Four cases of unintentional exposure to pentaborane at a US research laboratory were documented by Rozendaal (1951). The subjects were men, ages 23-31. The concentrations to which they were exposed were unknown. In the two milder cases, the men experienced nervousness, exhaustion, dizziness, and drowsiness typically after exposure ceased, and recovered sufficiently to return to work 3-4 days later. In the two more serious cases, the men were hospitalized and developed intermittent spasms of all voluntary muscles and opisthotonos. They were also confused and disoriented, had impaired recent memory, and EEG tracings showed irritation of the cerebral cortex. Their symptoms improved and they returned to work 7-10 days after the incident.

Lowe and Freeman (1957) described in detail several cases of occupational exposure to unknown concentrations of pentaborane vapor over a 3-year period at a chemical plant. The most common symptoms were drowsiness (78%), dizziness (71%), headache (28%), and cough (15%). In the most severe case, a 28-year old man exposed for about an hour became rigid and unconscious, had involuntary muscular contractions of the extremities, and became comatose with brief periods of restlessness and disorientation. He improved overnight, had light-headedness and headache, and developed periodic persistent hiccups for 6 days. Blood and urine tests revealed abnormalities in hepatic and renal function that in some cases (hepatic function) persisted until his discharge 40 days after exposure. Several exposures at lower concentrations of pentaborane were also described. The men experienced light-headedness, hiccups, flushing, drowsiness, nausea, muscle tremors, profuse perspiration, photophobia, and disorientation for a few hours to a few days. In one case, the worker experienced no symptoms until the day after exposure.

The effects of accidental human exposures to unknown concentrations of pentaborane were characterized in 14 workers by Sim (1958). Common symptoms soon after exposure were dizziness, vertigo, drowsiness, nervousness, restlessness, and hiccups. A number of delayed neurologic findings occurred about 40 h after exposure, including headache, visual disturbance, inability to concentrate, memory loss, incoordination, muscle pain, cramps, tremors, and convulsions. Blood chemistry evaluations suggested hepatic toxicity (positive cephalin-flocculation and thymol-turbidity tests and elevated serum albumin, globulin, and nonprotein nitrogen) in some individuals. Analyses of urinary and hematologic parameters were generally normal. Boron was detected in the urine in cases of severe (undefined) exposure, and persisted for more than a week.

Serial EEG tracings were used to evaluate CNS effects in 15 male workers exposed to pentaborane at two US aircraft facilities (North American Aviation, Inc. and Edwards Air Force Base) (Schoettlin et al. 1961). The exposure concentrations of pentaborane were unknown, but in some cases the men reported that they could briefly smell the gas. All 15 men (ages 23-43) had abnormalities in their EEG tracings (generalized slow response on the resting period and theta- or delta-activity in response to hyperventilation), even though six of them did not

experience any symptoms from exposure. In many cases, the EEGs returned to normal after 5-18 months without exposure. Reported symptoms included mental confusion, lack of coordination, and sleepiness.

Cordasco et al. (1962) studied the pulmonary effects of exposure to several boranes, including pentaborane, in workers exposed occupationally from 1956-1960. Of 166 exposed workers, only three had bronchopulmonary effects. However, all subjects had neurologic symptoms, including clonic movement of the extremities and neck, muscle spasms, diffuse fasiculations, opisthotonos, and catatonic state.

CNS toxicity occurred at a pentaborane-production facility where area air concentrations were measured using an MSA portable boranes detector (Roush et al. 1962). The detector could not measure concentrations greater than 1.0 ppm, which occurred infrequently (≤0.3 h/day). In "contaminated" areas, pentaborane concentrations were approximately 0.3-1.0 ppm (detection limit of 0.01 ppm). Exposure durations were estimated to be 0.1-1.6 h/day on the basis of job descriptions and locations; the C × t range was 0.02-0.64 ppm-h. No correlations were made, however, between exposure concentration, duration, and resulting symptoms. Potentially exposed workers wore protective gear, including full face masks with canister or air line, but could still occasionally smell pentaborane. Over a 12-month period there were 13 cases of intoxication. The most common toxic effects were dizziness, drowsiness and lethargy, headache, stiff neck, poor coordination, nervousness, apprehension, and muscle spasms. Workers recovered within a few hours or days.

Mindrum (1964) characterized the effects of pentaborane exposures at a company where air concentrations of pentaborane were monitored with a detector that registered "positive" upon reaching 1 ppm. The men wore a gas mask (self-contained or air line) or air pack when anticipating exposure, or after smelling pentaborane. In many cases of intoxication, there was no positive detector reading for pentaborane but its odor was detected. In some cases, symptoms occurred when the workers were unaware that they were exposed; the investigators speculated that this could have been due to other masking odors or olfactory fatigue. Signs of toxicity occurred up to 24 h after exposure. Mild symptoms, such as lethargy, confusion, fatigue, inability to concentrate especially when doing ordinary tasks (e.g., driving), chest constriction, headache, lightheadedness, lack of coordination, and inappropriate behavior (e.g., laughing uproariously during cranial nerve examination, driving through five stop signs on the way home from work) resolved after a few days. Moderate exposures caused slurred speech, sleepy appearance, difficulty focusing the eyes, sleeping for long periods, anorexia, and conjunctivitis; the effects resolved in about one week. Severe exposures caused incoordination, muscle spasms and tremors, areas of numbness, drooling, nausea, vomiting, convulsions (30-120 seconds), opisthotonus, increased blood pressure, tachycardia, fever, and profuse perspiration. The neurologic symptoms resolved within 3 weeks of exposure. The men

had abnormal EEGs; the severity of the abnormality increased with exposure severity and returned to normal within 5 weeks. No notable effects on pulmonary, cardiac, or hepatic function were found.

The effects of exposure to unknown concentrations of pentaborane on 13 emergency responders and a bystander during and after an industrial accident in 1982 were described by Hart et al. (1984) and Silverman et al. (1985, 1989). Persons examined within an hour of exposure had conjunctivitis and skin reddening, and those admitted to the hospital the next day reported dizziness, blurred vision, fatigue, myoclonic jerks, hallucinations, and memory loss, and had abnormal EEGs. All but one of the subjects had normal EEGs 4-12 weeks after exposure, although approximately half of the subjects had CT-scan abnormalities and mild brain dysfunction, as measured by deficits in functional tests (sustained attention, memory and learning, and constructional skills). The subjects had higher concentrations of neurotransmitters (as measured by homovanillic acid, 5-hydroxyindoleacetic acid, 3-methoxy-4-hydroxyphenolglycol) in their plasma or cerebrospinal fluid than reference values. Many subjects reported psychologic symptoms indicative of posttraumatic stress disorder and depression, which were not correlated with CT-scan abnormalities. A follow-up 18 months later showed that neuropsychologic functioning improved and that CT scans and the ventricular-brain ratio remained relatively unchanged, but that psychologic symptoms generally persisted or became worse.

2.3. Neurotoxicity

Pentaborane was shown to be a potent neurotoxin in all reports of accidental human exposure to the chemical (Rozendaal 1951; Lowe and Freeman 1957; Sim 1958; Schoettlin et al. 1961; Cordasco et al. 1962; Roush et al. 1962; Mindrum 1964; Hart et al. 1984; Yarbrough et al. 1984; Silverman et al. 1985, 1989). The exposure concentrations of pentaborane were not known with certainty in any of the cases, but neurotoxic effects occurred below the odor threshold of 1 ppm. The ability to detect the smell of pentaborane is subject to olfactory fatigue (Mindrum 1964). Common symptoms were dizziness, drowsiness, headache, nervousness, restlessness, exhaustion, hiccups, flushing, nausea, cough, profuse perspiration, photophobia, visual disturbance, and inability to concentrate. EEG tracings revealed abnormalities, even in cases when the individuals had no symptoms. More serious symptoms included memory loss, disorientation, incoordination, muscle pain, muscle spasms, and convulsions. In a number of cases, the neurologic symptoms occurred 1-2 days after exposure. In the most severe case documented, a worker had convulsions and spasms within 10 min of exposure and no electrical brain activity (measured by EEG) 6 h later (Yarbrough et al. 1984). He died 8 days after exposure, and autopsy revealed brain degeneration and pulmonary, hepatic, and testicular lesions.

Hart et al. (1984) and Silverman et al. (1985, 1989) found that in addition to the physiologic effects associated with pentaborane, exposed persons developed psychologic and emotional changes consistent with posttraumatic stress disorder, which in some cases persisted for 18 months after exposure.

2.4. Developmental and Reproductive Toxicity

No human developmental or reproductive toxicity studies of pentaborane were found. One case report of a 38-year old worker who died after acute exposure (inhalation and dermal) to pentaborane found a lack of mature spermatozoa in his testicles (Yarbrough et al. 1984).

2.5. Genotoxicity

No human studies of the genotoxic potential of pentaborane were found.

2.6. Carcinogenicity

No human studies of the carcinogenic potential of pentaborane were found.

2.7. Summary

Pentaborane has a pungent odor that has been characterized as unpleasant, sweetish, or smelling like sour milk, with a detection threshold of 0.97 ppm. A number of accidental occupational exposures to pentaborane have been documented, with unknown or uncertain exposure concentrations. These studies consistently show that neurotoxicity is the primary and most sensitive effect of exposure, and occurs below the odor threshold for pentaborane. Symptoms included dizziness, drowsiness, headache, nervousness, restlessness, exhaustion, hiccups, cough, nausea, flushing, profuse perspiration, visual disturbances, inability to concentrate, memory loss, incoordination, muscle spasms, and convulsions. EEG tracings revealed abnormalities, even in cases when the individuals had no symptoms. In some cases neurologic symptoms were delayed for one or two days after exposure. In the most severe cases, convulsions and spasms occurred within minutes, and there was evidence of brain, hepatic, pulmonary, and renal lesions. Some individuals exposed to pentaborane developed symptoms of posttraumatic stress disorder that persisted for at least 18 months after exposure.

No human studies were found that evaluated pentaborane genotoxicity, carcinogenicity, or developmental or reproductive toxicity, except that a 38-year old worker who died 8 days after acute exposure to pentaborane lacked mature spermatozoa.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Non-human Primates

Sooty mangabey monkeys of unspecified sex and age were exposed to pentaborane for 2 min in both an acute study (five unspecified concentrations; three animals per group) and a nonlethal toxicity study (described in Section 3.2.1) (Weeks et al. 1964). The test vapor was generated by passing nitrogen gas through chilled (-18 to -20°C) liquid pentaborane, followed by dilution with air. The concentration of pentaborane in the 0.4-m^3 dynamic exposure chamber was determined by a carmine method using air collected in Edgewood collection bubblers. Animals were placed into and removed from the chamber using a sliding carriage, which was not further described. The animals were observed for 7 days. Observations included tremors, ataxia, and convulsions, which ended with death within 24 h after exposure (data for individual test concentrations were not provided). The 2-min LC_{50} was 248 ppm, as determined by the method of Finney (1952).

3.1.2. Dogs

Weir et al. (1964) conducted a series of single- and repeat-exposure studies in which beagles (two to six per group) were exposed to pentaborane at 1.4-55 ppm for 5-60 min. These studies were not designed to be acute lethality studies, although death occurred in several cases. These studies are described in Section 3.2.2.

Weeks et al. (1964) determined LC_{50} values and characterized nonlethal toxicity in mongrel dogs (age and sex not specified) exposed to pentaborane for 2, 5, or 15 min, using methods very similar to that of Weir et al. (1964). The nonlethal toxicity study is described in Section 3.2.2. In the acute lethality study, groups of four dogs were exposed to five unspecified concentrations of pentaborane using a sliding carriage assembly. Animals were observed for toxicity and weight changes for 7 days after exposure. Toxic signs began with tremors and proceeded to ataxia, convulsions, and death within 24 h (data for individual test concentrations were not provided). LC_{50} values calculated by the method of Finney (1952) were 284, 126, and 36 ppm for the 2-, 5-, and 15-min exposures, respectively.

3.1.3. Rats

Rats of unspecified sex and strain had a 2-h LC_{50} of 17 ppm for a 2-h post-exposure observation period (Krackow 1953). Signs of CNS toxicity included weakness, incoordination, tremors, convulsions, coma, and ultimately death.

There was no evidence of pulmonary damage. No other experimental details were provided.

Svirbely (1954a) exposed male Carworth Farms Wistar (CFW) rats to pentaborane at 4.6-285 ppm for 15-240 min in a preliminary experiment, and at 10.0-20.2 ppm for 120 min in a second trial designed to determine the LC_{50}. The animals were exposed in an 18.5-L glass dynamic exposure chamber, and were observed for 2 weeks after exposure. Pentaborane vapor was generated by passing nitrogen gas through chilled (-40°C) liquid pentaborane, followed by dilution with air, and its chamber concentrations were calculated. The following observations occurred "to a greater or less degree depending on concentration and duration of exposure": tremors, jitteriness, convulsions, spasms, corneal opacity, decreased breathing, bulging eyes, abdominal distension, cyanosis, seminal ejaculate, running-like movements of the upper body, and "normal state." The tremors and jitteriness persisted for a "considerable" time after cessation of exposure. All deaths occurred within 24 h. The individual exposure concentrations and mortality rates are presented in Table 4-3. It is unclear why the investigators presented some mortality incidences as two data points instead of one (e.g., mortality of 4/5 at 20.2 ppm reported twice for male rats, instead of 8/10 once); the only difference between the two groups appeared to be mean body weight. The investigators calculated a 2-h LC_{50} of 19.5 ppm using Thompson's (1947) method of moving averages; only the deaths that occurred during the first 2 h of exposure were used in the calculation. Using benchmark dose software (EPA Version 1.3.2) to model the mortality that occurred over the 2-week observation period in the second experiment, an LC_{50} of 16.6 ppm ($BMCL_{05}$ = 13.1 ppm, BMC_{01} = 14.6 ppm) was calculated. When the data from both experiments were combined, the 2-h LC_{50} was 15.7 ppm ($BMCL_{05}$ = 8.3 ppm, BMC_{01} = 10.2 ppm).

In a separate experiment, Svirbely (1954b) examined the effect of repeated exposures on 15 adult male CFW rats. Animals were exposed to pentaborane vapor at 3.3 ppm (calculated concentration) for 5 h/day for up to 5 days, using exposure conditions as described for Svirbely (1954a). The first rat died 4.5 h after the beginning of exposure, and had mild convulsions and delayed, gasping breathing. The survivors appeared dazed and did not move. Neurotoxic effects increased with additional exposures. During the second exposure, some rats displayed a "belligerent" attitude and had mild tremors and convulsions, and nine more died. During the third exposure, the belligerent behavior was more pronounced and animals became very aggressive ("rage" behavior, biting others), and the rats had tremors, gasping, salivation, convulsions, and hyperexcitability. Four more rats died during or after the third exposure, and the remaining rat died after the fourth exposure. There was a dose-related decrease in weight of the treated rats (20-48 g), whereas a control group of three rats gained weight (3 g) over the same time period. Gross pathologic findings included dark-colored adrenal glands and congested liver and spleen after one exposure, congested lungs after two or more exposures, and corneal opacity and seminal ejaculate after four exposures.

TABLE 4-3 Mortality in Rats Exposed to Pentaborane

Experiment	Concentration (ppm)	Duration (min)	Mortality	2-h LC_{50}
First (preliminary)	235-285, 56.0, 24.0, 20.2, 20.2, 16.0, 16. 0, 13.2 (12-15), 13.2 (12-15), 4.3, 4.3, 4.6	15, 18, 85, 80, 80, 81, 81, 120, 120, 120, 120, 240	3/3, 2/3, 3/3, 4/5, 4/5, 2/5, 2/5, 2/6, 3/4, 0/7, 0/3, 0/10	15.7 ppm for all 120-min data, 2-wk observation period
Second (LC_{50})	10.0, 10.0, 12.6, 12.6, 16.0, 16.0, 20.2, 20.2	120	0/5, 1/5, 0/5, 0/5, 0/5, 3/5, 5/5, 5/5	

Source: Adapted from Svirbely 1954a.

Long et al. (1957) determined a mean survival time of 62-67 min for three male CFW rats exposed to pentaborane at 13.6 ppm. Pentaborane vapor was generated as described above for Svirbely et al. (1954a,b), and the concentrations were calculated. Other study details were not provided.

Groups of 8-10 week old male white rats (10/group) were exposed to pentaborane at 3.2-7.5 ppm for 4 h in a 400-L dynamic gassing chamber (Feinsilver et al. 1960). Additional groups of animals (number not specified) were "similarly" exposed and periodically killed and examined for pathologic changes in the lungs, trachea, liver, kidneys, spleen, and testes and compared with untreated controls. Pentaborane concentration was determined by hydrolysis of pentaborane collected with absorption bubblers containing cellosolve, and titration of the resulting boric acid with NaOH. The test concentrations (and resulting mortalities) for the 7-day observation period were 3.2 ppm (0/10), 3.8 ppm (0/10), 4.5 ppm (0/10), 4.8 ppm (1/10), 5.4 ppm (4/10), 5.9 ppm (4/10), 6.2 ppm (6/10), 7.1 ppm (9/10), and 7.5 ppm (10/10). The investigators determined a 4-h LC_{50} of 5.8 ppm using the Bliss-Finney method (Finney 1952); benchmark dose analyses (EPA Version 1.3.2) estimated LC_{50}, $BMCL_{05}$, and BMC_{01} values of 5.8, 4.2, and 4.3 ppm, respectively. Animals were irritable and aggressive and had respiratory distress, depression, ataxia, prostration, protruding eyeballs, diarrhea, tremors, clonic convulsions, and corneal opacity after death. Rats that died during or within a few hours after exposure to pentaborane at concentrations of 7.0 ppm or greater had alveolar edema and hemorrhage. Rats that survived 6-10 days had no pathologic changes.

Male Sprague-Dawley rats (350-450 g) were exposed to pentaborane vapor at approximately 0.25-0.6 mg/kg (approximately 6.5-15 ppm; see below) for 40 min in an 8-L static exposure chamber (Dost et al. 1963). The post-exposure observation period was not specified. The dose was determined by measuring the amount of pentaborane present in the chamber before and after the exposure, and assuming that the difference between the two values was due to absorption by the animals. Negligible amounts of pentaborane were adsorbed to the chamber walls and animal hair (data not provided). The LD_{50} was determined to be 0.42 mg/kg (0.38-0.46 mg/kg) by "probit analysis of percentage of test subjects responding below each dose level." (The chamber concentration of pentaborane was back-calculated to have been 11 ppm, assuming 100% absorption, an inha-

lation rate of 0.22 m^3/day, a body weight of 0.4 kg, and a 40-min exposure; the investigators refer to the air concentration as 10-20 ppm.)

Groups of 10 young male white rats (100-120 g; strain not specified) were exposed to pentaborane for 5 min (62.2-84.7 ppm), 15 min (29.0-34.3 ppm), 30 min (13.0-19.3 ppm), or 60 min (7.5-15.1 ppm) (Weir et al. 1961, 1964). Animals were placed into and removed from the 0.4-m^3 dynamic exposure chamber using a sliding carriage assembly, which was not further described. Animals were observed for 7 days after exposure. The test vapor was generated by passing nitrogen gas through chilled (2.0°C) liquid pentaborane, followed by dilution with air, and the concentration of pentaborane was determined by a carmine method using air collected in Edgewood collection bubblers. Toxic signs began with tremors, ataxia, convulsions, and red exudate around the mouth and nose. All deaths occurred within 24 h after exposure. The exposure concentrations and respective mortalities and LC_{50} values calculated by the method of Bliss (1952) are shown in Table 4-4. Identical LC_{50} values were obtained using benchmark dose software (EPA Version 1.3.2). The $BMCL_{05}$ values for the 5-, 15-, 30-, and 60-min exposures were 56.7, 24.5, 8.1, and 7.0 ppm, respectively, and the respective BMC_{01} values were 58.6, 26.4, 9.8, and 7.5 ppm.

3.1.4. Mice

All mice (10/10; unspecified sex and strain) exposed to pentaborane at 5 ppm for 4 h died within 24 h, the majority dying within 4 h (Krackow 1953). Mice exposed for 2 h had an LC_{50} of 11 ppm for a 2-h post-exposure observation period. Animals had signs of CNS toxicity (weakness, incoordination, tremors, convulsions, and coma) but no evidence of pulmonary damage. No other experimental details were provided.

Male CFW mice were exposed to pentaborane at 4.6-285 ppm for 15-240 min in a preliminary experiment, and at 10.0-20.2 ppm for 120 min in a second trial designed to determine the LC_{50} (Svirbely 1954a). The animals were exposed in an 18.5-L glass dynamic exposure chamber, and were observed for 2 weeks after exposure. Pentaborane vapor was generated by passing nitrogen gas through chilled liquid pentaborane, followed by dilution with air, and its chamber concentrations were calculated. Effects included tremors, jitteriness, convulsions, spasms, corneal opacity, running-like movements of legs, bulging eyes, abdominal distension, seminal ejaculate, cyanosis, and huddling. The tremors and

TABLE 4-4 Mortality in Rats Exposed to Pentaborane

Time (min)	Concentration (ppm)	Mortality	LC_{50} (ppm)
5	62.2, 66.5, 65.3, 70.2, 84.7	0/10, 4/10, 6/10, 8/10, 10/10	66.6
15	29.0, 32.5, 32.8, 34.3, 31.4	0/10, 7/10, 7/10, 8/10, 9/10	31.2
30	13.0, 14.7, 15.5, 17.1, 19.3	2/10, 4/10, 6/10, 7/10, 9/10	15.2
60	7.5, 9.8, 10.7, 12.9, 15.1	0/10, 3/10, 7/10, 9/10, 10/10	10.4

Source: Adapted from Weir et al. 1961.

jitteriness persisted for a "considerable" time after cessation of exposure. Effects were not reported in relation to exposure concentrations other than a general statement that severity depended on concentration and duration of exposure. All deaths occurred within 24 h. The individual exposure concentrations and mortality rates are shown in Table 4-5. The investigators calculated a 2-h LC_{50} of 14.1 ppm using Thompson's (1947) method of moving averages; only the deaths that occurred during exposure were included in the calculation. Using benchmark dose software (EPA Version 1.3.2) to model data combined from both experiments on mortality that occurred during the 2-week observation period, an LC_{50} of 12.4 ppm ($BMCL_{05}$ = 7.9 ppm, BMC_{01} = 8.6 ppm) was calculated.

Long et al. (1957) determined a mean survival time of 145-147 min for three male CFW mice exposed to pentaborane at 13.6 ppm. Pentaborane vapor was generated as by Svirbely et al. (1954a,b), and concentrations were calculated. No further study details were provided.

Mice of unspecified strain and sex were exposed to pentaborane for various durations in a dynamic exposure chamber by Weatherby (1958). The pentaborane concentration was measured analytically by collecting the air in cellosolve, water, and chromotropic acid, and measuring the formation of the resulting boric acid-chromotropate complex by spectrophotometry. All mice (six per group) exposed to pentaborane at 40, 20, and 10 ppm died after 29, 50, and 90 min of exposure, respectively; the first deaths occurred after 16, 26, and 72 min, respectively. Of 12 mice exposed to pentaborane for 60 min and observed for 5 days, 10 died (not specified when) and two survived and appeared normal. Two mice exposed to pentaborane at 5 ppm for 177 min had convulsions, but neither died and both appeared to recover after 24 h. No further experimental details were provided.

Groups of 10 female white mice (8-10 weeks old) were exposed to pentaborane at 3.0-5.6 ppm for 4 h, and additional groups of animals were similarly exposed and killed periodically to evaluate pathologic organ changes (Feinsilver et al. 1960), as described for male rats in Section 3.1.3. The exposure concentrations (and resulting mortalities) for the 7-day observation period were 3.0 ppm (2/10), 3.2 ppm (2/10), 3.3 ppm (5/10), 3.7 ppm (7/10), 5.6 ppm (10/10). The investigators determined a 4-h LC_{50} of 3.4 ppm using the Bliss-Finney method (Finney 1952). Benchmark dose analysis (EPA Version 1.3.2) of the data resulted in LC_{50}, $BMCL_{05}$, and BMC_{01} values of 3.5, 2.2, and 2.6 ppm, respectively. The animals were irritable and had respiratory distress, ataxia, depression, pros-

TABLE 4-5 Mortality in Mice Exposed to Pentaborane

Experiment	Concentration (ppm)	Duration (min)	Mortality	2-h LC_{50}
First (preliminary)	235-285, 56.0, 24.0, 20.2, 16.0, 13.2 (12-15), 4.3, 4.6	15, 18, 85, 80, 81, 120, 120, 240	5/5, 5/5, 5/5,10/10, 10/10, 10/10, 0/10, 10/10	12.4 ppm for all 120-min data, 2-wk observations period.
Second (LC_{50})	10.0, 12.6, 16.0, 20.2	120	2/10, 0/10, 10/10, 10/10	

Source: Adapted from Svirbely 1954a.

tration, protruding eyeballs, diarrhea, tremors, clonic convulsions, corneal opacity, and abdominal distension after death. Animals had "occasional" alveolar edema or hemorrhage at unspecified concentrations "soon" after exposure, but pathologic changes were absent in animals examined after 6-10 days.

Groups of 10 young female mice (20-24 g; strain not specified) were exposed to unspecified concentrations of pentaborane for 5, 15, 30, or 60 min in a 0.4 m^3-dynamic exposure chamber and observed for 7 days (Weir et al. 1961, 1964). Animals were placed into and removed from the chamber using a sliding carriage assembly, which was not further described. The pentaborane vapor was generated from liquid pentaborane and its concentration was determined by a carmine method in air collected in Edgewood collection bubblers. Toxic signs began with tremors, ataxia, convulsions, red exudate around the mouth and nose, and then death within 24 h after exposure. The exposure concentrations, mortalities, and LC_{50} values calculated by the method of Bliss (1952) are shown in Table 4-6. LC_{50} values obtained using benchmark dose software (EPA Version 2.4.0) for the 5-, 15-, and 60-min durations were similar (40.8, 18.7, and 7.8 ppm) to those calculated using the Bliss method. The respective $BMCL_{05}$ values were 27.3, 13.7, and 5.1 ppm, and BMC_{01} values were 28.7, 13.8, and 6.0 ppm. The 30-min data did not provide an adequate fit to the probit model.

Weir et al. (1964) exposed groups of 20 mice to pentaborane at 3.7 ppm for 60 min, 10.2 ppm for 15 min, or 19.8 ppm for 5 min for 4 days. The animals had convulsions after each exposure, but the incidence in each group was not specified. No mice died the first day. Mortality was high in the groups exposed for 15 or 60 min (15/20 and 16/20, respectively), and occurred by the end of the fourth exposure day. In the group exposed for 5 min, 2/20 animals died 5 days after exposure ended.

LC_{50} values were determined for young adult female mice (strain not specified; 10/group) exposed for 0.5, 2, 5, or 15 min in another study at the same institution (Weeks et al. 1964). Five unspecified exposure concentrations were tested using a protocol similar to that described by Weir et al. (1964). Animals were observed for 7 days and weighed daily, as well as before exposure. Toxic signs began with tremors and proceeded to ataxia, convulsions, and death within 24 h (data for individual test concentrations not provided). LC_{50} values calculated by the method of Finney (1952) were 401, 133, 53, and 19 ppm for the 0.5-, 2-, 5-, and 15-min durations, respectively.

The acute lethality studies of pentaborane are summarized in Table 4-7.

TABLE 4-6 Mortality in Mice Exposed to Pentaborane

Time (min)	Concentration (ppm)	Mortality	LC_{50} (ppm)
5	28.7, 33.5, 36.4, 36.4, 38.8, 37.5, 43.5	0/10, 1/10, 1/10, 2/10, 2/10, 5/10, 7/10	40.5
15	15.4, 18.4, 18.8, 20.4, 18.9, 21.9	1/10, 2/10, 5/10, 7/10, 8/10, 10/10	18.6
30	10.5, 13.0, 13.2, 9.6, 12.7, 15.8	2/10, 5/10, 6/10, 7/10, 8/10, 10/10	10.6
60	6.9, 7.3, 6.9, 7.4, 7.5, 11.6	0/10, 1/10, 3/10, 3/10, 5/10, 10/10	7.8

Source: Adapted from Weir et al. 1961.

TABLE 4-7 Summary of Acute Lethality Data on Pentaborane from Animal Studies

Species	Concentrations (ppm)	Duration (min)	Mortality	Effect (Reference)
Monkey	Five tested, but unspecified	2.0	LC_{50} = 248 ppm	Tremors, ataxia, and convulsions (Weeks et al. 1964).
Rat (M)	62.2-84.7	5	LC_{50} = 66.6 ppm	Tremors, ataxia, convulsions, and red exudate from mouth and nose; death within 24 h after exposure (Weir et al. 1961, 1964).
	29.0-34.3	15	LC_{50} = 31.2 ppm	
	13.0-19.3	30	LC_{50} = 15.2 ppm	
	7.5-15.1	60	LC_{50} = 10.4 ppm	
Rat	~6.5-15	40	LC_{50} = ~11 ppm	Not specified (Dost et al. 1963).
Rat	16.0-285	15-85	4/10-3/3 each	Tremors, jitteriness, convulsions, corneal opacity, bulging eyes, decreased breathing, and cyanosis (Svirbely 1954a).
	4.3-20.2	120	LC_{50} = 15.7 ppm	
	4.6	240	0/10	
Rat	3.3	300 × 4	1/15, 10/15, 14/15, 15/15 after 1, 2, 3, 4 exposures	Convulsions, gasping, tremors, aggressiveness, salivation, and organ lesions (Svirbely 1954b).
Rat	Unspecified	120	LC_{50} = 17 ppm (2-h observation)	Weakness, incoordination, tremors, convulsions, and coma (Krackow 1953).
Rat	13.6	145-147	3/3	Mean survival time (Long et al. 1957).
Rat	3.2-7.5	240	LC_{50} = 5.8 ppm	Respiratory distress, ataxia, depression, aggressiveness, tremors, convulsions, corneal opacity, and pulmonary lesions (Feinsilver et al. 1960).
Mouse	Five tested, but unspecified	0.5, 2.0, 5.0, 15.0	LC_{50} = 401, 133, 53, 19 ppm	Tremors, ataxia, convulsions, and death within 24 h (Weeks et al. 1964).
Mouse	28.7-43.5	5	LC_{50} = 40.5 ppm	Tremors, ataxia, convulsions, and red mouth and nasal exudate; death within 24 h after exposure (Weir et al. 1961, 1964).
	15.4-21.9	15	LC_{50} = 18.6 ppm	
	9.6-15.8	30	LC_{50} = 10.6 ppm	
	6.9-11.6	60	LC_{50} = 7.8 ppm	

(Continued)

TABLE 4-7 Continued

Species	Concentrations (ppm)	Duration (min)	Mortality	Effect (Reference)
Mouse	16.0-285	11-81	5/5 or 10/10 each	Tremors, jitteriness, running-like movements, convulsions, spasms, corneal opacity, bulging eyes, cyanosis, and huddling (Svirbely 1954a).
	4.3-20.2	120	LC_{50} = 12.4 ppm	
	4.6	240	10/10	
Mouse	19.8	5 × 4	2/20	Convulsions; death after 2 or more exposures (Weir et al. 1964).
	10.2	15 × 4	15/20	
	3.7	60 × 4	16/20	
Mouse	Unspecified	120	LC_{50} =11 ppm (2-h observation)	Weakness, tremors, incoordination, coma, and convulsions (Krackow 1953).
	5	240	10/10	
Mouse	13.6	62-67	3/3	Mean survival time (Long et al. 1957).
Mouse	40, 20, 10	29, 50, 90	LC_{100}	No details provided.
	5	177	None in 24 h.	Convulsions; appeared normal after 24 h (Weatherby 1958).
	10	60	10/12 in 5 d	Survivors appeared normal (Weatherby 1958).
Mouse	3.0-5.6	240	LC_{50} = 3.4 ppm	Respiratory distress, ataxia, depression, irritability, tremors, convulsions, corneal opacity, and pulmonary lesions (Feinsilver et al. 1960).
Dog	Five tested, but unspecified	2	LC_{50} = 284 ppm	Tremors, ataxia, convulsions, and death within 24 h (Weeks et al. 1964).
		5	LC_{50} = 126 ppm	
		15	LC_{50} = 36 ppm	
Dog	5.0, 10.5	60	1/2 at each concentration	Tremors, salivation, and convulsions (Weir et al. 1964)
	3.7 × 3	60	1/3 after third exposure	Miosis, irritability, aggressiveness, ocular lesions, and convulsions (Weir et al. 1964).

3.2. Nonlethal Toxicity

3.2.1. Nonhuman Primates

Sooty mangabey monkeys of unspecified sex and age were exposed to pentaborane for 2 min in both an acute lethality study (described in Section 3.1.1) and a nonlethal toxicity study (Weeks et al. 1964). In the latter study, groups of three monkeys were exposed for 2 min to pentaborane at 37, 60, or 143 ppm, concentrations intended to be approximately one-half, one-fourth, or one-eighth of the LC_{50} of 248 ppm. Animals were placed into and removed from the exposure chamber using a sliding carriage assembly, which was not further described. Hematology parameters (erythrocytes, packed erythrocyte volume, hemoglobin, and leukocyte counts) were examined one day after exposure and weekly for up to 4 weeks. Bromsulfalein retention was also measured at unspecified intervals. Animals were killed 1, 2, and 4 weeks after treatment for gross and microscopic pathologic analyses. Brain sections were also stained with Nissl to examine the neurons. Monkeys exposed to pentaborane at 37 or 60 ppm had no signs of toxicity. Animals exposed at 143 ppm had convulsions and tremors within 1 h of exposure but not the next day. None of the groups had treatment-related gross or microscopic lesions or alterations in hematologic parameters or bromsulfalein retention.

3.2.2. Dogs

Weir et al. (1964) conducted a series of single- and repeat-exposure studies in which beagles (two to six per group) were exposed to pentaborane at 1.4-55 ppm for 5-60 min. Death occurred in several cases. Dogs were exposed either head-only or whole-body in the single-exposure studies and whole-body in the repeat-exposure studies. The test vapor was generated by passing nitrogen gas through chilled (2.0°C) liquid pentaborane, followed by dilution with air. The concentration of pentaborane was determined by a carmine method using air collected in Edgewood collection bubblers. The dogs were exposed in a 0.4-m^3 dynamic chamber with a port through which the head could be placed either inside or outside the chamber. Dogs were suspended in a harness during exposure to restrict movement, and were observed for 7 days. The dogs were examined before exposure to determine their general physical condition and neurologic, behavioral, and ophthalmoscopic status. In some trials, the boron content in serum and urine samples was measured by a curcumin and carmine method, respectively. The urine was collected for a week before and after exposure.

Some dogs were trained to perform a conditioned avoidance response (CAR) by the method of Solomon and Wynne (1953). In the CAR test, the dogs had to jump over a barrier within 5 seconds after a stimulus (light + buzzer) or they would get an electric shock through the floor (during training only). Each test session consisted of 20 jump trials. Dogs were considered trained when they completed five sessions over a 5-day period without error. The test was con-

ducted 1, 2, and 24 h after exposure, and for a few (unspecified) days thereafter. The harmonic mean of response time was calculated for each session of 20 trials, and compared to pre-exposure values.

The head-only and whole-body single exposures produced consistent results. For exposure durations of 5, 15, and 60 min, no toxic signs were seen at concentrations of 28, 12, and 3.2 ppm, respectively. Severe toxicity was evident at higher (unspecified) concentrations, including apprehensiveness, tremors, salivation, and tonic and clonic convulsions, which increased in severity with the exposure concentration. Death resulted from 60-min exposures at 5.0 or 10.5 ppm; one of two dogs died in each case. Survivors had decreased appetite and were lethargic, apprehensive, and irritable for several days after exposure. Serum boron concentrations increased to 0.2 μg/mL during the first hour after exposure to higher (undefined) concentrations, and then subsided to below detectable concentrations (0.05 μg/mL). The 24-h urinary boron concentrations were increased in a concentration-related manner in all groups, generally subsiding to nearly pre-exposure concentrations by 48 h.

In one series of repeat-exposure studies conducted by Weir et al. (1964) (Experiment 1), beagles were exposed two or three times on successive days to pentaborane at 3.7-19.8 ppm for 5-60 min, except that the third 60-min exposure was terminated after 48 min because one animal had convulsions. After the first exposure, only mild to moderate bloodshot eyes were found in eight of 11 dogs, but there was no concentration-response relationship. After the second exposure, more severe ocular lesions occurred (bloodshot eyes, miosis, and hemorrhage of the iris), as well as severe neurotoxicity (manifest as convulsions during and after exposure) and vicious behavior followed by lethargy. One animal exposed for 60 min died after the third exposure. The study did not report the results of the CAR tests, other than to state that the response time in the CAR test increased to the point that the dogs would not participate for 2-6 days after the last exposure. The boron concentration in the serum of the dogs did not increase, but urinary concentrations increased after each exposure, returning to pre-exposure levels 72 h after the last exposure. A similar study (Experiment 2) was conducted at approximately half the exposure concentration (1.4-9.3 ppm for 5-60 min), but animals were exposed for 5 days. No neurologic effects or CAR impairment occurred after the first exposure. Animals in all the groups began to exhibit CNS effects after the second exposure. By the fifth exposure, effects included increased irritability, aggressiveness, decreased activity, and miosis (concentration related). Latency increased in the CAR test with each exposure, and by the fourth or fifth exposure the dogs were indifferent to the stimuli, although the response was re-established 5-6 days after pentaborane exposure ended.

To determine the effect of retreatment interval on toxicity, Weir (1964) exposed groups of three dogs to pentaborane at 2.5 ppm for 60 min. Dogs were exposed two to five times, with rest periods between exposures varying from 24 to 96 h. Miosis was seen after each exposure, reaching a minimum after the third exposure and then remaining constant. Impaired performance on the CAR test was seen after the second exposure in at least one dog of each group. Signs of

toxicity occurred during or after the second exposure, and were the most severe in dogs exposed on successive days (brief convulsions, tremors, and cyanosis). Signs in dogs exposed to pentaborane on non-successive days included tremors of the neck, apprehensiveness, and increased sensitivity to noise and movement. Toxicity decreased in severity as the interval between exposures increased.

The results of the Weir et al. (1964) dog studies are summarized in Table 4-8.

Weeks et al. (1964) characterized the acute lethality (described in Section 3.1.2.) and nonlethal toxicity in mongrel dogs (age and sex not specified) exposed to pentaborane for 2, 5, or 15 min. The exposure method was as described by Weir et al. (1964). The dogs were exposed to approximately one-eighth, one-fourth, and one-half of the LC_{50} for each exposure duration. The concentrations were 33, 73, and 144 ppm for the 2-min exposures; 16, 33, and 58 ppm for the 5-min exposures; and 5.2, 9.1, and 18 ppm for the 15-min exposures. The dogs were trained to perform CAR tests, and their behavior and performance during the CAR tests (consisting of 20 trials) were evaluated 10 min and 1, 2, and 24 h after exposure, and then daily for another few days. The clinical signs and results of the CAR tests are presented in Table 4-9. Dogs exposed to pentaborane at 33 ppm for 5 min lay down after each exposure. No clinical signs were observed at the other concentrations. Exposure at 5.2 ppm for 15 min resulted in a slight decrease in mean latency response time, but the investigators noted that the decrease was not significant and no alterations were observed in dogs exposed to pentaborane at 9.1 ppm for 15 min. More severe effects occurred at the high concentrations for all three exposure durations, consisting of convulsions, tremors, and CAR performance delays; some animals did not even perform the CAR test (2- and 5-min exposures).

Groups of eight male mongrel dogs were exposed to pentaborane at 14.0-28.0 ppm for either 30 or 60 min, although the specific combinations of exposure concentration and duration were not specified (Weir et al. 1965; Weir and Meyers 1966; further described in Section 4.2.). The observation period also was not specified. Dogs exposed at lower (unspecified) concentrations were cooperative and quiet and appeared sedated, whereas those exposed at higher (unspecified) concentrations exhibited nausea, tremors, convulsions, defecation, miosis, and bradycardia.

3.2.3. Rats

In a mechanistic study, male Sprague-Dawley rats were exposed to pentaborane at 7.6 ppm for 30 min and their brain serotonin and norepinephrine concentrations were measured periodically for 7 days (Weir et al. 1965). The rats were killed 3, 6, 12, 24, 48, 72, 96, and 168 h (serotonin only) after exposure. The brains were immediately removed and homogenized, and serotonin

TABLE 4-8 Effects Observed in Dogs Exposed to Pentaborane

Duration	Concentration (ppm)	Effects
Single Exposure		
5 min	Head only: 28.0 (n = 6)	No toxic signs.
	Head only: 38.0 or 55.0 (n = 2/group)	Tremors, salivation, clonic convulsions, and apprehensiveness.
	Whole body: 14.0 or 26.0 (n = 2/group)	No toxic signs.
	Whole body: 46.0 (n = 2)	Tremors and convulsions.
15 min	Head only: 12.0 (n = 4)	No toxic signs
	Head only: 18.0 (n = 4) or 30.0 (n = 2)	Tremors and apprehensiveness.
	Head only: 19.0 (n = 2)	Clonic convulsions.
60 min	Head only: 3.2 (n = 2)	No toxic signs.
	Head only: 5.0, 5.7, 6.9, or 10.5 (n = 2/group)	Tremors, convulsions, and salivation; one death at 5.0 and 10.5 ppm.
	Whole body: 0.3, 0.4, 0.8, 1.5, or 3.0 (n = 3/group)	No toxic signs.
	Whole body: 4.5 (n = 3)	Convulsions.
	Whole body: 7.5 (n = 3)	Convulsions and two deaths.
Multiple Exposure		
5 min	9.3 × 5 (n = 4)	CAR-d, miosis, irritability, and aggressiveness after second exposure.
	19.8 × 2 (n = 4)	Slightly bloodshot eyes, miosis, and convulsions after second exposure.
15 min	5.0 × 5 (n = 4)	CAR-d, miosis, irritability, and aggressiveness after second exposure.
	10.2 × 2 (n = 4)	Markedly bloodshot eyes, miosis, and convulsions after second exposure.
60 min	1.4 × 5 (n = 3)	CAR-d, miosis, irritability, and aggressiveness after second exposure.
	3.7 × 3 (n = 3)	Convulsions, viciousness, lethargy, ocular lesions after second exposure, and one death after third exposure.
60 min	2.5 (n = 3) × 2; 24 h apart	Convulsions, tremors, CAR-d after second exposure, and miosis.
	2.5 (n = 3) × 5; 48 h apart	Neck tremors, apprehensiveness, CAR-d after second exposure, and miosis.
	2.5 (n = 3) × 4; 72 h apart 2.5 (n = 3) × 4; 96 h apart	Neck tremors, lethargy, noise sensitivity, CAR-d after second exposure, and miosis (72 or 96 h apart).

Abbreviations: CAR-d, conditioned-avoidance-response delay. Source: Data from Weir et al. 1964.

TABLE 4-9 Effects Observed in Dogs Exposed to Pentaborane

Concentration (ppm)	Clinical signs	CAR performance
2-min exposure		
33	None	Not affected.
73	None	1/3, some increase in mean latency response time 2 h after exposure.
144	2/3 convulsions	2/3, increase in CAR mean latency response time; 1/3, no jumps 1 and 2 h after exposure.
5-min exposure		
16	None	Not affected.
33	2/3 lay down after each response	2/3, increase in CAR mean latency response time.
58	2/3 convulsions	2/3, no jumps 1 and 2 h after exposure; 3/3, increase in CAR mean latency response time.
15-min exposure		
5.2	None	3/3, slight, but not significant, increase in mean response time.
9.1	None	Not affected.
18	1/3, convulsions; 2/3, tremors	2/3, increase in mean latency response time.

Source: Adapted from Weeks et al. 1964.

(5-hydroxytryptamine) and norepinephrine were extracted and measured fluorometrically. There was a marked depletion in brain serotonin (≤63% decreased from controls) and a modest decrease in norepinephrine (≤29% decreased from controls) that were maximal 3-12 h after exposure. Concentrations of serotonin and norepinephrine returned to normal 7 and 2 days after exposure, respectively. No other results were reported.

3.2.4. Mice

As part of their experiment to determine the toxic mechanism of pentaborane, Weir et al. (1965) measured the pentobarbital sleeping time in mice exposed to pentaborane at 3.5-4.0 ppm or 8.5-9.0 ppm for 30 min. Groups of 10 mice were injected intraperitoneally with sodium pentobarbital (30.0 or 45.0 mg/kg) 1, 8, 18, or 24 h after inhaling pentaborane. The greatest increase in sleeping time occurred 1-8 h after exposure, and was greater at the higher pentaborane concentration. No other effects on the animals were noted.

The nonlethal toxicity studies of pentaborane are summarized in Table 4-10; the table also shows the lethal responses in the dog studies of Weir et al. (1964).

TABLE 4-10 Summary of Nonlethal Toxicity of Pentaborane from Animal Studies

Species	Concentration (ppm)	Duration (min)	Effects	Reference
Monkey	37, 60	2.0	No toxic signs or organ lesions.	Weeks et al. 1964
	143	2.0	Convulsions and tremors first day, no organ lesions.	
Rat	7.6	30	Decreased (≤63%) brain serotonin and norepinephrine (≤29%) within 3 h, reversible after 7 and 2 d, respectively.	Weir et al. 1965
Mouse	3.5-4.0	30	Increased pentobarbital (45 mg/kg) sleeping time.	Weir et al. 1965
	8.5-9.0	30	Increased pentobarbital (30 mg/kg) sleeping time.	
Dog	14-55	5	Tremors, salivation, and convulsions at ≥38 ppm.	Weir et al. 1964
	18, 30	15	Tremors at 18 ppm; convulsions at 30 ppm.	
	0.3-10.5	60	Convulsions and tremors at ≥ 4.5 ppm; 1/2 died at 5.0 and 10.5 ppm.	
Dog	9.3 × 5 19.8 × 2	5	At all concentrations: miosis, irritability, tremors, bloodshot eyes, aggressiveness, and convulsions after second exposure. One of three dogs died after third exposure at 3.7 ppm.	Weir et al. 1964
	5.0 × 5 10.2 × 2	15		
	1.4 × 4 2.5 × 2 3.7 × 3	60		
Dog	33	2.0	No effects.	Weeks et al. 1964
	73	2.0	No toxic signs and CAR-d.	
	144	2.0	Convulsions and CAR-d.	
	16	5.0	No effects.	
	33	5.0	Lethargy and CAR-d.	
	58	5.0	Convulsions and CAR-d.	
	5.2	15.0	No toxic signs and equivocal CAR-d.	
	9.1	15.0	No effects.	
	18	15.0	Convulsions, tremors, and CAR-d.	
Dog	14.0-28.0	30-60	Dogs appeared sedated at "lower" concentrations. Nausea, tremors, convulsions, defecation, miosis, and bradycardia at "higher" concentrations. Observation period not specified.	Weir et al. 1965; Weir and Meyers 1966

Abbreviations: CAR-d, conditioned-avoidance-response delay.

3.3. Neurotoxicity

Animal studies consistently showed that the CNS is the target of pentaborane toxicity. Toxicity increased with exposure duration and concentration, and was cumulative in multiple-exposure studies. Neurotoxic signs included appre-

hensiveness, drooling, nausea, decreased appetite, weight loss, lethargy, irritability, jitteriness, corneal opacity, aggressiveness, defecation, miosis, ataxia, tremors, spasms, and convulsions. Signs resolved within a day after mild exposure but persisted for several days after more severe intoxication.

3.4. Developmental and Reproductive Toxicity

No developmental or reproductive toxicity studies of pentaborane were found, although reproductive toxicity was reported in a subchronic animal study. Exposure to pentaborane at 0.6 ppm for up to 6 months resulted in testicular atrophy in two of 17 hamsters and one of 15 rats, and minimal or absent spermatogenesis in three of 17 hamsters and one of 15 rats, whereas none of these effects were found in the controls (Levinskas et al. 1958). Both species also had neurotoxic effects and pathologic organ changes.

Boric acid, a hydrolysis product of pentaborane, has been shown be a developmental and reproductive toxicant after repeated inhalation or oral exposure (HSDB 2012).

3.5. Genotoxicity

No genotoxicity studies of pentaborane were found.

3.6. Subchronic and Chronic Toxicity

Levinskas et al. (1958) conducted a subchronic toxicity study in which male CFW mice, male albino guinea pigs, male New Zealand albino rabbits, and male CFW rats were exposed to pentaborane at 1.0 ppm for 6 h/day, 5 days/week for 4 weeks (20 exposures). The test concentrations were calculated, but a subsequent publication by this laboratory showed that the analytic measurements were 47-130% of the nominal concentration at 3.0-13.8 ppm, but were 10-80% of the nominal concentration at 0.2 ppm (Hill and Merrill 1960). Levinskas et al. (1958) similarly exposed rabbits, rats, monkeys, dogs, and golden hamsters to pentaborane at 0 or 0.2 ppm for 6 h/day, 5 days/week for 6 months. The 6-month survival in treated animals was 0/2 for monkeys, 3/4 for dogs, 8/12 for rabbits, 24/30 for rats, and 17/20 for hamsters; in controls, the survival was 0/1 for monkeys, 2/3 for dogs, 6/6 for rabbits, 11/15 for rats, and 12/15 for hamsters. The monkeys were the first to die (one died after four exposures), and hamsters required the greatest number of exposures before death occurred (75). The results of this study are summarized in Table 4-11; they are considered equivocal because of the unexplained deaths in the control groups and questionable test concentrations.

3.7. Carcinogenicity

No studies of the potential carcinogenicity of pentaborane were found.

TABLE 4-11 Effects Observed in in Laboratory Animals Exposed to Pentaborane

Concentration	Duration	Species (sex)	Effects
0.2 ppm[a]	6 h/d, 5 d/wk for 6 mo	Monkey (M)	2/2 died after 4 and 15 exposures (1/1 control died after 16 exposures); low appetite, apathy, vomiting, muscle tremors, and impaired mobility.
		Rat (M)	6/30 died after ≥49 exposures (4/15 controls died after ≥47 exposures); nasal and/or ocular discharge, lethargy, viciousness, no grooming, and testicular lesions.
		Dog (F)	1/4 died after 52 exposures (1/3 controls died after 16 exposures); low appetite, ocular and nasal discharge, emaciation, muscle tremors, and impaired mobility.
		Hamster (M)	3/20 died after ≥75 exposures (3/25 controls after ≥10 exposures); brief periods of lethargy and testicular lesions.
		Rabbit (M)	4/12 died after ≥ 21 exposures (0/6 controls died); ocular and nasal discharge, decreased appetite, scrawny, unclean, and aggressive when handled.
1.0 ppm[a]	6 h/d, 5 d/wk for 4 wk	Mouse (M)	Weight loss and 9/11 died after ≥3 exposures.
		Rat (M)	Nasal discharge, lethargy, weight loss, and 9/12 died after ≥12 exposures.
		Rabbit (M)	Ocular irritation, impaired motion, weight loss, and 6/6 died after ≥9 exposures.
		Guinea pig (M)	Nasal discharge, weight loss, and 2/2 died after 10 exposures.

[a]Nominal concentration. A subsequent publication by Hill and Merrill (1960) showed that the analytic measurements were 47-130% of the nominal concentration at 3.0-13.8 ppm, and were 10-80% of the nominal concentration at 0.2 ppm. Source: Data from Levinskas et al. 1958.

3.8. Summary

Single- and multiple-exposure studies of pentaborane were conducted using monkeys, dogs, rats, mice, hamsters, rabbits, and guinea pigs. The studies consistently show that the CNS is the target of pentaborane; toxicity increased with exposure duration and concentration. Neurotoxic signs included apprehensiveness, lethargy, corneal opacity, aggressiveness, miosis, ataxia, tremors, and convulsions. In the single-exposure studies, all deaths occurred within 24 h. The most sensitive test of neurotoxicity was the CAR test for dogs, which found decreased performance from exposures that produced no apparent signs of toxicity (Weeks et al. 1964).

No gross or microscopic pathologic lesions were found in a single-exposure study of monkeys exposed to pentaborane at 37, 60, or 143 ppm for 2 min (Weeks et al. 1964). However, pathologic findings were noted in two multiple-exposure studies (Svirbely 1954b; Levinskas et al. 1958), including lesions in the adrenal glands, liver, spleen, lungs, testes, and eyes of rats. Pentaborane decreased brain concentrations of serotonin markedly and norepinephrine slightly in rats 3-12 h after exposure, and increased the pentobarbital sleeping time in mice (Weir et al. 1965).

No genotoxicity, carcinogenicity, or developmental or reproductive toxicity studies of pentaborane were found, although chronic exposure to pentaborane at 0.2 ppm caused testicular lesions in hamsters and rats.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

The metabolism and disposition of pentaborane has not been elucidated in humans or animals. Pentaborane hydrolyzes after several hours in body-temperature water to produce the much less toxic compounds boric acid (borane) and hydrogen, as well as heat. It is unknown to what extent the hydrolysis products contribute to pentaborane toxicity.

Workers accidentally exposed to high (undefined) concentrations of pentaborane had CNS effects, and boron was detected in their urine (Sim 1958). Urinary concentrations were the highest the first 2 days after exposure, followed by low levels for days 3-6, and slightly higher levels for several days after that (data not provided), suggesting slow elimination of boron.

Several dog studies indicated that the urinary concentrations of pentaborane are a better indicator of exposure than serum concentrations (Weir et al. 1964). Borane was undetectable in the serum after "low" (undefined) exposures, whereas it increased to 0.2 µg/mL during the first hour after exposure at "higher" (undefined) concentrations and then subsided to below detectable levels (0.05 µg/mL). However, the 24-h urinary boron measurements were increased in a concentration-related manner in all groups, generally subsiding to nearly pre-exposure concentrations after 48 h. In a repeat-exposure study, Weir et al. (1964) found that dogs exposed two or three times on successive days to pentaborane at 3.7-19.8 ppm for 5-60 min had unchanged serum boron concentrations, but their urinary boron increased after each exposure, returning to pre-exposure concentrations after 72 h.

Reed et al. (1964) examined the metabolic fate of pentaborane in rats and rabbits injected intraperitoneally with pentaborane-H^3 liquid (2.5 mg/kg). Rats exhaled 37% of the radiolabel as $H_2{}^3$ within 2 h, with negligible additional exhalation of $H_2{}^3$ thereafter. This pattern might reflect initial hydrolysis that formed an acid-labile intermediate containing nonvolatile and nonionizable tritium, which was present mainly in the liver and blood. The subsequent decrease in radiolabel in the liver and blood 3 h after exposure (relative to 10 min after ex-

posure) was postulated to be due to a slow hydrolysis of the nonvolatile intermediate to form ionizable hydrogens that can be exchanged with water. The latter theory is supported by a study in which pentaborane-H^3 radiolabel was incorporated into nonvolatile blood solids of anesthetized rabbits at approximately the same time (about 15 min after exposure) as the initial hydrolysis of pentaborane to form H_2^3 and nonvolatile intermediates in rats.

4.2. Mechanism of Toxicity

The mechanism of pentaborane toxicity is unknown, but might involve decreased brain serotonin and norepinephrine concentrations. Pentaborane is a potent reducer capable of reacting with ammonia, organic amines, and unsaturated hydrocarbons. The mechanism of toxicity appears to be similar among species, as the CNS was consistently the primary target of pentaborane.

A series of experiments in mice, rats, and dogs examined the mechanism of action of pentaborane (Weir et al. 1965; Weir and Meyers 1966). Pentobarbital-induced (intraperitoneal injection) sleeping time in mice was increased maximally 1-8 h after exposure to pentaborane at concentrations of 3.5 ppm or greater for 30 min. Serotonin was markedly decreased and norepinephrine was slightly decreased in brain homogenates of rats 3-168 h after exposure to pentaborane at 7.6 ppm for 30 min. The decreases were maximal 3-12 h after exposure. Concentrations returned to normal after 7 days for serotonin and after 2 days for norepinephrine. A similar effect on brain serotonin concentrations was observed in rats injected intraperitoneally with pentaborane at 8.0 mg/kg, although serotonin concentrations returned to normal more quickly (after 4 days).

Conscious dogs treated with pentaborane at 0.6-3.6 mg/kg by intraperitoneal injection or at 14.0-28.0 ppm by inhalation for 30 or 60 min had signs of neurotoxicity, as well as a large decrease in blood pressure and bradycardia that returned to normal after 4 h (Weir et al. 1965; Weir and Meyers 1966). (Information about the combinations of exposure concentration and duration and the length of the observation periods was not specified.) Anesthetized dogs injected intraperitoneally with pentaborane at 1.2-3.6 mg/kg had an initial increase in arterial blood pressure (after 2-5 min), which then fell slowly over 48 h. The dogs had bradycardia and decreased response (compared to pre-exposure) to bilateral carotid occlusion (20 seconds with hemostats) and intravenously injected tyramine (increases blood pressure and heart rate), but no effects on vagal stimulation (electrodes) or response to epinephrine. Administration of norepinephrine partially restored the decreased blood pressure, pulse rate, and responsiveness to carotid occlusion and tyramine.

4.3. Structure-Activity Relationships

Pentaborane is a member of a class of seven chemicals known as the boron hydrides or boranes, of which only two other chemicals are stable, diborane

(B_2H_6) and decaborane ($B_{10}H_{14}$). They are soluble in organic solvents and insoluble in water, but hydrolyze on contact with water within a few seconds (diborane), within several hours at body temperature (pentaborane), or in about 30 days (decaborane) (Sim 1958).

Krackow (1953) evaluated acute lethality studies conducted with pentaborane, diborane, and decaborane, and concluded that pentaborane was the most toxic. Rats and dogs exposed to diborane had pulmonary edema and hemorrhage, whereas animals exposed to pentaborane (rats and mice) and decaborane (rats, mice, and rabbits) primarily had neurologic effects, including loss of coordination and convulsions.

Because of the differences in toxicity among the boranes, structure-activity comparisons were not used in the derivation of AEGL values for pentaborane.

4.4. Other Relevant Information

4.4.1. Species Variability

The CNS was the target of pentaborane in all tested species, including humans; effects included incoordination, muscle spasms, convulsions, decreased appetite, and drooling. A comparison of animal studies indicates that the mouse is the most sensitive to the acute toxicity of pentaborane. Rats, dogs, and monkeys were similarly sensitivity to pentaborane.

Acute lethality studies in rats and mice were consistent in finding slightly lower LC_{50} values for mice. For example, Weir et al (1961, 1964) reported mouse LC_{50} values of 40.5, 18.6, 10.6, and 7.8 ppm for 5-, 15-, 30-, and 60-min exposures, respectively, whereas the analogous rat LC_{50} values were 66.6, 31.2, 15.2, and 10.4 ppm. Similarly, Svirbely (1954a) reported 120-min LC_{50} values of 12.4 ppm for mice and 15.7 ppm for rats, and Feinsilver et al. (1960) estimated 240-min LC_{50} values of 3.4 ppm for mice and 5.8 ppm for rats.

A comparison of the acute lethality of pentaborane in monkeys, dogs, and mice by Weeks et al (1964) indicated that mice were more sensitive than dogs and monkeys, but the latter two species were similarly sensitive. LC_{50} values for a 2-min exposure were 133 ppm for mice, 248 ppm for monkeys, and 284 ppm for dogs. Comparison of acute lethality between dogs and mice for 5- and 15-min exposures also showed that mice were more sensitive than dogs. Studies of nonlethal concentrations of pentaborane indicated that monkeys and dogs were similarly susceptible. Monkeys exposed for 2 min to pentaborane at 37 or 60 ppm had no toxic signs, but at 143 ppm the animals had convulsions and tremors. Dogs exposed for 2 min to pentaborane at 33 or 73 ppm had no toxic signs, but had convulsions at 144 ppm. The subchronic exposure studies of Levinskas et al. (1958) suggested that monkeys were more susceptible than rats, mice, rabbits, dogs, guinea pigs, and hamsters because the monkeys died after fewer exposures to pentaborane than the other species. However, as noted in Section 3.6, that study is considered unreliable because deaths also occurred in the control groups and the accuracy of the exposure concentrations was questionable.

Thus, the overall species variability in the toxic response to pentaborane was low. The LC_{50} values for exposures of 2-240 min varied by approximately a factor of 2 in four animal species, and similar responses were seen at comparable nonlethal concentrations in dogs and monkeys.

4.4.2. Susceptible Populations

No information on populations especially sensitive to pentaborane was found.

4.4.3. Concentration-Exposure Duration Relationship

ten Berge et al. (1986) determined that 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. The value of n ranged from 1 to 3 for 90% of the chemicals examined in that study.

The value of n for pentaborane was calculated to be 1.3 by linear regression analysis of rat LC_{50} data (5-60 min exposure durations) from the studies of Weir et al. (1961, 1964). See Appendix D for the calculations. Similar values for n can be calculated by linear regression analysis using LC_{50} data from dog and mouse studies: n = 1.0 using the 2-15–min LC_{50} data in dogs (Weeks et al. 1964), n = 1.47 using the 5-60–min LC_{50} values in mice (Weir et al. 1961, 1964), and n = 1.11 using the 0.5-15–min LC_{50} data in mice (Weeks et al. 1964).

If the 4-h LC_{50} values obtained by Feinsilver et al. (1960) for rats and mice are combined with the 5-60–min LC_{50} values of Weir et al. (1961, 1964), the values of n would increase from 1.30 to 1.55 for the rat and from 1.47 to 1.57 for the mouse. The slightly larger n values were not used, however, because Feinsilver et al. (1960) used a different analytic method to determine pentaborane concentrations than Weir et al. (1961, 1964).

Although the AEGL-2 values for pentaborane were derived on the basis of a dog study (Weir et al. 1964), the value of n calculated from dog LC_{50} data (Weeks et al. 1964) was not used to extrapolate across time because the exposure durations for the dogs were for just 2-15 min whereas they were 5-60 min for the rats. Furthermore, a larger number of rats (200) were studied than dogs (60). Using a value of n derived from a rat lethality study was considered appropriate because neurotoxic effects are on the continuum of effects leading to death, neurotoxicity was the primary toxic effect in both species, and dogs and rats were similarly sensitive to pentaborane.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Pentaborane has an odor threshold of approximately 1 ppm. Occupational studies have shown that humans exposed to pentaborane at concentrations with

an undetectable odor developed CNS effects characteristic of pentaborane intoxication (Schoettlin et al. 1961; Mindrum 1964).

5.2. Animal Data Relevant to AEGL-1

No animal studies of pentaborane evaluating end points relevant to AEGL-1 values were found. A study with dogs trained to do the CAR test showed that decrements in performance on the test occurred in dogs otherwise showing no apparent signs of toxicity from pentaborane (Weeks et al. 1964).

5.3. Derivation of AEGL-1 Values

AEGL-1 values are not recommended for pentaborane because no relevant human or animal studies were available. Human studies showed either no effects or CNS toxicity of severity greater than that defined by AEGL-1.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No experimental human studies of pentaborane were found. Occupational exposure studies indicated that the CNS is the target of pentaborane toxicity and that CNS effects can occur at concentrations with an undetectable odor. However, none of the studies determined exposure concentrations, exposure durations, and resulting effects simultaneously.

6.2. Animal Data Relevant to AEGL-2

Dog studies conducted by Weir et al. (1964) and Weeks et al. (1964) were potential candidates for developing AEGL-2 values. Those studies examined the effects of pentaborane on the dogs' behavior and performance in the CAR test. None of the acute lethality studies in rats or mice were used because the studies either did not adequately describe exposure concentrations and responses or tested only one concentration. The study of sooty mangabey monkeys exposed to pentaborane at 37-143 ppm (Weeks et al. 1964) involved just a 2-min exposure, a duration considered too short to serve as the basis of AEGL-2 values.

In the Weir et al. (1964) single-exposure studies, dogs were exposed to pentaborane for 5, 15, or 60 min, but they were either not subjected to the CAR test or the results of the CAR tests were not reported. CNS effects increased in severity with exposure concentration, and death occurred from 60-min exposures at 5.0 and 10.5 ppm.

Three multiple-exposure studies were conducted by Weir et al. (1964); the results reported after the first exposure to pentaborane in each of those cases was

considered. In one study, dogs exposed to pentaborane at 3.7-19.8 ppm for 5-60 min had mildly to moderately bloodshot eyes after one exposure, with no evidence of a concentration-response relationship. Two or more exposures caused bloodshot eyes, miosis, hemorrhage of the iris, CNS effects (convulsions, vicious behavior, and lethargy), and one death (after three exposures of 60 min). The only CAR test result reported was that dogs would not participate for 2-6 days after the last 60-min exposure. In the second experiment, dogs were exposed to pentaborane at 1.4-19.8 ppm for 5-60 min for 5 successive days. No neurologic effects or CAR delays occurred after the first exposure. After the second exposure, all groups began to exhibit CNS effects, including increased irritability, aggressiveness, decreased activity, and miosis (concentration related). Latency increased in the CAR test with each exposure. In the third experiment, dogs were exposed to pentaborane at 2.5 ppm on 2-5 occasions, with a reexposure interval of 24-96 h. Pupil size was decreased after each exposure. After the second exposure, animals had impaired performance on the CAR test and signs of toxicity (brief convulsions, tremors, cyanosis, apprehensiveness, and sensitivity to noise and movement) that decreased in severity as the exposure interval increased.

Weeks et al. (1964) exposed dogs to pentaborane at 33-144 ppm for 2 min, 16-58 ppm for 5 min, and 5.2-18 ppm for 15 min. CNS toxicity was dose-related, ranging from absent to severe. In some cases CAR delays occurred despite the lack of obvious signs (2 min at 73 ppm; 15 min at 5.2 ppm).

6.3. Derivation of AEGL-2 Values

The AEGL-2 values are based on the no-observed-effect level for CNS toxicity. Selection of that end point was intended to avoid even minor effects on CNS function, which could impair judgment of humans and result in accidents and injury (Mindrum 1964). The point-of-departure was a single 60-min exposure to pentaborane at 1.4 ppm (the first exposure in a five-exposure study), which caused no neurologic signs or CAR impairment in dogs (Weir et al. 1964). Dogs similarly exposed a second time (the following day) began to exhibit CNS effects, including decreased activity, miosis, and CAR delays, and additional exposures caused irritability and aggressiveness. This scenario was chosen instead of the 60-min single exposure study in which 3.0 or 3.2 ppm produced no toxic signs (Weir et al. 1964), because the investigators did not state whether the dogs had CAR delays. Furthermore, 3.0 and 3.2 ppm are close to a concentration that caused convulsions (4.5 ppm) after a single 60-min exposure. The 5-min exposure to pentaborane at 16 ppm (Weeks et al. 1964) also could have been used to derive very similar AEGL-2 values, but the Weir et al. (1964) study was chosen because the exposure duration was longer. A total uncertainty factor of 10 was applied. An interspecies uncertainty factor of 3 was applied because pentaborane caused similar effects (CNS toxicity) in humans and four species of laboratory animals, and because LC_{50} values varied less than 3-fold among species. An intraspecies uncertainty factor of 3 was applied because the

homogeneous response among species and steep concentration-response curve for lethality indicate that there would be little variability among humans.

Time scaling was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986), where n ranges from 0.8 to 3.5 for many irritant and systemically acting vapors and gases. A value of n = 1.3 was determined by linear regression analysis of acute lethality data from studies of mice exposed for 5-60 min (Weir et al. 1961, 1964), as described in Section 4.4.3. The resulting AEGL-2 values are presented in Table 4-12, and the calculations are detailed in Appendix A. The AEGL-2 values are supported by studies of monkeys exposed to pentaborane for 2 min and dogs exposed for 5 min (Weeks et al. 1964), which would have yielded similar or higher AEGL-2 values. The latter were not used because the exposure durations of the studies were too short, and the monkeys were not subjected to the CAR test.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No relevant human data were available for deriving AEGL-3 values for pentaborane.

7.2. Animal Data Relevant to AEGL-3

Acute lethality data were available from studies of monkeys (2 min), rats (5-240 min), mice (0.5-240 min), and dogs (2-15 min). The studies portrayed a consistent picture of pentaborane intoxication, which was manifested as tremors, weakness, ataxia, aggressiveness, and convulsions. LC_{50} values were comparable for monkeys, rats, and dogs, but were consistently lower for mice; however, the values in mice were generally less than 2-fold lower than other tested species.

7.3. Derivation of AEGL-3 Values

Reliable LC_{50} values were identified in several species for durations ranging from 2 min to 4 h. In general, there was less than a 3-fold difference in the LC_{50} values in rats, mice, dogs, and monkeys for a given exposure duration indicating very little species differences. The lowest LC_{50} values were found in mice. The 60-min lethality data from the study by Weir et al. (1961, 1964) and

TABLE 4-12 AEGL-2 Values for Pentaborane

10 min	30 min	1 h	4 h	8 h
0.56 ppm (1.4 mg/m^3)	0.24 ppm (0.62 mg/m^3)	0.14 ppm (0.36 mg/m^3)	0.048 ppm (0.12 mg/m^3)	0.028 ppm (0.072 mg/m^3)

the 4-h data from the study by Feinsilver et al. (1960) were considered possible sources of points-of-departure for AEGL-3 values. Benchmark dose software (EPA Version 1.3.2 and 2.4.0) was used to calculate LC_{50}, $BMCL_{05}$, and BMC_{01} values. The respective values for the 60-min study were 7.75, 5.08, and 6.04 ppm, and for the 4-h study were 3.5, 2.2, and 2.6 ppm. The $BMCL_{05}$ of 5.08 ppm was selected as an estimate of the threshold for lethality. Concentrations were scaled across time using the equation $C^{1.3} \times t = k$ (ten Berge et al. 1986), as described in Section 4.4.3. A total uncertainty factor of 10 was applied. An interspecies uncertainty factor of 3 was used because pentaborane caused similar effects (CNS toxicity) in humans and four species of laboratory animals, and LC_{50} values varied less than 3-fold among species. An intraspecies uncertainty factor of 3 was applied because the homogeneous response among species and the steep concentration-response curve for lethality indicate that there would be little variability among humans.

Potential AEGL-3 values calculated on the basis of the 4-h $BMCL_{05}$ would have resulted in 10-min, 30-min, 1-h, 4-h, and 8-h values of 2.5, 1.1, 0.64, 0.22, and 0.13 ppm, respectively, which are similar to those calculated from the 60-min data. The 60-min $BMCL_{05}$ of 5.08 ppm was selected as the point-of-departure for the AEGL-3 values because it yielded slightly lower AEGL-3 values. The AEGL-3 values for pentaborane are supported by the LC_{50} values of Weir et al. (1961, 1964) for rats exposed for 60 min, which would have yielded slightly higher AEGL-3 values. The lethality data from studies of monkeys exposed for 2 min and dogs exposed for 2-15 min (Weeks et al. 1964) also would have yielded similar AEGL-3 values, but were not used because of the short exposure durations. The AEGL-3 values for pentaborane are presented in Table 4-13, and the calculations are detailed in Appendix A.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity End Points

AEGL-1 values were not developed for pentaborane because no relevant human or animal studies were available. The AEGL-2 and AEGL-3 values were based on dog and mouse studies, respectively. Neurotoxicity was considered the critical end point. CNS effects were the predominant toxic effect from exposure to pentaborane, and they were the most sensitive indicator in animals and humans. The CNS toxicity and progression profile was consistent among species. The AEGL values for pentaborane are presented in Table 4-14.

TABLE 4-13 AEGL-3 Values for Pentaborane

10 min	30 min	1 h	4 h	8 h
2.0 ppm (5.2 mg/m^3)	0.87 ppm (2.2 mg/m^3)	0.51 ppm (1.3 mg/m^3)	0.17 ppm (0.44 mg/m^3)	0.10 ppm (0.26 mg/m^3)

TABLE 4-14 AEGL Values for Pentaborane

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)	0.56 ppm (1.4 mg/m^3)	0.24 ppm (0.62 mg/m^3)	0.14 ppm (0.36 mg/m^3)	0.048 ppm (0.12 mg/m^3)	0.028 ppm (0.072 mg/m^3)
AEGL-3 (lethal)	2.0 ppm (5.2 mg/m^3)	0.87 ppm (2.2 mg/m^3)	0.51 ppm (1.3 mg/m^3)	0.17 ppm (0.44 mg/m^3)	0.10 ppm (0.26 mg/m^3)

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

TABLE 4-15 Standards and Guidelines for Pentaborane

Guideline	10 min	15 min	30 min	1 h	4 h	8 h
AEGL-1	NR	–	NR	NR	NR	NR
AEGL-2	0.56 ppm	–	0.24 ppm	0.14 ppm	0.048 ppm	0.028 ppm
AEGL-3	2.0 ppm	–	0.87 ppm	0.51 ppm	0.17 ppm	0.10 ppm
IDLH (NIOSH)[a]	–	–	1 ppm	–	–	–
TLV-TWA (ACGIH)[b]	–	–	–	–	–	0.005 ppm
PEL-TWA (OSHA)[c]	–	–	–	–	–	0.005 ppm
REL-TWA (NIOSH)[d]	–	–	–	–	–	0.005 ppm
TLV-STEL (ACGIH)[e]	–	0.015 ppm	–	–	–	–
REL-STEL (NIOSH)[f]	–	0.015 ppm	–	–	–	–
MAK (Germany)[g]	–	–	–	–	–	0.005 ppm
MAK Peak Limit (Germany)[h]	–	0.015 ppm	–	–	–	–
MAC (The Netherlands)[i]	–	–	–	–	–	0.005 ppm

[a]IDLH (immediately dangerous to life or health, National Institute for Occupational Safety and Health) (NIOSH 1994) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms, or any irreversible health effects.
[b]TLV-TWA (threshold limit value – time-weighted average, American Conference of Governmental Industrial Hygienists) (ACGIH 2013) is the time-weighted average concentration for a normal 8-h workday and a 40-h workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.
[c]PEL-TWA (permissible exposure limit – time-weighted average, Occupational Safety and Health Administration) (29 CFR Part 1910 [2006]) is defined analogous to the ACGIH TLV-TWA, but is for exposures of no more than 10 h/day, 40 h/week.
[d]REL-TWA (recommended exposure limit – time-weighted average, National Institute for Occupational Safety and Health) (NIOSH 2011) is defined analogous to the ACGIH TLV-TWA.
[e]TLV-STEL (threshold limit value – short-term exposure limit, American Conference of Governmental Industrial Hygienists) (ACGIH 2013) 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]REL-STEL (recommended exposure limit – short-term exposure limit) (NIOSH 2011) is defined analogous to the ACGIH TLV-STEL.

[g]MAK (maximale arbeitsplatzkonzentration [maximum workplace concentration], Deutsche Forschungsgemeinschaft [German Research Foundation]) (DFG 2010) is defined analogous to the ACGIH TLV-TWA.

[h]MAK Spitzenbegrenzung (peak limit category II, excursion factor 2, Deutsche Forschungsgemeinschaft [German Research Foundation]) (DFG 2010) constitutes the maximum average concentration to which workers can be exposed for a period 15 min with no more than four exposure periods per work shift with 1-h intervals; total exposure may not exceed 8-h MAK.

[i]MAC (maximaal aanvaaarde concentratie [maximal accepted concentration], Dutch Expert Committee for Occupational Standards, The Hague, The Netherlands) (MSZW 2007) is defined analogous to the ACGIH TLV-TWA.

8.2. Other Standards and Guidelines

A comparison of the AEGL values with other standards and guidelines for pentaborane is presented in Table 4-15. The concentration of pentaborane that is immediately dangerous to life or health was determined by the National Institute for Occupational Safety and Health (NIOSH) to be 1 ppm on the basis of the acute inhalation studies of Jacobson (1958), Levinskas et al. (1958), and Weir et al. (1964). (The data attributed to Jacobson [1958] appear to be those generated by Feinsilver et al. [1960].) The American Conference of Governmental Industrial Hygienists established a threshold limit value–time-weighted average (TWA) of 0.005 ppm and a short-term exposure limit (STEL) of 0.015 ppm, both of which are intended to prevented adverse CNS effects, such as convulsions and neurologic impairment in workers (ACGIH 2001, 2013). The Occupational Safety and Health Administration (OSHA) adopted 0.005 ppm as the permissible exposure limit (PEL)-TWA "to protect exposed workers against the significant risk of CNS neuropathic effects, such as tremors and convulsions, behavioral changes, and loss of judgment, potentially associated with exposure to pentaborane above the PEL" (29CFR 1910 [2006]). In concurrence with OSHA, NIOSH adopted 0.005 ppm as its recommended exposure limit (REL)-TWA and 0.015 ppm as the REL-STEL.

8.3. Data Adequacy and Research Needs

Case reports of occupational exposures to pentaborane are available, but none of them provide quantitative data adequate for deriving AEGL values. They do show, however, that exposure to pentaborane at concentrations below the odor threshold can cause significant CNS toxicity.

Animal data on pentaborane were adequate for deriving AEGL-2 and AEGL-3 values. Studies in four species were available, and consistent results were found among species. Studies conducted in the 1960s were considered more reliable than those conducted in the 1950s, because an analytic method for measuring pentaborane was not available in the 1950s.

The key studies used to derive the AEGL values for pentaborane were well conducted and reported. One shortcoming was that only one study was available in which the exposure duration was longer than 1 h and for which analytic concentrations were available (Feinsilver et al. 1960) for the purpose of determining the exposure concentration-time relationship for pentaborane.

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APPENDIX A

DERIVATION OF AEGL VALUES FOR PENTABORANE

Derivation of AEGL-1 Values

AEGL-1 values for pentaborane are not recommended because of insufficient data. The absence of AEGL-1 values does not imply that exposures at concentrations below the AEGL-2 values are without adverse effects.

Derivation of AEGL-2 Values

Key study:	Weir, F.W., V.M. Seabaugh, M.M. Mershon, D.G. Burke, and M.H. Weeks. 1964. Short exposure inhalation toxicity of pentaborane in animals. Toxicol. Appl. Pharmacol. 6:121-131.
Toxicity end point:	No-observed-effect level for CNS toxicity in dogs; 1.4 ppm for a 60-min exposure. Dogs exposed a second time (the following day), however, began to exhibit CNS effects including decreased activity, miosis, and CAR delays. Additional exposures at 1.4 ppm caused irritability and aggressiveness.
Time scaling:	$C^n \times t = k$; an empirical value for n of 1.3 was determined by linear-regression analysis of rat lethality data (LC_{50} values for exposures of 5-60 min [Weir et al. 1961, 1964]). Acute lethality data from studies in dogs yielded an n = 1.0, but that value was not used because the exposure durations were only 2-15 min (Weeks et al. 1964). Use of the rat studies to determine the value of n was considered appropriate because neurotoxicity was the primary toxic effect in both rats and dogs, and they were similarly sensitive to pentaborane. $(1.4 \text{ ppm})^{1.3} \times 60 \text{ min} = 93 \text{ ppm-min}$
Uncertainty factors:	3 for interspecies differences; similar effects (CNS toxicity) were found in humans and four species of laboratory animals, and LC_{50} values varied less than 3-fold among the species. 3 for intraspecies variability; the homogenous response among species and the steep concentration-response curve for lethality indicate that there would be little variability among humans.

Modifying factor: None

Calculations:

10-min AEGL-2: $C^{1.3} \times 10$ min = 93 ppm-min
C = 5.6 ppm
5.6 ppm ÷ 10 = 0.56 pm (1.4 mg/m^3)

30-min AEGL-2 $C^{1.3} \times 30$ min = 93 ppm-min
C = 2.4 ppm
2.4 ppm ÷ 10 = 0.24 ppm (0.62 mg/m^3)

1-h AEGL-2 C = 1.4 ppm
1.4 ppm ÷ 10 = 0.14 ppm (0.36 mg/m^3)

4-h AEGL-2 $C^{1.3} \times 240$ min = 93 ppm-min
C = 0.48 ppm
0.48 ppm ÷ 10 = 0.048 ppm (0.12 mg/m^3)

8-h AEGL-2 $C^{1.3} \times 480$ min = 93 ppm-min
C = 0.28 ppm
0.28 ppm ÷ 10 = 0.028 ppm (0.072 mg/m^3)

Derivation of AEGL-3 Values

Key studies: Weir, F.W., D.W. Bath, and M.H. Weeks. 1961. Short-term Inhalation Exposures of Rodents to Pentaborane-9. ASD Technical Report 61-663. Aerospace Medical Laboratory, Wright-Patterson Air Force Base, OH. December 1961.

Weir, F.W., V.M. Seabaugh, M.M. Mershon, D.G. Burke, and M.H. Weeks. 1964. Short exposure inhalation toxicity of pentaborane in animals. Toxicol. Appl. Pharmacol. 6:121-131.

Toxicity end point: Lethality threshold in mice; $BMCL_{05}$ = 5.08 ppm

Time scaling: $C^n \times t = k$; an empirical value for n of 1.3 was determined by linear-regression analysis of rat lethality data (LC_{50} values for exposures of 5-60 min [Weir et al. 1961, 1964]).

$(5.08)^{1.3} \times 60$ min = 496 ppm-min

Uncertainty factors: 3 for interspecies differences; similar effects (CNS toxicity) were found in humans and four species of laboratory animals, and LC_{50} values varied less than 3-fold among the species.

	3 for intraspecies variability; the homogenous response among species and the steep concentration-response curve for lethality indicate that there would be little variability among humans.
Modifying factor:	None
Calculations:	
10-min AEGL-3	$C^{1.3} \times 10$ min = 496 ppm-min C = 20 ppm 20 ppm ÷ 10 = 2.0 ppm (5.2 mg/m^3)
30-min AEGL-3	$C^{1.3} \times 30$ min = 496 ppm-min C = 8.7 ppm 8.7 ppm ÷ 10 = 0.87 ppm (2.2 mg/m^3)
1-h AEGL-3	C = 5.1 ppm 5.1 ppm ÷ 10 = 0.51 ppm (1.3 mg/m^3)
4-h AEGL-3	$C^{1.3} \times 240$ min = 496 ppm-min C = 1.7 ppm 1.7 ppm ÷ 10 = 0.17 ppm (0.44 mg/m^3)
8-h AEGL-3	$C^{1.3} \times 480$ min = 496 ppm-min C = 1.0 ppm 1.0 ppm ÷ 10 = 0.10 ppm (0.26 mg/m^3)

APPENDIX B

CATEGORY PLOT FOR PENTABORANE

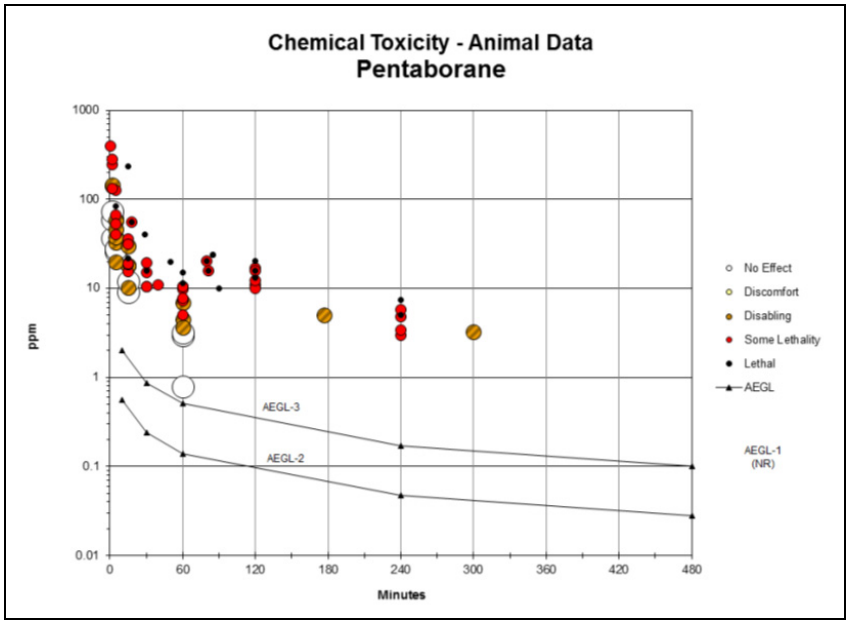


FIGURE B-1 Category plot of toxicity data and AEGL values for pentaborane. The data include single-exposure data from studies of monkeys, dogs, rats, and mice. Results from multiple-exposure studies that have information on effects from the first exposure to pentaborane are also included. No human data on pentaborane were available.

TABLE B-1 Data Used in Category Plot for Pentaborane

Source	Species	ppm	Minutes	Category	Comments
AEGL-2		0.56	10	AEGL	
AEGL-2		0.24	30	AEGL	
AEGL-2		0.14	60	AEGL	
AEGL-2		0.048	240	AEGL	
AEGL-2		0.028	480	AEGL	
AEGL-3		2.0	10	AEGL	
AEGL-3		0.87	30	AEGL	
AEGL-3		0.51	60	AEGL	
AEGL-3		0.17	240	AEGL	
AEGL-3		0.1	480	AEGL	
Weeks et al. 1964	Monkey	37	2	0	No toxic signs
Weeks et al. 1964	Monkey	60	2	0	No toxic signs
Weeks et al. 1964	Monkey	143	2	2	Convulsions and tremors
Weeks et al. 1964	Monkey	248	2	SL	LC_{50}
Weeks et al. 1964	Dog	73	2	0	No toxic signs
Weeks et al. 1964	Dog	144	2	2	Convulsions
Weeks et al. 1964	Dog	284	2	SL	LC_{50}
Weeks et al. 1964	Dog	16	5	0	No toxic signs
Weeks et al. 1964	Dog	33	5	2	Lethargy
Weeks et al. 1964	Dog	58	5	2	Convulsions
Weeks et al. 1964	Dog	126	5	SL	LC_{50}
Weeks et al. 1964	Dog	9.1	15	0	No toxic signs
Weeks et al. 1964	Dog	18	15	2	Convulsions, tremors

(Continued)

TABLE B-1 Continued

Source	Species	ppm	Minutes	Category	Comments
Weeks et al. 1964	Dog	36	15	SL	LC_{50}
Weir et al. 1964	Dog	26	5	0	No toxic signs (head-only exposure)
Weir et al. 1964	Dog	28	5	0	No toxic signs (whole-body exposure)
Weir et al. 1964	Dog	38	5	2	Tremors, salivation, clonic convulsions, apprehension
Weir et al. 1964	Dog	46	5	2	Tremors, convulsions
Weir et al. 1964	Dog	12	15	0	No toxic signs
Weir et al. 1964	Dog	18	15	2	Tremors, apprehension
Weir et al. 1964	Dog	30	15	2	Clonic convulsions
Weir et al. 1964	Dog	0.80	60	0	No toxic signs
Weir et al. 1964	Dog	3.0	60	0	No toxic signs (whole-body exposure)
Weir et al. 1964	Dog	3.2	60	0	No toxic signs (head-only exposure)
Weir et al. 1964	Dog	4.5	60	2	Convulsions
Weir et al. 1964	Dog	5.0	60	SL	Tremors, convulsions, salivation, death (1/2)
Weir et al. 1964	Dog	6.9	60	2	Tremors, convulsions, salivation
Weir et al. 1964	Dog	7.5	60	SL	Convulsions, death (2/3)
Weir et al. 1964	Dog	10.5	60	SL	Tremors, convulsions, salivation, death (1/2)
Dost et al. 1963	Rat	11	40	SL	LC_{50}
Feinsilver et al. 1960	Rat	4.8	240	SL	Mortality: 1/10
Feinsilver et al. 1960	Rat	5.8	240	SL	LC_{50}
Feinsilver et al. 1960	Rat	7.5	240	3	Mortality: 10/10
Krackow 1953	Rat	17	120	SL	LC_{50}
Svirbely 1954a	Rat	235	15	3	Mortality: 3/3
Svirbely 1954a	Rat	56	18	SL	Mortality: 2/3
Svirbely 1954a	Rat	20.2	80	SL	Mortality: 4/5

Svirbely 1954a	Rat	16	81	SL	Mortality: 2/5
Svirbely 1954a	Rat	24	85	3	Mortality: 3/3
Svirbely 1954a	Rat	15.7	120	SL	LC_{50}
Svirbely 1954a	Rat	20.2	120	3	Mortality: 5/5
Svirbely 1954b	Rat	3.3	300	2	Convulsions, gasping, tremors, aggressiveness, salivation, organ lesions
Weir et al. 1961, 1964	Rat	66.6	5	SL	LC_{50}
Weir et al. 1961, 1964	Rat	84.7	5	3	Mortality: 10/10
Weir et al. 1961, 1964	Rat	31.2	15	SL	LC_{50}
Weir et al. 1961, 1964	Rat	15.2	30	SL	LC_{50}
Weir et al. 1961, 1964	Rat	19.3	30	SL	Mortality: 9/10
Weir et al. 1961, 1964	Rat	9.8	60	SL	Mortality: 3/10
Weir et al. 1961, 1964	Rat	10.4	60	SL	LC_{50}
Weir et al. 1961, 1964	Rat	15.1	60	3	Mortality: 10/10
Feinsilver et al. 1960	Mouse	3	240	SL	Mortality: 2/10
Feinsilver et al. 1960	Mouse	3.4	240	SL	LC_{50}
Krackow 1953	Mouse	5	240	3	Mortality: 10/10
Krackow 1953	Mouse	11	120	SL	LC_{50}
Svirbely 1954a	Mouse	56.0	18	3	Mortality: 5/5
Svirbely 1954a	Mouse	20.2	80	3	Mortality: 10/10
Svirbely 1954a	Mouse	16	81	3	Mortality: 10/10
Svirbely 1954a	Mouse	24.0	85	3	Mortality: 5/5
Svirbely 1954a	Mouse	10	120	SL	Mortality: 2/10
Svirbely 1954a	Mouse	12.4	120	SL	LC_{50}
Svirbely 1954a	Mouse	13.2	120	3	Mortality: 10/10
Svirbely 1954a	Mouse	16	120	3	Mortality: 10/10

(Continued)

TABLE B-1 Continued

Source	Species	ppm	Minutes	Category	Comments
Weatherby 1958	Mouse	40	29	3	Mortality: 6/6
Weatherby 1958	Mouse	20	50	3	Mortality: 6/6
Weatherby 1958	Mouse	10	90	3	Mortality: 6/6
Weatherby 1958	Mouse	5.0	177	2	Convulsions, appeared normal after 24 h
Weir et al. 1961, 1964	Mouse	40.5	5	SL	LC_{50}
Weir et al. 1961, 1964	Mouse	15.4	15	SL	Mortality: 1/10
Weir et al. 1961, 1964	Mouse	18.4	15	SL	Mortality: 2/10
Weir et al. 1961, 1964	Mouse	18.6	15	SL	LC_{50}
Weir et al. 1961, 1964	Mouse	21.9	15	3	Mortality: 10/10
Weir et al. 1961, 1964	Mouse	10.5	30	SL	Mortality: 2/10
Weir et al. 1961, 1964	Mouse	10.6	30	SL	LC_{50}
Weir et al. 1961, 1964	Mouse	15.8	30	3	Mortality: 10/10
Weir et al. 1961, 1964	Mouse	7.3	60	SL	Mortality: 1/10
Weir et al. 1961, 1964	Mouse	7.8	60	SL	LC_{50}
Weir et al. 1961, 1964	Mouse	11.6	60	3	Mortality: 10/10
Weir et al. 1964	Mouse	19.8	5	2	Convulsions; death after repeated exposures
Weir et al. 1964	Mouse	10.2	15	2	Convulsions; death after repeated exposures
Weir et al. 1964	Mouse	3.7	60	2	Convulsions; death after repeated exposures
Weeks et al. 1964	Mouse	401	0.5	SL	LC_{50}
Weeks et al. 1964	Mouse	133	2.0	SL	LC_{50}
Weeks et al. 1964	Mouse	53	5.0	SL	LC_{50}
Weeks et al. 1964	Mouse	19	15	SL	LC_{50}

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

APPENDIX C

ACUTE EXPOSURE GUIDELINE LEVELS FOR PENTABORANE

Derivation Summary

AEGL-1 VALUES

AEGL-1 values for pentaborane are not recommended because of insufficient data. The absence of AEGL-1 values does not imply that exposures at concentrations below the AEGL-2 values are without adverse effects.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
0.56 ppm (1.4 mg/m^3)	0.24 ppm (0.62 mg/m^3)	0.14 ppm (0.36 mg/m^3)	0.048 ppm (0.12 mg/m^3)	0.028 ppm (0.072 mg/m^3)
Key reference: Weir, F.W., V.M. Seabaugh, M.M. Mershon, D.G. Burke, and M.H. Weeks. 1964. Short exposure inhalation toxicity of pentaborane in animals. Toxicol. Appl. Pharmacol. 6:121-131.				
Test species/Strain/Number: Dogs; beagle; unspecified sex; 3/concentration				
Exposure route/Concentrations/Durations: Inhalation; 1.4 ppm for 60 min; 5 consecutive days.				
Effects: No toxic signs or conditioned avoidance response (CAR) impairment occurred after the first 60-min exposure at 1.4 ppm. Dogs exposed a second time (the following day) began to exhibit CNS effects, including decreased activity, miosis, and CAR delays. Additional exposures at 1.4 ppm caused irritability and aggressiveness.				
End point/Concentration/Rationale: CNS toxicity; no-effect level of 1.4 ppm for a single 60-min exposure				
Uncertainty factors/Rationale: Total uncertainty factor: 10 Interspecies: 3, similar effects (CNS toxicity) occurred in humans and four species of laboratory animals, and LC_{50} values varied less than 3-fold among species. Intraspecies: 3, the homogenous response among species and the steep concentration-response curve for lethality indicate that there would be little variability among humans.				
Modifying factor: None				
Animal-to-human dosimetric adjustment: Not applied				
Time scaling: $C^n \times t = k$; an empirical value for n of 1.3 was determined by linear regression analysis of rat lethality data (Weir et al. 1961, 1964).				
Data adequacy: The data set on pentaborane was sufficient. The AEGL-2 values are supported by studies in monkeys exposed for 2 min and dogs exposed for 5 min (Weeks et al. 1964), which would have yielded similar or higher AEGL-2 values. The latter were not used because the exposure durations were too short, and the monkeys were not subjected to the CAR test.				

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
2.0 ppm (5.2 mg/m^3)	0.87 ppm (2.2 mg/m^3)	0.51 ppm (1.3 mg/m^3)	0.17 ppm (0.44 mg/m^3)	0.10 ppm (0.26 mg/m^3)

Key references:
(1) Weir, F.W., V.M. Seabaugh, M.M. Mershon, D.G. Burke, and M.H. Weeks. 1964. Short exposure inhalation toxicity of pentaborane in animals. Toxicol. Appl. Pharmacol. 6:121-131.
(2) Weir, F.W., D.W. Bath, and M.H. Weeks. 1961. Short-term Inhalation Exposures of Rodents to Pentaborane-9. ASD Technical Report 61-663. Aerospace Medical Laboratory, Wright-Patterson Air Force Base, OH. December 1961.

Test species/Strain/Number: Mice; white (strain not specified); male; 10/concentration

Exposure route/Concentrations/Durations: Inhalation; 6.9, 7.3, 6.9, 7.4, 7.5, and 11.6 ppm for 60 min

Effects: Tremors, ataxia, convulsions, red exudate around the mouth and nose, and death occurred within 24 h. The LC_{50} was 7.75 ppm, and the $BMCL_{05}$, and BMC_{01} values were 5.08 and 6.04 ppm, respectively.

End point/Concentration/Rationale: The $BMCL_{05}$ of 5.08 ppm was considered the threshold for lethality in mice.

Uncertainty factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, similar effects (CNS toxicity) occurred in humans and four species of laboratory animals, and LC_{50} values varied less than 3-fold among species.
Intraspecies: 3, the homogenous response among species and the steep concentration-response curve for lethality indicate that there would be little variability among humans.

Modifying factor: None

Animal-to-human dosimetric adjustment: Not applied

Time scaling: $C^n \times t = k$; an empirical value for n of 1.3 was determined by linear regression analysis of rat lethality data (Weir et al. 1961, 1964).

Data adequacy: The data set was adequate. LC_{50} values were available for four animal species, and had low variability among them. The AEGL-3 values are supported by lethality data in mice exposed for 4 h (Feinsilver et al. 1960), rats exposed for 60 min (Weir et al. 1961, 1964), and monkeys and dogs exposed for 2-15 min (Weeks et al. 1964), which would yield similar values.

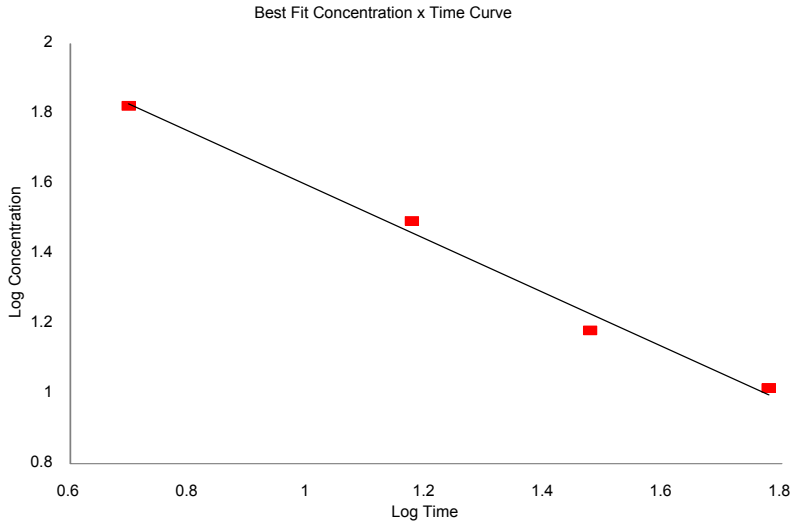
APPENDIX D

CONCENTRATION-EXPOSURE DURATION RELATIONSHIP FOR PENTABORANE

The concentration-exposure duration 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 2.5 (ten Berge et al. 1986). For pentaborane, the value of n was determined using lethality data from studies in rats by Weir et al. (1961, 1964). Rat LD_{50} values (see Table D-1) were analyzed by linear regression to calculate a value of n = 1.3.

TABLE D-1 Pentaborane Lethality in Rats

Input Data					
Concentration	Log Concentration	Time (min)	Log Time	Regression Output	
66.6	1.8235	5	0.6990	Intercept	2.3670
31.2	1.4942	15	1.1761	Slope	-0.7702
15.2	1.1818	30	1.4771	R squared	0.9901
10.4	1.0170	60	1.7782	Correlation	-0.9951
n = 1.3				Degrees of freedom	2
k = 1,183.27				Observations	4



APPENDIX E

BENCHMARK DOSE CALCULATIONS (VERSION 2.4.0)

Probit Model. (Version: 3.3; Date: 2/28/2013)
Input Data File:
C:/USEPA/BMDS240/Data/Pentaborane/pro_pentaborane_60min_mouse_Prb-BMR05.(d)
Gnuplot Plotting File:
C:/USEPA/BMDS240/Data/Pentaborane/pro_pentaborane_60min_mouse_Prb-BMR05.plt
Thu Aug 29 13:13:50 2013

BMDS_Model_Run

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

Dependent variable = Effect
Independent variable = Dose
Slope parameter is not restricted

Total number of observations = 6
Total number of records with missing values = 0
Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial (and Specified) Parameter Values
background = 0
intercept = -5.65795
slope = 0.663177

Asymptotic Correlation Matrix of Parameter Estimates

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

	intercept	slope
intercept	1	-1
slope	-1	1

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
Intercept	-10.5843	5.89507	-22.1384	0.969797
Slope	1.36615	0.813011	-0.227318	2.95963

Analysis of Deviance Table

Model	Log (likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-22.3996	6			
Fitted model	-26.072	2	7.3449	4	0.1187
Reduced model	-39.4295	1	34.0598	5	<.0001

AIC: 56.1441

Goodness of Fit

Dose	Est. Prob.	Expected	Observed	Size	Scaled Residual
6.9000	0.1235	1.235	0.000	10	-1.187
7.3000	0.2705	2.705	1.000	10	-1.214
6.9000	0.1235	1.235	3.000	10	1.697
7.4000	0.3175	3.175	3.000	10	-0.119
7.5000	0.3676	3.676	5.000	10	0.868
11.6000	1.0000	10.000	10.000	10	0.001

Chi-square = 6.53 d.f. = 4 P-value = 0.1630

Benchmark Dose Computation
Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95
BMD = 6.54353
BMDL = 5.08379