National Toxicology Program
U.S. Department of Health and Human Services

Center For The Evaluation Of Risks To Human Reproduction

NTP-CERHR EXPERT PANEL REPORT on the REPRODUCTIVE and DEVELOPMENTAL TOXICITY of 1-BROMOPROPANE

MARCH 2002 **NTP-CERHR-1-BP-02**

PREFACE

The National Toxicology Program (NTP) and the National Institute of Environmental Health Sciences (NIEHS) established the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR) in June 1998. The purpose of the CERHR is to provide timely, unbiased, scientifically sound evaluations of human and experimental evidence for adverse effects on reproduction, including development, caused by agents to which humans may be exposed.

1-Bromopropane (1-BP) was nominated by NIOSH and selected for evaluation by the CERHR based primarly on documented evidence of worker exposures and published evidence of reproductive and developmental toxicity in rodents. 1-BP is used in spray adhesives and as a precision cleaner and degreaser. It may also be used as an intermediate in the synthesis of pharmaceuticals, insecticides, quaternary ammonium compounds, flavors, and fragrances and as a solvent for fats, waxes, or resins.

The evaluation of 1-BP was a 4-month effort by a 10-member panel of academic, private, and government scientists that culminated in a public meeting in December 2001. At that meeting, the expert panel reviewed the scientific evidence on 1-BP and reached conclusions regarding its potential effects on human reproduction and development. The background information on 1-BP and findings of the expert panel are contained within this report. The Expert Panel Report on 1-Bromopropane is intended to (1) interpret the strength of scientific evidence that a given exposure or exposure circumstance may pose a hazard to reproduction and the health and welfare of children; (2) provide objective and scientifically thorough assessments of the scientific evidence that adverse reproductive/developmental health effects are associated with exposure to specific chemicals or classes of chemicals, including descriptions of any uncertainties that would diminish confidence in assessment of risks; and (3) identify knowledge gaps to help establish research and testing priorities. Staff scientists from the CERHR and members of the CERHR Core Committee (oversight committee to the CERHR whose members include NTP participating agencies) have reviewed the report and the CERHR will seek public review and comment through a Federal Register notice.

Subsequent to this comment period, the NTP will prepare the NTP-CERHR Report on 1-Bromopropane that contains its conclusions regarding the potential for 1-BP to adversely affect human reproduction or development. The NTP will base its conclusions on the Expert Panel Report on 1-Bromopropane, any public comments received on that report, and any relevant information available since the expert panel meeting. The NTP-CERHR report will include the public comments and the expert panel report as appendices. The NTP-CERHR Report on 1-Bromopropane will be made publicly available and transmitted to health and regulatory agencies.

The NTP and the CERHR wish to thank the members of the Bromopropanes Expert Panel for their contributions to the evaluation of 1-BP. We greatly appreciate their time, effort, and objectivity during this evaluation process. We also wish to thank the contract staff for their support in convening the expert panel and preparing the expert panel report.

The NTP-CERHR is headquartered at NIEHS, Research Triangle Park, NC and is staffed and administered by scientists and support personnel at NIEHS and at Sciences International, Inc., Alexandria, Virginia.

Reports can be obtained from the website (http://cerhr.niehs.nih.gov**) or from:**

Michael D. Shelby, Ph.D.
NIEHS EC-32
PO Box 12233
Research Triangle Park, NC 27709
919-541-3455
shelby@niehs.nih.gov

A Report of the CERHR Bromopropanes Expert Panel

Name	Affiliation
Kim Boekelheide, MD, Ph.D., Chairman	Brown University, Providence, RI
Cynthia F. Bearer, MD, Ph.D.*	Case Western Reserve U., Cleveland, OH
Sally Perreault Darney, Ph.D.	EPA, Research Triangle Park, NC
George P. Daston, Ph.D.	Proctor & Gamble, Cincinnati, OH
Raymond M. David, Ph.D.	Eastman Kodak Company, Rochester, NY
Ulrike Luderer, MD, Ph.D.	University of California-Irvine, Irvine, CA
Andrew F. Olshan, Ph.D.	University of North Carolina, Chapel Hill, NC
Wayne T. Sanderson, Ph.D., CIH	NIOSH, Cincinnati, OH
Calvin C. Willhite, Ph.D.	DTSC, State of California, Berkeley, CA
Susan Woskie, Ph.D., CIH	University of Massachusetts, Lowell, MA

*Dr. Bearer was unable to attend the Expert Panel meeting or contribute to the development of summaries and conclusions in Section 5 of this report.

With the Support of CERHR Staff:

NTP/NIEHS

Michael Shelby, Ph.D.	Director, CERHR
Christopher Portier, Ph.D.	Director, Environmental Toxicology Program
Lynn Goldman, MD	Technical Consultant

Sciences International, Inc.

John Moore, DVM, DABT	Principal Scientist
Annette Iannucci, MS	Toxicologist
Gloria Jahnke, DVM	Toxicologist

Note to Reader:

This report is prepared according to the Guidelines for CERHR Panel Members established by NTP/NIEHS. The guidelines are available from the CERHR web site (http://cerhr.niehs.nih.gov/). The format for Expert Panel Reports includes synopses of studies reviewed, followed by an evaluation of the Strengths/Weaknesses and Utility (Adequacy) of the study for a CERHR evaluation. Statements and conclusions made under Strengths/Weaknesses and Utility evaluations are those of the Expert Panel and are prepared according to the NTP/NIEHS guidelines. In addition, the Panel often makes comments or notes limitations in the synopses of the study. Bold, square brackets are used to enclose such statements. As discussed in the guidelines, square brackets are used to enclose key items of information not provided in a publication, limitations noted in the study, conclusions that differ from authors, and conversions or analyses of data conducted by the Panel.

ABBREVIATIONS

ALAT	alanine amino transferase
ANOVA	analysis of variance
ASAT	aspartate aminotransferase
ASTM	American Society for Testing and Materials
1-BP	1-Bromopropane
2-BP	2-Bromopropane
BMD	benchmark dose
BMDL	benchmark dose 95th percentile lower confidence limit
BSOC	Brominated Solvents Consortium
BUN	blood urea nitrogen
bw	bodyweight
C	Celsius
C_2	second carbon
C_3	third carbon
CAS RN	Chemical Abstract Service Registry Number
CBC	complete blood count
CERHR	Center for the Evaluation of Risks to Human Reproduction
CFC	chlorofluorocarbon
CNS	central nervous system
d	days
DL	distal latency
DMSO	dimethyl sulfoxide
F	female
F_0	parental generation
F_1	first filial generation
F_2	second filial generation
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestation day
GLP	Good Laboratory Practices
GSH	glutathione
GST	glutathione S-transferase
h	hour
HCFC	hydrochlorofluorocarbon
2,5-HD	2,5-hexanedione
HSDB	Hazardous Substances Data Bank
ip	intraperitoneal
IPI	interpulse intervals
IR	infrared
Kg	kilogram
K_m	Michaelis constant
K_{ow}	octanol-water partition coefficient
L	liter
LC_{50}	lethal concentration, 50% mortality
LC_{100}	lethal concentration,100% mortality
LD_{50}	lethal dose, 50% mortality
LH	luteinizing hormone

LOAEC	lowest observed adverse concentration, synonymous with lowest observed adverse effect level (LOAEL)
LPO	lipid peroxides
M	male
m^3	meters cubed
MCV	motor nerve conduction velocity
MFO	mixed function oxidase
mg	milligram
ML	motor latency
mL	milliliter
mm Hg	millimeters mercury
mmol	millimole
MQL	minimal quantification limit
MRI	magnetic resonance imaging
MSDS	Material Safety Data Sheet
mw	molecular weight
n	number
ng	nanogram
NIEHS	National Institute of Environmental Health Sciences
NOAEC	no observed adverse effect concentration, synonymous with no observed adverse effect level (NOAEL)
NOEC	no observed effect concentration, synonymous with no observed effect level (NOEL)
NIOSH	National Institute of Occupational Safety and Health
NTP	National Toxicology Program
OECD	Organization for Economic Co-operations and Development
OSHA	Occupational Safety and Health Administration
RBC	red blood cell
PE/NE	polychromatic/normochromatic erythrocyte
pnd	postnatal day
pNPH	p-nitrophenol hydroxylase
PPE	personal protective equipment
ppm	parts per million
PPR	paired-pulse ratios
PS	paired-pulse population spike
S	Sulfur
sc	subcutaneous
SD	standard deviation
SNAP	Significant New Alternatives Program
TWA	time weighted average
UNEP	United Nations Environment Programme
US EPA	United States Environmental Protection Agency
V_{max}	maximal velocity of metabolism
wk	week
w/v	weight per volume
µg	microgram
µM	micromolar
µmole	micromole

TABLE OF CONTENTS

LIST OF TABLES

List of Figures

1.0 CHEMISTRY, USE, AND HUMAN EXPOSURE

1.1 Chemistry

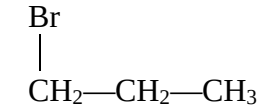
1.1.1 Nomenclature

1-Brompropane: CAS RN=106-94-5

Synonyms: Propyl bromide; n-Propyl Bromide

1.1.2 Formula and Molecular Mass

Figure 1-1. Chemical Structure of 1-Bromopropane (1-BP)



C_3H_7Br mw=123.0

1.1.3 Chemical and Physical Properties

Conversion Factors: $1mg/m^3 \cong 0.198$ ppm; $1ppm \cong 5.03$ mg/m^3

Table 1-1. Physicochemical properties of 1-BP

Property	Value
Boiling Point	71°C at 760 mm Hg
Melting Point	-110°C
Flashpoint	25.6°C[a]
Specific Gravity	1.353 at 20°C
Solubility in Water	2,450 mg/L
Vapor Pressure	110.8 mm Hg at 20°C
Stability	Stable*
Reactivity	Reacts with strong oxidizing agents and bases*
Flammability	Flammable[a]
Log K_{ow}	2.10

HSDB (*1*), *Aldrich (*2*)

[a]This flashpoint was reported in a Material Safety Data Sheet by Aldrich (*2*). However, no flashpoint was reported in closed or open cup testing of Ensolve (*3*), a solvent mixture containing >90.5% 1-BP (*4*). The results of 11 flammability studies were summarized in a letter submitted to the US EPA (*5*). It was asserted (*6*) that when a flashpoint was determined, it was at a temperature greater than the level that would classify a compound as flammable under the classification systems developed by the National Fire Protection Agency and four national or international governmental agencies.

1.1.4 Technical Products and Impurities

Two Material Safety Data Sheets (MSDS) from manufacturers of laboratory reagents reported the purity of 1-BP to be 99% (*2, 7*). The Occupational Safety and Health Administration (OSHA)

analyzed samples of 1-BP and detected 2-bromopropane (2-BP) at concentrations ranging from 0.1–0.2% (*8*). Since that time, ASTM standard D6368 (*9*) for vapor degreasing and general solvent grade 1-BP was amended to specify that 2-BP levels remain below 0.1%. Table 1-2 lists ASTM (*9*) specifications for vapor-degreasing and general grade 1-BP.

Table 1-2. Specifications for Vapor-Degreasing Grade and General Grade 1-BP (*9*)

Property	Specification	ASTM Test Method
Specific gravity, 25/25°C	1.320 to 1.350	D 2111
Distillation range (760 mm Hg)		D 1078
Initial boiling point, °C, min	70.0	
Dry point, °C, max	88.0	
Acidity (as HCl), weight %, max	0.0010	D2989
Alkalinity (as NaOH), weight %, max	0.020	D 2989
Water, weight %, max	0.0150	D 3401
Appearance	clear and free from Suspended matter	D 3741
Color, APHA, max	15	D 2108
Free halogen	passes test	D 4755
Nonvolatile residue, weight %, max	0.0010	D 2109
Acid acceptance (as NaOH), weight %, min	0.15	D 2942
Aluminum scratch	passes test	D 2943
Normal-propyl bromide content, weight %, min	93	GC
Iso-propyl bromide content, weight %, max	0.1	GC

Neat 1-BP is unusable as a solvent and is therefore sold as a mixture containing stabilizers or additives for solvent applications (*10*). Five MSDS were identified in an Internet search for 1-BP solvent mixtures. The compositions of the solvents included 1-BP at 70–95% with 1-BP levels exceeding 90% in the majority of products (*4, 11-14*). Other ingredients listed in these MSDS included butylene oxide, 1,3-Dioxolane, nitromethane, dimethoxymethane, t-butanol, 1,1,1-2-tetrafluoroethane, and a terpene blend.

Tradenames for 1-BP solvent mixtures include Hypersolve, Abzol, Lenium, Contact Cleaner – NPB Heavy Duty, Leksol, Teksol, Ensolv, Solvon, Vapor Edge 1100, X-Cel, VDS-3000, Cobar-Clean NPB, No Flash Nu Electro Cleaner, Heavy Duty Degreaser II, and 1640 Bulk (*15*). Trade names of adhesives containing 1-BP include Whisper Spray (Imperial Adhesive), and Fire Retardant Soft Seam 640 (Mid South Adhesive) (*16*). Of relevance to this Expert Panel review is that the test material used in a 13-week rat inhalation study was designated by the testing facility as ALBTA1 (*6*). This material contained no stabilizers or additives.

1.2 Use and Human Exposure

1.2.1 Production Information

1-BP is produced by reacting n-propyl alcohol with hydrogen bromide and then removing the water that forms in the process (*15*). 1-BP can also be produced by the dehydration of propanol with bromine or hydrogen bromide in the presence of sulfur catalyst (*17*).

Manufacturers of 1-BP that are part of the Brominated Solvents Consortium (BSOC) include Albemarle Corporation, Dead Sea Bromine Group/AmeriBrom, and Great Lakes Chemical Corporation (*18*). ATOFINA (formerly Elf Atochem) is also a manufacturer of 1-BP (*19*).

Additional manufacturers of 1-BP may include Diaz Chemical Corporation, Lambent Technologies, Talstar Western Chemical Inc., Cobar Americas, LPS Laboratories, CRC Industries, and Vineland Chemical Company (*1*). Other companies that have or are marketing 1-BP solvent blends include Petroferm, M.G. Chemicals, Albatross USA, Alpha Metals, Amity UK, Enviro Tech International, Poly Systems USA, Tech Spray, and Baker (*15*).

Between 1999 and 2000, 1.5 million pounds per year of 1-BP were produced and 2.8 million pounds per year imported for use in the United States (*10*). The BSOC estimated that global sales and emissions of 1-BP for solvent and adhesive applications as 4,839 metric tonnes **[10.6 million pounds]**, 3,152 metric tonnes **[6.9 million pounds]**, and 3,736 metric tonnes **[8.2 million pounds]** for the years 2000, 2001, and 2002, respectively (*6*). The United Nations Environment Program (*15*) n-BP Task Force estimated current worldwide annual use and emissions of 1-BP at 5,000–10,000 metric tons **[11–22 million pounds]**. Future consumption levels of 1-BP have been estimated but are not being addressed in this report. However, the future growth rate for sale of 1-BP in the United States is not anticipated to exceed the current growth rate of 2.34% per year (*10*).

1.2.2 Use

1-BP is reported to be used as a solvent for fats, waxes, or resins and as an intermediate in the synthesis of pharmaceuticals, insecticides, quaternary ammonium compounds, flavors, or fragrances (*1*). 1-BP is also used in spray adhesives, in precision cleaning, and as a degreaser (*10, 16*).

1-BP is currently under review per the US EPA Significant New Alternatives Policy (SNAP) program in identification of substitutes for ozone-depleting substances (*20*). 1-BP is being considered as a possible replacement for CFC-113, methyl chloroform, and HCFC-141b for non-aerosol solvent cleaning of metals and electronics and for adhesives, coatings, aerosol propellant, and solvent applications.

At least three manufacturers are limiting or eliminating use of 1-BP for solvent applications. Great Lakes Chemical no longer sells 1-BP solvent blends (*15*). ATOFINA (*19*) has decided not to market 1-BP for solvent applications. Albemarle has stated that use of 1-BP in adhesive and other applications in which 1-BP exposure cannot be controlled should be restricted or prohibited (*21*).

1.2.3 Occurrence

There is very little information documenting the presence of 1-BP in ambient air, drinking or surface waters, food, or consumer products. An unspecified level of 1-BP was detected in the drinking water from an unreported location (*1*). Schwarzenbach et al. (*22*) reported on an investigation of leaks from a wastewater tank at a Swiss alkyl halide factory at which 1-BP was manufactured (>5 tons/year). After the plant ceased operation, the underlying aquifer was found to be heavily polluted. Following soil excavation and continuous groundwater pumping for 7 years, substantial concentrations of bromobenzene and chlorobenzene were found, but neither 1-BP, nor 2-BP, nor its corresponding alcohol metabolites could be detected in groundwater. *In vitro* studies by Schwarzenbach et al. (*22*) confirmed the rapid hydrolysis of 1-BP (half life of 26 days) under anaerobic conditions.

The atmospheric lifetime of 1-BP is reported to be less than 20 days due to reactions with hydroxyl that result in the release of bromine atoms and formation of brominated acetone (*23*). Unreported levels of 1-BP were detected in the volatile emissions from household waxes, liquid pastes, and detergents (*1*). 1-BP was also detected in six species of marine microalgae at

unreported levels; it was postulated that the 1-BP was a product of monohalo and dihalo-oxo-fatty acid hydrolysis and that it could be transported from the algae to the marine environment (*1*).

1.2.4 Human Exposure

Until occupational exposure limits are set, the US EPA is recommending an 8-hour time weighted average (TWA) exposure limit of 50–100 ppm (*20*). Doull and Rozman (*24*) recommended a TWA-threshold limit value of 60–90 ppm with a notation for skin absorption. Albemarle Corporation is recommending a TWA limit of 25 ppm (*25*). ATOFINA (*19*) is recommending an 8-hour occupational exposure limit value of 5 ppm.

NIOSH measured 1-BP levels in the breathing zones (personal samples) of workers in three plants where a 1-BP-containing spray adhesive was used in the manufacture of seat cushions for aircraft or furniture. In the first plant that used a bromopropane-containing adhesive to manufacture seat cushions for aircraft, 8-hour TWA exposures of 69 workers ranged from 60–381 ppm with a mean of 169 ppm (*26*). The 8-hour TWA exposures of 16 workers from the second plant which manufactured cushions for sofas and similar types of seats ranged from 18 to 254 ppm with a mean of 96 ppm (*27*). An evaluation of 1-BP exposure was conducted in a third plant where a 1-BP-containing spray adhesive was used in the manufacture of sofa furniture cushions in the presence of a local exhaust system (*28*). Personal 8-hour TWA exposures in 12 sprayers were 41–143 ppm (mean 66 ppm) and 8.7–19.4 ppm, respectively. Fifteen-minute, short-term exposures of 9 sprayers were measured at 34–174 ppm and 5-minute ceiling exposures were measured at 40–152 ppm in 11 sprayers.

NIOSH reevaluated 1-BP levels at the first and third plants after local exhaust, ventilation, and work practice changes were made. After the installation of spray booths with local exhaust ventilation at the first plant, personal 8-hour TWA exposures in 30 workers ranged from 1.2 to 58 ppm with a mean of 19 ppm (*16*). Short-term exposures (15 minutes) were measured in 12 workers from the assembly or covers department. The range of short-term exposures in the assembly and covers departments ranged from 12 to 26 ppm and 13 to 96 ppm, respectively. After the third plant enclosed the local exhaust ventilation to create spray booths and increase capture efficiency, 8-hour TWA personal breathing zone samples measured for 12 assembly workers over 3 days (n=34) ranged from 7.7 to 35 ppm (mean=19 ppm) (*29*). These evaluations demonstrate that worker exposures can be dramatically reduced by implementation of exhaust and ventilation controls.

NIOSH also measured 1-BP concentrations in a plant where 1-BP was used as a cold bath degreaser that was recently enclosed in a room with local exhaust ventilation to vent vapors from the workplace (*25*). Personal samples were obtained from 20 employees who worked in the area of the degreaser. TWA 1-BP exposures only exceeded the minimal quantification limit of 0.02 ppm in 7 workers and ranged from 0.04 to 0.63 ppm.

The results of selected air sampling surveys for 1-BP conducted by Albemarle Corporation for some of their customers were submitted for review (*10*). Three surveys of area and personal breathing zone samples indicated that worker exposures across metal cleaning and adhesive users were variable ranging from below the limit of detection (<0.1 ppm) to 92 ppm. The exposures of adhesive users were typically much higher than metal cleaning workers. These measurements fall within the range of adhesive worker exposures measured by NIOSH after the installation of ventilation controls, but are lower than measurements made before these controls were implemented.

The Expert Panel noted that it is likely that worker exposures and absorbed doses also occur through dermal contact. No surveys have yet evaluated dermal exposure. Due to the volatility of 1-BP, it may be difficult to directly measure human dermal exposure and absorption. Biological monitoring may be the best way to evaluate the contribution of dermal exposure to total absorbed dose in humans.

1.3 Utility of Data

The exposure data reviewed by the Expert Panel are of limited utility for assessment. Very little data are available on consumer or general population exposures to 1-BP. No information on the volume of usage or number of US workers exposed to 1-BP is available. The data available on current 1-BP exposures in the United States are based on exposure surveys conducted by NIOSH of three spray adhesive and one cold degreasing operation that used 1-BP, and some selected exposure surveys conducted by a manufacturer of 1-BP products. These surveys do not represent a cross-section of potential exposures since these investigations were prompted by request from the workers or management of the companies involved. No industry-wide exposure study has been conducted. None of the exposure evaluations to date have characterized the potential contribution of dermal exposures to the worker.

1.4 Summary of Human Exposure Data

Within the United States, 1-BP is used as a solvent in spray adhesives (*16*), in vapor degreasing (*25*), and in precision cleaning (*10*). 1-BP may also be used as a solvent for fats, waxes, or resins or as an intermediate in the synthesis of pharmaceuticals, insecticides, quaternary ammonium compounds, flavors, or fragrances (*1*). In the future it is possible that 1-BP may be used as a substitute for hydrochlorofluorocarbons (HCFC) (*20*). Current usage of 1-BP is less than 5 million pounds (*10*). One manufacturer of 1-BP is recommending that 1-BP not be used in solvent applications in which exposures cannot be controlled (*21*); while two other manufactures are not marketing 1-BP for solvent applications (*15, 19*). No information was found that documents exposure of the public to 1-BP through contact with air, drinking water, food, or consumer products.

NIOSH collected 8-hour TWA personal breathing zone measurements for 1-BP in three plants where 1-BP-containing spray adhesives were used (n=99) and in one plant where 1-BP was used as a cold vapor degreaser (n=20). In the plants where 1-BP was being used as a spray adhesive, exposures ranged from 18 to 381 ppm (mean=142 ppm) (*26-28*). After ventilation control improvements had been implemented in two of the adhesive-using plants, NIOSH found that exposures had decreased to a range of 1.2–58 ppm (n=64; mean=19 ppm) (*16, 29*). In the plant where 1-BP was used as a vapor degreaser, only 7 of 20 8-hour personal TWA exposures exceeded the minimal quantification limit of 0.02 ppm with a range of 0.04–0.63 ppm (*25*); the degreaser had recently been enclosed in a room with local exhaust ventilation installed to vent vapors outside the workplace. Numerous additional exposure measurements have been collected by industry, but were not assessed by the Panel. The NIOSH exposure measurements evaluated here were from a few selected locations and cannot be considered an accurate representation of the cross-section of exposure levels nationwide.

It is likely that worker exposures also occur through dermal contact with 1-BP. No measurements have evaluated dermal exposure. Biological monitoring may be the best way to evaluate the contribution of dermal exposure to total absorbed dose.

2.0 GENERAL TOXICOLOGICAL AND BIOLOGICAL PARAMETERS

2.1 Toxicokinetics and Metabolism

No human kinetic or metabolism data were identified.

Empirical evidence from rodent toxicity studies indicates that 1-BP is absorbed by the inhalation route. However, animal studies that characterize and quantify absorption and distribution of 1-BP by any route were not found. The blood:air partition coefficients for humans (7.08) and rats (11.7) indicate that 1-BP is readily soluble in blood; the fat:air partition coefficient for humans is 128 and for rats is 236 (*30*). The studies described below discuss metabolism and excretion of 1-BP.

Tachizawa et al. (*31*) studied the metabolism of 1-BP *in vitro* using hepatic microsomal enzyme preparations from phenobarbital-induced rats. Microsomes were prepared from Sprague-Dawley rats treated with phenobarbital according to the procedure of Neal (*32*), and incubated with ^{14}C-labeled-1-BP. Metabolites detected by gas chromatography (GC) included 1,2-propane-diol, propionic acid, and propene (a volatile metabolite) in order of relative amount produced. When glutathione was added to the incubation mixture, *S*-propyl glutathione and *S*-(2'-hydroxy-1'-propyl) glutathione were produced. Thin layer chromatography was used to detect glutathione metabolites.

Strength/Weaknesses: This is a well-conducted study of potential metabolites of 1-BP. Efforts were made to identify substances using appropriate analytical methods. The study does not provide kinetic constants for metabolism, but there are no perceived limitations.

Utility (Adequacy) for CERHR Evaluation Process: This study provides information of the metabolites formed from 1-BP. The data are adequate to provide indications of potential toxic metabolites.

Kim et al. (*17*) examined the inducibility of hepatic cytochrome P450 isoenzymes and other related enzymes in microsomes of 7-week-old male and female Sprague-Dawley rats that inhaled 50, 300, or 1,800 ppm 1-BP (analytical grade) for 6 hours/day, 5 days/week, for 8 weeks**. [It was verified that units of concentration were ppm and not ppm/kg (*33*)]**. Chamber concentrations of 1-BP were monitored by GC every 15 minutes. Enzyme activities were studied in 10 rats/sex/group. Methods of statistical analyses were paired-sample t-test using SPSS according to the original report (*34*). 1-BP treatment resulted in significantly increased activities of NADH b_5 reductase and p-nitrophenol hydroxylase (pNPH) in high-dose males and females. Western blot analyses from 1-BP treated rats revealed a strong signal for CYP2E. Glutathione S-transferase (GST) activity significantly increased in male rats of all dose groups **[Expert Panel notes that no dose-related increase was observed]** and female rats in the two highest dose groups. Glutathione peroxidase activity was significantly increased in all treated rats. Lipid peroxides (LPO) were significantly increased in females of the two highest dose groups and males in the highest dose group. In most cases, enzyme activities were higher in male than in female rats. The authors concluded that the metabolism of 1-BP is sex-dependent; the CYP2E1 isoenzyme is possibly responsible for 1-BP metabolism; free radicals are produced by activated intermediates as halide radicals; and GST is involved in detoxification and protection of tissues against oxidative damage induced by halide radicals.

Strength/Weaknesses: This study demonstrates a concentration-related increase in overall metabolic enzyme activity that may be important in the activation or deactivation of 1-BP. Sufficient numbers of animals were used, and the methodology for enzyme assays was adequately described. However, conclusions concerning the hepatic metabolism of 1-BP by GST pathways to non-toxic substances appear to be unsupported.

Utility (Adequacy) for CERHR Evaluation Process: The data are adequate to provide some indication of alterations in metabolism in response to 1-BP exposure.

Kaneko et al. (*35*) studied the *in vitro* metabolism of 1-BP in hepatic microsomes of male Wistar rats by measuring the rate of substrate disappearance and rate of product (n-propyl alcohol) formation. The authors demonstrated that there were two sets of V_{max} and K_m metabolic constants. According to authors, differences in rate between substance disappearance and n-propyl alcohol formation suggested the possibility of alternate pathways besides metabolism of 1-BP to n-propyl alcohol or that n-propyl alcohol is further metabolized. The procedures and results for this experiment were reported in the form of a short communication.

Strength/Weaknesses: This study provides information on the metabolism of 1-BP by microsomal enzymes (likely cytochrome P-450). In addition, there is a clear indication of two enzymatic pathways, both of which have reasonable affinity for 1-BP, but a low capacity for metabolism.

Utility (Adequacy) for CERHR Evaluation Process: The data demonstrate that 1-BP is metabolized by hepatic microsomal enzymes, although to a minor extent. This information may be important in assessing risk for systemic toxicity since metabolism from mixed function oxidase (MFO) enzymes is not likely to play a significant part in activation of 1-BP to active metabolites.

Khan and O'Brien (*36*) incubated isolated rat hepatocytes in the presence of 100 μM 1-BP or 6 other 1-bromoalkanes for up to 1 hour and measured intracellular glutathione levels. 1-BP caused a time-related reduction in glutathione level. The magnitude of glutathione depletion was directly related to the chain length of the bromoalkane. Incubation with 1-BP resulted in minimal decreases (32% lower than untreated cells) in intracellular glutathione levels compared with long-chain bromoalkanes (88% lower than untreated cells).

Strength/Weaknesses: This is a well-designed study that provides direct evidence that 1-BP can react with glutathione and deplete hepatocyte GSH levels.

Utility (Adequacy) for CERHR Evaluation Process: This study supports the findings of Kim et al. (*17*) indicating that glutathione reacts with 1-BP.

Barnsley et al. (*37*) fed 4 male rats **[age and strain unspecified]** a diet containing ^{35}S-labelled yeast for 3 days, injected 2 of the rats subcutaneously with 1 mL of 40% w/v solution of 1-BP **[purity not specified]** in arachis oil on the fourth day, collected urine for the 24 hours after dosing, and measured metabolites in urine by radiochromatography. Three metabolites were detected in the urine of treated but not control rats: n-propylmercapturic acid, 2-hydroxypropylmercapturic acid, and n-propylmercapturic acid sulphoxide.

Strength/Weaknesses: Although this study lacks the analytical sophistication that is common to current studies, it provides direct evidence of conjugation and excretion of 1-BP with glutathione, presumably via glutathione-S-transferases.

Utility (Adequacy) for CERHR Evaluation Process: This study is important in understanding the value of the GST pathway in the metabolism of 1-BP. GST activation is an important component of haloalkane metabolism and toxicity. For some haloalkanes, biotransformation to an active metabolite leads to systemic toxicities. However, there is no indication that active metabolites are produced from 1-BP exposures in quantities that lead to long-term adverse health effects. In fact, the data from Barnsley et al. (*37*) suggest that GST activation is minimal compared with other haloalkanes.

Jones and Walsh (*38*) further characterized metabolites of 1-BP in rats. Male Sprague-Dawley rats **[230–260 g; age and number treated not specified]** were treated orally with 1-BP **[purity not specified]** in arachis oil at 200 mg/kg bw/day for 5 days and the urine was pooled and examined by thin layer chromatography. Three mercapturic acid compounds identified in urine were the same as those identified by Barnsley et al. (*37*): N-acetyl-S-propyl-cysteine, N-acetyl-S-(2-hydroxypropyl)cysteine, and N-acetyl-S-propylcysteine-S-oxide. Three additional compounds were also identified in urine: N-acetyl-S-(3-hydroxypropyl)cysteine, N-acetyl-S-(2-carboxyethyl)cysteine, and 3-bromopropionic acid. *In vitro* metabolism studies with 1-BP demonstrated that oxidation of C_3 and C_2 occurs before conjugation of the alkyl group with glutathione. Figure 2-1 illustrates a possible metabolic pathway of 1-BP as determined by Jones and Walsh (*38*).

Jones and Walsh (*38*) studied the excretion of 1-BP in the expired air and urine of Sprague-Dawley rats following a single intraperitoneal (ip) injection with 200 mg/kg bw. Initial excretion of unchanged 1-BP in expired air was rapid, with 56% and 60% exhaled after 2 and 4 hours, respectively. Only trace amounts were detected in expired air after 4 hours. Twenty-five percent of the administered bromide was excreted in urine over a period of 100 hours.

Strength/Weaknesses: This study further characterizes the metabolism of 1-BP, demonstrating the exhalation of a significant amount of unmetabolized 1-BP following parenteral exposure. On the other hand, details on the methodology are unclear with numbers of animals used not specified.

Utility (Adequacy) for CERHR Evaluation Process: The value of this study is to define the metabolic pathway of 1-BP and identify intermediate metabolites.

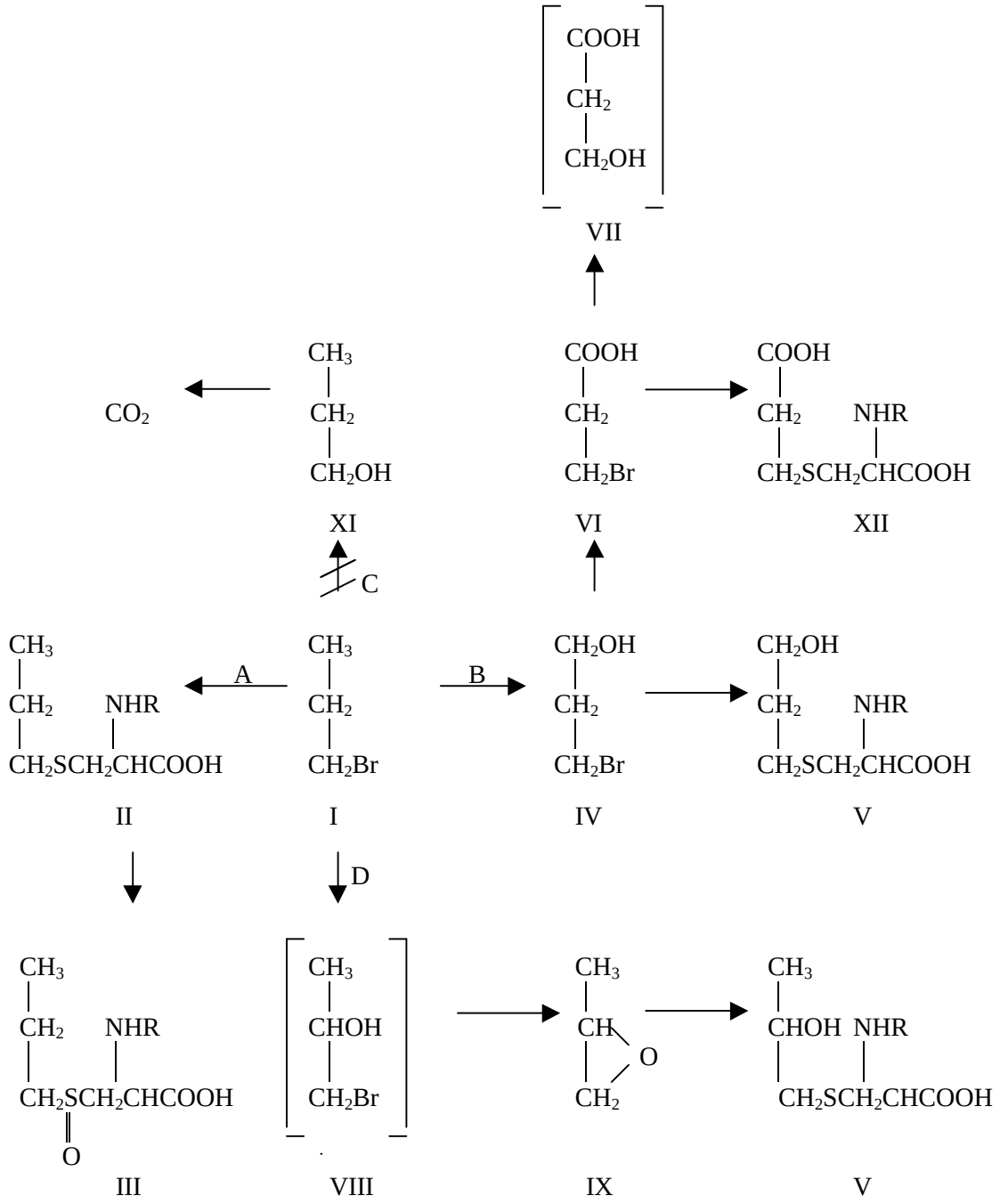


Figure 2-1. Possible Metabolic Pathway for 1-BP in the Rat. Compounds in parentheses were not isolated in urine. Reproduced with permission from Jones and Walsh (*38*).

2.2 General Toxicity

2.2.1 Human Data

Sclar (*39*) published a case report of a 19-year-old male who experienced weakness of the lower extremities and the right hand, numbness, and difficulty swallowing and urinating after a 2-month occupational exposure to a degreasing and cleaning solvent. The solvent consisted primarily of 1-BP (95.5%) and also butylene oxide (<0.5%), 1,3-dioxolane (<2.5%), and nitromethane (<0.25%). Levels of exposure were not measured and it is not clear by which route(s) exposure occurred. Although the patient wore gloves (material unspecified), the skin on his right (preferentially exposed) hand darkened, suggesting that the gloves may not have offered sufficient protection. Nerve conduction tests revealed prolonged distal motor and F response latencies with slower extremity sensory nerve conduction velocities but preserved amplitude response. Magnetic resonance imaging (MRI) scans revealed patchy areas of increased T_2 signal in the periventricular white matter and root enhancement in the lumbar region of the spinal cord. An analysis of spinal fluid did not detect antibodies for infectious agents. According to the author, the evidence suggested that the patient was suffering from a symmetric demyelinating polyneuropathy with central nervous system (CNS) involvement. Because similar symptoms were observed in rats exposed to 1-BP, the author hypothesized that the patient's symptoms may have resulted from 1-BP exposure.

Strength/Weaknesses: This study reports information from a single patient without exposure information. There was no demonstration that appropriate personal protective equipment (PPE) was used.

Utility (Adequacy) for CERHR Evaluation Process: Very limited utility. Because this is only a case-report involving a single individual, less weight is given to it as true evidence of 1-BP adverse health effects in humans.

In 1998, NIOSH conducted a health hazard evaluation at a plant where a 1-BP-containing spray adhesive was used in the manufacture of seat cushions (*40*). Forty-three employees (34 females and 9 males) provided a blood sample for a complete blood count (CBC) and answered a medical questionnaire. Individuals were 18–64 years of age (mean=31 years). Based on industrial hygiene data, 1-BP exposures in those employees were categorized as 'low' (117 ppm **[585 mg/m^3]**), 'medium' (170 ppm **[850 mg/m^3]**), or 'high' (197 ppm **[985 mg/m^3]**). NIOSH concluded that there were no CBC abnormalities related to individual or categorical exposure. Employees in the high exposure group reported headaches at least once each week. NIOSH stated that the headaches could have been related to 1-BP exposure but noted the lack of an exposure-response trend since the lower exposure groups reported a similar frequency of headache. **[The Expert Panel found the information incomplete and could not reach a conclusion as to the effect of 1-BP exposure.]** The questionnaire also included questions about reproductive function that are discussed under Section 4.

Strength/Weaknesses: This study evaluates hematology parameters in humans from a cohort of workers whose exposure to 1-BP is known. It is possible to compare, directly, these results with animal data. A weakness of the study is that only 61% of individuals (43 of 70) completed the survey, and that raw data were not presented for hematology. The investigators should have compared the exposure data between those who completed the survey and those who failed to complete the survey in order to gauge potential selection bias. In addition, pre-exposure hematology values for these individuals were not available to ascertain if occupational 1-BP exposure resulted in changes.

Utility (Adequacy) for CERHR Evaluation Process: The value of this study is that effects on hematology were assessed and can be compared with animal data. Unfortunately, no raw data were presented. The authors indicated that there was no correlation of reduced erythrocyte count and exposure. Although there was a suggestion of an exposure-response gradient with respect to low red blood cell count, the small numbers of subjects and lack of an unexposed comparison group reduce the utility of the preliminary study.

2.2.2 Animal Data

An acute oral toxicity study of 1-BP (*41*) was located, but is not reported here because those data were not considered to have direct utility for the evaluation of potential adverse reproductive or developmental effects.

An acute Good Laboratory Practices (GLP) dermal toxicity study of 1-BP was conducted (*42*) using Sprague-Dawley rats obtained from Iffa Credo, France. Animals were 283 g (males) and 233 g (females) and at least 8 weeks of age at the initiation of exposure. Neat 1-BP (99.3% purity; 2,000 mg/kg bw) was applied to the shaved skin on the dorsal area of 5 rats/sex and wrapped with a gauze pad (semi-occlusive wrap) for 24 hours. The animals were observed for signs of toxicity, and bodyweight was measured weekly. No concurrent control animals were used but bodyweight gain was compared to historical control data. At termination of the 14-day observation period, animals were sacrificed, necropsied, and examined macroscopically for evidence of organ toxicity. There were no clinical signs of toxicity. One female lost weight during the first week, but all other animals gained weight. There was no evidence of dermal irritation, and there were no gross lesions at necropsy. The authors concluded that the dermal LD_{50} is higher than 2,000 mg/kg bw. **[The Expert Panel noted that the lack of an occlusive wrap may have resulted in evaporation of the test substance and a less-than-optimal exposure period.]**

Strength/Weaknesses: This is a well-conducted study according to current guidelines. A weakness is that the test substance was covered with a semi-occlusive wrap rather than an occlusive wrap. This may have allowed the test substance, which is known to be volatile, to evaporate from the application site resulting in a less-than optimal exposure period.

Utility (Adequacy) for CERHR Evaluation Process: The data have limited utility in assessing the potential for dermal penetration of 1-BP. Because no effects were observed, it is unclear if this represents a lack of systemic toxicity from dermal exposure or the lack of dermal penetration.

An acute inhalation toxicity study of 1-BP (*43*) was conducted using 7–9 week old male and female Wistar rats obtained from Charles River France (SPF, WISTAR Crl rats: (WI) BR). The study was conducted according to GLP. In a limit test, 5 rats/sex/group were exposed to 0 or 34.6 g/m^3 **[34, 600 mg/m^3, equivalent to 6,879 ppm]**. In the main part of the study, 5 males and 5 females/group were exposed to 0, 30.2, 35.1, 37.0, or 42.5 g/m^3 **[30,200, 35,100, 37,000, or 42,500 mg/m^3, equivalent to 6,003, 6,997, 7,355 and 8,448 ppm, respectively]** 1-BP (99.5%). Five satellite males/group were exposed to 0 or 36.4 g/m^3 **[36,400 mg/m^3, equivalent to 7,237 ppm]** and blood was collected 24 hours and 13 days after exposure for hematology. All exposures were conducted for 4 hours in a nose-only chamber (flow-past system). Concentrations were verified by GC. Animals were observed for 14 days following treatment. Bodyweights were measured daily. Lungs and testes from control animals and those exposed to 34.6 (males only) and 42.5 g/m^3 were weighed and examined microscopically (tissue fixed in 10% formalin). All animals exposed to 37.0 and 42.5 g/m^3 died on test. Most animals exposed to

35.1 g/m^3 died (7/10) and some animals exposed to 34.6 g/m^3 died (3/10). The LC_{50} was estimated at 35.0 g/m^3 **[6,958 ppm]**. Clinical signs included respiratory distress and "general weakness." Surviving animals gained weight over the 14 days. There was an increase in leukocyte count, hemoglobin, and packed cell volume on day 2 for the 36.4 g/m^3 group **[no statistical evaluation]**, but these differences resolved by day 14. There was no apparent change in relative testis weight and no microscopic testicular lesions in animals exposed to 1-BP. Pulmonary lesions consisting of edema and "emphysema" were observed in the 1-BP-exposed animals. **[The Expert Panel selected a NOEC of 30.2 g/m^3.]**

Strength/Weaknesses: This study reports acute lethality after inhalation of very high concentrations of 1-BP. Adequate numbers of animals were used and procedures conform to current standards and practices. A weakness of the study is the use of 10% formalin for fixation of the testes. This fixative is recognized as inadequate to properly evaluate subtle effects on the testes. No ovarian or female reproductive tract data were reported.

Utility (Adequacy) for CERHR Evaluation Process: This study demonstrates the acute toxicity of 1-BP under conditions of exposure that permit direct comparison to toxic effects seen with other substances. The measurements of testicular weight and histopathology are helpful in ascertaining adverse effects that occur following acute 1-BP exposure.

Kim et al. (*44*) studied the acute and repeated inhalation toxicity of 1-BP in 11-week-old male and female Sprague-Dawley rats (SPF grade, from Dae Han Laboratory Animal Research Center). In both parts of the experiment, rats inhaled reagent grade 1-BP and concentrations within chambers were monitored and confirmed by GC every 15 minutes. For the acute study, 5 rats/sex/group inhaled 0, 11,000, 13,000 15,000, or 17,000 ppm **[55,337, 65,398, 75,460, or 85,521 mg/m^3]** 1-BP for 4 hours. Rats were observed for 2 weeks following exposure. Clinical signs of toxicity in treated groups during exposure included piloerection, reduced activity, ataxia, lacrimation, and reduced response to noise. Death was observed within 24 hours of exposure in groups exposed to 13,000 ppm and higher; incidence of death was dose-related and reached 100% in the highest dose. All surviving rats clinically recovered 24 hours after the exposure period. An LC_{50} of 14,374 ppm (95% confidence limit: 13,624–15,596 ppm) was calculated. The lowest lethal concentration was <11,833 ppm and the LC_{100} was >18,186 ppm. At the end of the observation period, all surviving rats were sacrificed by carbon dioxide and necropsied; abnormal tissues were examined histologically. Cytoplasmic vacuolation of hepatocytes surrounding the central vein was observed in an unspecified number of treated rats but the effect was not dose-dependent. **[The Expert Panel selected a NOEC of 11,000 ppm.]**

In the repeated inhalation portion of the Kim et al. (*44*) study, 10 rats/sex/group inhaled 0, 50, 300, or 1,800 ppm 1-BP **[252, 1,509, or 9,055 mg/m^3]** for 6 hours/day, 5 days/week, for 8 weeks. **[The rationale for dose selection was not discussed.]** Bodyweight and feed consumption were measured twice per week. Urine samples were collected over a 24-hour period prior to termination. Analytical chamber data indicate there were 40 exposure days; food was removed during the last day of exposure, and necropsy was performed the next day (*34*). At termination, rats were sacrificed, blood was collected under anesthesia, and hematology, clinical biochemistry, and urinalyses were conducted. Data were analyzed by two-way analysis of variance (ANOVA) and Duncan's multiple t-test. Thymus, adrenal, testis, heart, lung, kidney, spleen, liver, and brain were weighed and fixed in 10% neutral buffered formalin, stained with hematoxylin-eosin or PAS-hematoxylin, and examined histologically. Clinical signs of toxicity included reduced activity and mild ataxia in the 1,800 ppm rats during exposure. Bodyweight gain was reduced in males and females of the high dose group (1,800 ppm), but food intake was not affected. Some

statistically significant changes in hematological, blood chemistry, and urinalysis parameters were noted in treated rats. The authors stated that most values were within normal ranges but did not specify which values were outside normal limits. Minimal effects on hemoglobin, hematocrit, and red blood cell values were observed for the high-dose group; **[the Expert Panel considered the toxicological significance of these effects to be unclear]**. Significant decreases in some serum biochemistry values were observed, **[these are considered by the Expert Panel to be of no toxicological significance]**. Significant increases in male relative organ weights were noted for the left adrenal (≥50 ppm), liver and brain (≥300 ppm), and the right kidney and both testes (1,800 ppm). In the 1,800 ppm females, significant increases in relative organ weights were noted for ovaries, kidneys, and liver; thymus weight was significantly reduced at 50 and 1,800 ppm. **[The Expert Panel noted that bodyweight was reduced for the 1,800 ppm group; this may have contributed to the increase in relative testicular, ovarian, renal, hepatic, and brain weights.]** Histopathological evaluations revealed cytoplasmic vacuolation of hepatocytes surrounding the central vein in all treated animals, but the effect was not dose-dependent and liver enzymes (ALAT, ASAT) were not increased. **[Therefore the increased liver weight at doses of 300 ppm and higher were not considered adverse by the authors or the Expert Panel.]** Renal tubular casts were seen in females of the 1,800 ppm group. However, there was no increase in either BUN or creatinine. There were no lesions observed in the other organs, including testes. **[The Expert Panel agreed with the authors' conclusion about lack of biological significance for hematology, blood chemistry, and urinalysis findings. Given the lack of histopathologic effects in brain, thymus, and adrenal, the Expert Panel did not conclude that increased weights of these organs were adverse effects. A NOAEC of 300 ppm was selected by the Expert Panel.]**

Strength/Weaknesses: These studies used an adequate number of animals in a well-designed experiment. The details of exposure are adequate to assess how the exposures were conducted, and the inhalation procedures conform to standard practices. A weakness was that the fixative used to preserve testes is known to be inadequate to properly evaluate subtle histopathological effects.

Utility (Adequacy) for CERHR Evaluation Process: This study demonstrates the acute and subchronic toxicity of 1-BP under conditions of exposure that are directly comparable to other substances. There is a clear dose-response for effects. The study is judged to be adequate for use in the evaluation process.

Two additional repeated-exposure inhalation studies were conducted: a 28-day repeated exposure study (*45*) and a 13-week repeated exposure study (*46*). The 28-day study was a range-finding study from which to select doses for the subsequent 13-week study. Both studies were conducted according to GLP. In the 28-day study, male and female 6-week old Sprague-Dawley CD rats (Crl:CD(SD)BR; Charles River Canada Inc., St. Constant, Quebec) were divided into 4 groups of 10 animals/sex/group and exposed to 0, 2.0, 5.0, or 8.0 mg/L **[2,000, 5,000, or 8,000 mg/m^3, equivalent to 398, 993 and 1,590 ppm]** 1-BP for 6 hours/day, 5 days/week for 4 consecutive weeks (concentrations confirmed by IR spectrometry). Purity of the 1-BP was >99% (*47*). Exposure concentrations were selected on the basis of a 10-day range-finding study. Animals were observed daily, and functional tests for neurotoxicity were performed prior to initiation of the study and at termination. Bodyweight and feed consumption was measured weekly. Ophthalmologic examination was performed prior to study start and termination. Urine samples were collected overnight prior to sacrifice. At termination on day 29 (day 1 was the first day of exposure), blood was collected for hematology and clinical biochemistry. Animals were necropsied 3 days after the last exposure. Brains and respiratory systems from all dose groups and all tissues from the control and 8.0 mg/L groups were examined microscopically. Data were

analyzed for homogeneity using a Bartlett's test. Homogeneous data were analyzed using an ANOVA followed by a Dunnett's test. Heterogeneous data were analyzed using a Kruskal-Wallis tests followed by a Dunn's test. Nearly all males (8/10) and a few females (3/10) exposed to 8.0 mg/L died or were sacrificed in a moribund condition. Animals in the 5.0 mg/L group showed clinical signs of toxicity. An abbreviated functional observational battery performed on surviving 2 male and 7 female rats revealed impaired gait (ataxia and hypotonic gait) in the 8.0 mg/L group. These animals may have been in an emaciated condition (*6*). No sign of neurotoxicity was seen in the other groups. Bodyweight and feed consumption were significantly lower for the 8.0 mg/L group. No ophthalmologic findings were reported. Hematology for the 8.0 mg/L male group could not be evaluated because only 2 animals survived, but decreased erythrocyte count, hemoglobin, and hematocrit values were seen for the 7 surviving females in the 8.0 mg/L group. Erythrocyte count and hemoglobin levels were significantly decreased for the male and female 5.0 mg/L groups. Females in the 5.0 mg/L group also had lower hematocrit values. **[The Expert Panel concluded that no toxicologically significant changes were seen in serum biochemistry or urinalysis].** Relative weights (to bodyweight) of the liver, lungs, and kidneys were higher for the 5.0 mg/L male group compared with the controls. **[The organ weights for the 8.0 mg/L male group could not be evaluated by the Expert Panel because of the high mortality]**. Relative weights of the liver, spleen, thyroid/parathyroid glands, and kidneys were significantly higher for the 5.0 and 8.0 mg/L female groups compared with the controls. Females in the 8.0 mg/L group also had increased relative lung and brain weights, and lower thymic weight. Microscopic vacuolation of the brain white matter considered to be chemically related was observed in about 50% of rats in all treated groups (9/20, 11/20, and 11/20 in low to high dose groups, respectively). Dose-related, mild-to-moderate, vacuolation of gray matter was observed in all rats from the 5.0 and 8.0 mg/L groups, and in 1 animal from the 2.0 mg/L group (*48*). Vacuolation of the spinal cord and lesions of the kidneys and urinary tract and nasal cavity were seen in the high-dose animals. Lesions in the bone marrow thymus, spleen, and lymph nodes of high dose animals may have been related to treatment. The two surviving males in the high-dose group had atrophic changes recorded as hypo/aspermatogenesis (testes fixed in Zenker's fluid). No ovarian lesions were observed at the high dose.

Strength/Weaknesses: These studies used an adequate number of animals in a well-designed experiment. The details of exposure are adequate to assess how the exposures were conducted, and the inhalation procedures conform to standard practices. Testes were fixed in a fixative that permitted detailed microscopic evaluation. A weakness is that the majority of tissues from the low- and mid-dose groups were not evaluated for histopathology.

Utility (Adequacy) for CERHR Evaluation Process: This study demonstrates the subchronic toxicity of 1-BP in rats under conditions of controlled inhalation that are directly comparable to other substances. There is a clear dose-response for histopathologic effects in the nervous system. The study is judged to be adequate for use in the evaluation process.

A 13-week repeated exposure study (*46*) was conducted in which male and female 7–7.5-week-old Sprague-Dawley CD rats (Crl:CD(SD)BR; Charles River Canada Inc., St. Constant, Quebec) were divided into 5 groups of 15 animals/sex/group and exposed to 0, 0.5, 1.0, 2.0, or 3.0 mg/L **[500, 1,000, 2,000, or 3,000 mg/m^3, equivalent to 99, 199, 397 and 596 ppm]** 1-BP for 6 hours/day, 5 days/week for 13 consecutive weeks (concentrations monitored by IR spectrometry and confirmed by GC). Purity of 1-BP was >99% (*47*). Exposure concentrations were selected based on the results of the 28-day study. Animals were observed daily, and functional tests for neurotoxicity were performed prior to study start and during weeks 4, 8, and 13. Bodyweight and feed consumption were measured weekly. Ophthalmologic examination was performed prior to study start and at termination. Urine samples were collected overnight prior to sacrifice. At

termination, 3 days after the last exposure, blood was collected for hematology and clinical biochemistry. All tissues from the control and high-dose groups were examined microscopically; respiratory tissues and tissues with lesions were examined at all doses. Data were analyzed for homogeneity using a Bartlett's test. Homogeneous data were analyzed using an ANOVA followed by a Dunnett's test. Heterogeneous data were analyzed using a Kruskal-Wallis test followed by a Dunn's test. No clinical signs were observed that could be ascribed to 1-BP. No evidence of neurotoxicity was apparent. No differences in bodyweight were noted; feed consumption was significantly lower for the high-dose female group only during weeks 3 and 4. No ophthalmologic findings were reported. No toxicologically significant effects were seen in hematology, clinical biochemistry, or urinalysis. A concentration-related increase in relative liver weight was seen for males with the liver weight of the 3.0 mg/L group significantly greater than controls. No liver weight effect was seen for female rats. Treatment-related vacuolation of the liver was observed in 3/15 and 6/15 male rats at the 2.0 and 3.0 mg/L dose, respectively, and 1/15 female rats at the 2.0 mg/L dose. This lesion was characterized as a diffuse slight to mild vacuolation in the centrolobular region of the liver. The vacuolation in brain tissue, observed at higher doses in the 28-day study was not observed in this study. No testicular or ovarian effects were noted (testes fixed in Zenker's fluid). The study authors identified a no observed effect concentration (NOEC) of 1.0 mg/L (1,000 mg/m^3) based on liver histopathology.

Strengths/Weaknesses: This is a well-conducted study according to current guidelines and practices. Sufficient numbers of animals were used to evaluate the potential effects of subchronic exposure. There are no perceived weaknesses. However, the lack of perfusion with a fixative appropriate for neurohistopathologic evaluation reduces the utility of this study to detect subtle microscopic effects in the nervous system.

Utility (Adequacy) for CERHR Evaluation Process: This study is adequate to assess the potential subchronic systemic toxicity and functional neurotoxicity of inhaled 1-BP.

Several studies have evaluated the potential neurotoxicity of 1-BP.

In a short communication, Yu et al. (*49*) reported the results of a study in which 10-week old male Wistar rats (9 per group from Shizuoka Laboratory Animal Center) were exposed to a concentration of 1,000 ppm **[5,031 mg/m^3]** 1-BP (99.4% purity) or filtered air in a chamber for 8 hours/day for up to 7 weeks as a companion group for a study of 2-BP. Exposures were conducted 7 days/week (*50*). This study by Yu et al. (*49*) was reported in greater detail by Yu et al. (*51*). The exposure concentrations were monitored and confirmed by GC. Parameters examined included motor nerve conduction velocity (MCV), distal latency (DL), and histopathology. Hematology was examined in 5 rats/group. Organs examined histologically included testis, epididymis, prostate, seminal vesicle, femur, liver, kidney, heart, lung, thymus, brain, and sciatic or tibial nerves. Data were analyzed by ANOVA followed by the Tukey-Kramer multiple comparison method. By the fifth week of exposure, 6 of 9 treated animals demonstrated altered locomotor activity with paddle-like gait and hindlimb paralysis. All treated animals exhibited hind-limb paralysis by the sixth week of exposure. Because the treated rats began showing signs of paralysis and emaciation, 4 exposed animals were sacrificed following 5 weeks of exposure, and the remaining 5 plus 5 unexposed controls were sacrificed after 7 weeks. MCV was significantly reduced in exposed animals, and there was degeneration of peripheral nerves particularly of the myelin sheath. Sections of peripheral nerve were dissected from the tibial nerve and preserved in osmium tetroxide following fixation with 10% formalin. Histopathological evaluation of the nervous system revealed degeneration of the peripheral nerve and axonal swelling in the gracilis of the spinal cord. No histopathological effects were noted in the testis (fixed in Bouin's solution and stained with periodic acid-Schiff's reagent), liver, kidney,

or bone marrow, and there were no changes in hematology parameters. Serum creatine kinase was significantly reduced in exposed animals. The authors concluded that 1-BP was a more potent nervous system toxicant, but less potent reproductive and hematopoietic system toxicant than 2-BP.

Strength/Weaknesses: A strength of this study is that appropriate methods were used for histopathologic evaluation of the nervous system and testes. A weakness is that the numbers of animals evaluated was minimal although it was adequate to draw reliable conclusions.

Utility (Adequacy) for CERHR Evaluation Process: This study provides good histopathologic evidence for 1-BP-induced neurotoxicity and the lack of testicular effects.

Ichihara et al. (*52*) conducted a study to examine the dose- and duration- neurotoxicity response to 1-BP exposure. Eleven 10-week-old male Wistar rats/group (from Shizuoka Laboratory Animal Center) were exposed to air or 200, 400, or 800 ppm **[1,006, 2,012, or 4,025 mg/m^3]** 1-BP vapors 8 hours/day for 12 weeks. Exposures were conducted 7 days per week under dynamic conditions (*50*). The highest nominal concentration was based on preliminary studies that noted debilitation of rats exposed to 1,000 ppm. Chamber concentrations were measured by GC. Neurological function was tested in 9 rats/group at weeks 0, 4, 8, and 12. Data were analyzed using one-way ANOVA followed by Dunnett's method. Mean bodyweights for the 400 and 800 ppm groups were significantly lower than controls after 8 weeks of exposure. Significant decreases in hindlimb grip strength were observed for all groups at 4 weeks, and for the 800 ppm group at 8 and 12 weeks. Hindlimb grip strength was also decreased for the 400 ppm group at 12 weeks. Significant decreases in forelimb grip strength were seen for the 400 and 800 ppm groups at 8 weeks, and for the 800 ppm group at 12 weeks. **[The Expert Panel only considered reductions in grip strength to be treatment-related if they were statistically significant and consistently related to duration of treatment. Therefore, reductions in hindlimb grip strength and forelimb grip strength were considered treatment related at ≥400 ppm and 800 ppm, respectively].** MCV was reduced for the 800 ppm group at weeks 8 and 12, and distal latency (DL) was increased for this group at weeks 4, 8, and 12. The rats in the 800 ppm group also displayed weak kicking and an inability to stand on a slope. At sacrifice, brain weight and blood chemistry were analyzed from 9 animals per group. At necropsy, two animals from each group were perfused for neurohistopathology with either 10% formalin or Zamboni's solution (one for each fixative). Muscular nerves were dissected out and post-fixed in osmium tetroxide. The weights of the cerebrum and gastrocnemius muscle were significantly reduced for the 800 ppm group. No differences in weight were seen for other parts of the brain or soleus muscle. Plasma creatinine phosphokinase activities for the 400 and 800 ppm groups were significantly reduced compared with controls. No changes were seen in the activities of lactate dehydrogenase, aspartate transaminase, alanine transferase, or alkaline phosphatase. Serum cholesterol was reduced in a dose-dependent manner, and plasma total protein and albumin were increased in a dose-related manner. Significant differences in cholesterol, aspartate transaminase, and alanine transaminase were seen for the 400 and 800 ppm groups. Plasma globulin levels were also significantly increased for the 800 ppm group. Morphological evidence of neurotoxicity was only noted in the high dose group (800 ppm) and included ovoid or bubble-like debris in myelin sheaths of peripheral nerves, swelling of preterminal axons of the gracile nucleus, and irregular banding of soleus muscle fibers. There was no degeneration or vacuolation of brain tissue. Authors noted that reductions in grip strength could not be explained by adverse changes in the nervous system alone, in that grip strength represents total vital factors in limb function. In comparing the result of this study to those obtained in a preliminary study with 2-BP, the authors concluded that 1-BP is a more potent neurotoxicant than 2-BP and is potentially

neurotoxic to humans. **[The Expert Panel determined a subchronic inhalation neurotoxicity NOAEC of 200 ppm.]**

Strength/Weaknesses: Concentration-related changes were observed in a thorough study of neurotoxicity. The fixation procedures were appropriate for adequate microscopic evaluation of nerves and muscles. A weakness is that the numbers of animals evaluated was minimal, especially for neurohistopathology. The number of animals for functional assessment was deemed to be sufficient for adequate conclusions to be drawn. Another weakness is that the grip strength data were not analyzed using a repeated-measures analysis. The lack of repeated measures analysis does not invalidate the conclusions concerning exposure-related effects.

Utility (Adequacy) for CERHR Evaluation Process: The data adequately define neurotoxicity in animals inhaling high concentrations of 1-BP. This information is useful for hazard assessment of 1-BP.

Zhao et al. (*53*) compared the neurotoxicity of 1-BP, 2-BP, and 2,5-hexanedione (2,5-HD) administered separately to rats. Seven to nine male Wistar rats/group (age not specified; from Seiwa Experimental Animal Institute) were injected subcutaneously (sc) with each chemical in olive oil once/day, 5 days/week, for 4 weeks. Doses administered were 3.7 or 11 mmol/kg bw 1-BP **[455 or 1,353 mg/kg bw]**; 1.1, 3.7, or 11.0 mmol/kg bw 2-BP **[135, 455 or 1,353 mg/kg bw]**; and 2.6 mmol/kg bw 2,5-HD **[296 mg/kg bw]**. Purity of all chemicals was >97%. A control group of nine rats was injected with the olive oil vehicle. According to the study authors, doses of 1.1, 3.7, and 11 mmol/kg bw are calculated to be equivalent to doses received by inhalation of 100, 300, and 1,000 ppm BP over an unspecified time period. Calculations were based upon respiratory data reported in a study by Mauderly et al. (*54*). Bodyweights were measured weekly. MCV and motor latency (ML) were measured every 2 weeks using an electrophysiological method. Data were analyzed by one-way ANOVA followed by Duncan's multiple range test. Bodyweight gain in the 11 mmol 1-BP/kg bw group was lower than the control group. By 2 weeks of exposure, the MCV began decreasing in treated rats and reached statistical significance in the 11 mmol 1-BP/kg bw group at week 4. Increases in ML occurred, but were not statistically significant. All three compounds, 2-BP, 1-BP, and 2,5-hexanedione, produced qualitatively similar responses in MCV and ML. The authors concluded that 1-BP and 2-BP administered parenterally were equally potent neurotoxicants and both compounds were less potent neurotoxicants than 2,5-hexanedione.

Strength/Weaknesses: This study utilized a reference neurotoxicant (2,5-hexanedione) for comparison of MCV and ML. Sufficient numbers of animals were used for comparison, and varying dose levels were used to establish a dose-response. A weakness is the calculation of the dose to be administered based on calculations for inhalation of vapors in laboratory animals. In the absence of pharmacokinetic information, these can only be estimates of absorbed dose. Based on previous information indicating that a significant amount of 1-BP is exhaled unmetabolized, the calculated amounts of absorbed dose are likely to have been overestimated.

Utility (Adequacy) for CERHR Evaluation Process: The utility of this study for the evaluation process is unclear. Although there are interesting data provided, the basis for dose selection cannot be verified. Therefore, the value of the study in human health hazard assessment is unclear.

Fueta et al. (*55*) reported in a short communication changes in neuronal excitability in the brain of Wistar rats inhaling 1-BP for 6 hours/day, 5 days per week, for up to 4 weeks (under dynamic conditions). A total of 30, 6-week-old male rats were exposed to 1,500 ppm **[7,546 mg/m^3]** 1-BP

vapors **[purity not specified]** or air (n=14–16/exposure condition) for 6 hours/day, 5 days/week for 1, 3, or 4 weeks. Some animals exposed for 4 weeks were allowed to recover for 1 week prior to termination. This study is a follow-up to that reported by Ohnishi et al. (*56*) **[Not available in English].** Transverse hippocampal slices were prepared following exposure for 1, 3, and 4 weeks and following a 1 week recovery period in rats exposed for 4 weeks. Brain slices were incubated in artificial cerebrospinal fluid during the stimulation of neurons and measurement of paired-pulse population spike (PS) responses in the granule cell layer of the dentate gyrus. When two pulses separated by a 10 msec interval were applied, a strong depression of the second PS was observed in control rats, but a nearly complete second PS response was seen in the 1-BP-treated rats. Paired-pulse ratios (PPR) were calculated by dividing the second PS by the first PS at interpulse intervals (IPI) ranging from 5–1,000 msec. PPRs significantly increased in all treated rats when interpulse intervals ranged from 5 to 20 msec. At interpulse intervals ranging from 500 to 1,000 msec, significant increases in PPRs were only observed in rats exposed to 1-BP for 4 weeks, with and without the 1-week recovery period, although the magnitude of the difference after recovery was lower. Ataxic gait and convulsions were observed in the rats during the fourth week of exposure. The authors concluded that changes in the CNS (dentate gyrus), in conjunction with peripheral nerve damage, may explain neurobehavioral changes. The authors imply that adverse effects were observed in the testes, although no data are presented.

Strength/Weaknesses: This study reports on time-related changes in the CNS that can be correlated with behavioral changes in animals. A strength of the study is that the exposure regimen conforms to standard practices, although details of monitoring the chamber concentrations were lacking. Another weakness is that no dose-response information is available.

Utility (Adequacy) for CERHR Evaluation Process: The adequacy of these data to the evaluation process is unclear. Effects were observed in the CNS before alterations in behavior were seen. Thus the correlation of CNS effects with behavioral changes is lacking. There is some evidence for recovery following cessation of exposure.

In a study that focused on reproductive toxicity, Ichihara et al. (*57*) exposed 10-week-old male Wistar rats to 0, 200, 400, or 800 ppm **[1,006, 2,012, or 4,025 mg/m^3]** 1-BP vapors for 8 hours/day for 12 weeks (8–9 animals per group). The exposure concentrations were monitored and confirmed by GC. Exposures were conducted 7 days per week under dynamic conditions (*50*). Bodyweight gain was reduced in the 400 and 800 ppm groups. Significant changes included increased relative liver weight (400 and 800 ppm) and absolute liver weight (800 ppm), and decreased absolute spleen weight (800 ppm). Histological effects observed in the livers of rats in the 800 ppm group included scanty spots in the cytoplasm of cells that were possibly glycogen, and reduced number and size of fat droplets around the central vein. There were no histopathological effects on the other non-reproductive organs examined (adrenal, thymus, spleen, lungs, heart, pituitary, and kidney). The only significant hematological effects noted were increased mean corpuscular volume at 800 ppm and decreased mean corpuscular hemoglobin concentration at 400 and 800 ppm. Blood chemistry was not evaluated. A detailed description of reproductive findings and other study details is included in Section 4. **[The Expert Panel determined 200 ppm to be a subchronic inhalation systemic NOAEC in rats.]**

Strength/Weaknesses: This study provides dose-response information for general toxicity and identifies a systemic NOAEC in male rats following repeated exposure. A weakness is that the numbers of animals evaluated was minimal although adequate to draw conclusions.

Utility (Adequacy) for CERHR Evaluation Process: This study is the first to have identified adverse effects of 1-BP inhalation on the male reproductive tract. The utility of the Ichihara et al. (*57*) study is discussed below in Section 4 (Reproductive Toxicity).

In a study sponsored by the BSOC, WIL Research Laboratories (*58*) evaluated the potential adverse effects of 1-BP whole-body inhalation exposure in F_0 and F_1 parental rats. The reproductive toxicity endpoints are discussed later in this document (Section 4). Groups of 25 male and female Crl:CD(SD)IGS BR rats were exposed to filtered air or 100, 250, 500, or 750 ppm **[0, 503, 1,257, 2,514, 3,771 mg/m^3]** 1-BP vapors (99.8% purity) for 6 hours/day, 7 days/week. Exposure concentrations within each chamber were measured 9–10 times during each exposure period by a validated GC method. Exposure of F_0 rats commenced at 7 weeks of age and F_1 rats began direct exposure at weaning. Exposures were conducted for at least 70 days prior to mating. Females were not exposed on postnatal days (pnd) 0-4 and only they, not their litters, were exposed during pnd 5–21. Therefore, offspring (litters) were indirectly exposed to the test chemical *in utero* and through nursing. In addition, the F_1 pups selected randomly for propagation of F_2 litters were directly exposed from pnd 22 forward. Significant reductions in cumulative weight gain of about 12% were noted in F_0 males in the 750 ppm group throughout the study, while food consumption was increased in the same group. Weekly bodyweight gains were significantly reduced in F_1 males of the 500 ppm group. In contrast, bodyweights of F_0 females were significantly depressed only at treatment weeks 7 and 8 in the 750 ppm group, while the food consumption of females in both the 500 and 750 ppm groups also increased throughout the 10-week treatment period. In addition, bodyweights were significantly lower in pregnant F_0 females at gestation day (gd) 20 in the 250 mg group, and at gd 14 and 20 in the 500 ppm group. The latter difference persisted throughout lactation. No clinical signs of toxicity were observed in the F_0 or F_1 generations. Significant reductions in absolute but not relative brain weight were seen in F_1 males (≥100 ppm), F_0 males (≥250 ppm), and F_0 and F_1 females (≥500 ppm). Significant increases in relative liver weight were seen in F_0 males and F_1 males and females (≥500 ppm) and F_0 females (750 ppm). Absolute thymus weights were increased in F_1 males exposed to ≥250 ppm, but no histological lesions were reported.

Upon termination of each generation, males and females underwent necropsy. All organs were preserved in 10% buffered formalin for microscopic evaluation. The study was conducted in compliance with GLP. For the F_0 generation, exposure-related effects were seen in the liver, kidneys, and spleen. Minimal-to-mild centrilobular hepatocellular vacuolation was noted in males from the 250, 500, and 750 ppm groups (7/25, 22/25, 24/25), and females from the 500 and 750 ppm groups (6/24, 16/25). Female rats were also observed to have increased glycogen in the liver. The liver lesions were considered to be not adverse by the authors. Minimal pelvic mineralization of the kidneys was seen in 250, 500, and 750 ppm males (1/25, 2/25, 6/25), and minimal-to-mild mineralization of the kidneys in 250, 500, and 750 ppm females (5/25, 12/24, 14/25). Brown pigment was observed with increasing severity in the spleen of 250, 500, and 750 ppm male and female rats. Histopathologic evaluation of the brain did not indicate any treatment-related lesions. **[Therefore reductions in absolute brain weight were not considered to be adverse effects by the Expert Panel.]**

For the F_1 generation, exposure-related effects were also seen in the liver, kidneys, and spleen. Minimal-to-mild centrilobular hepatocellular vacuolation was noted in males from the 250 and 500 ppm groups (15/25 and 23/25), and females from the 250 and 500 ppm groups (2/25 and 6/25). Female rats were also observed to have increased glycogen in the liver. The liver lesions were considered to be "not adverse" by the authors. Minimal-to-mild pelvic mineralization of the kidneys was seen in 500 ppm males (3/25), and minimal to mild mineralization of the kidneys in

250 and 500 ppm females (7/25 and 8/25). Brown pigment was observed with increasing severity in the spleen of 500 ppm female rats. Lesions of the reproductive tract are discussed in the section concerning Reproductive Toxicity (Section 4).

[The Expert Panel identified a lowest observed adverse effect concentration (LOAEC) for systemic toxicity of 250 ppm based on effects in kidneys of the F_0 and F_1 generations. The NOAEC was 100 ppm.]

Strength/Weaknesses: This study provides additional information on the histopathologic effects following exposure during the prenatal, perinatal, and adult periods. The methods used were appropriate and the study was well-conducted. A weakness is that the method of tissue fixation was not optimal to detect subtle lesions in nervous tissue.

Utility (Adequacy) for CERHR Evaluation Process: This study is adequate and useful to evaluate the effects of prolonged exposure to 1-BP.

2.3 Genetic Toxicity

Barber et al. (*59*) examined the mutagenicity of 1-BP in *Salmonella* strains TA1535, TA1537, TA1538, TA98, and TA100 with and without S9 (from Arochlor-induced rat livers) metabolic activation. The protocol employed a closed, inert incubation system designed to test volatile compounds. Five concentrations ranging from 1.1 to 20.3 μmole/plate **[135–2497 μg/plate]** were tested in a total of 5 replicates. Reference mutagens included methyl-N-nitro-N'-nitrosguanidine, 2-aminoanthracene, 9-aminoacridine, and picrolonic acid. Control cultures were incubated without the addition of any chemicals. 1-BP treatment increased the mutation frequency in strains TA1535 and TA100 with and without metabolic activation. It does not appear that cytotoxicity occurred at the highest concentration. Negative results were obtained in all other strains. Authors noted that for 1-BP, the closed method of testing is a superior technique for assessing mutagenicity in volatile compounds because previous testing according to the standard plate method gave negative results.

Strength/Weaknesses: This study provides information of genetic toxicity in relevant strains of bacteria. The study was well conducted and used techniques for exposure to vapors. There are no perceived weaknesses.

Utility (Adequacy) for CERHR Evaluation Process: The study provides evidence that 1-BP can induce mutations in prokaryotes with or without metabolic activation. It is of interest that mutagenic events were observed only in strains TA1535 and TA100, not in other strains. Strains TA100 and TA1535 are known to possess nascent glutathione transferase (GST) activity (*60, 61*), which may be linked to the mutations observed.

Elf Atochem (*62*) examined the mutagenicity of 1-BP (>99% purity) in *Salmonella* strains TA1535, TA1537, TA1538, TA98, and TA100 with and without S9 (from male Sprague-Dawley rats induced with Aroclor 1254) metabolic activation. Culture plates were incubated in closed stainless-steel vessels. The test substance was introduced into the culture using dimethyl sulfoxide (DMSO) as the vehicle. Concentrations ranging from 100 to 10,000 μg/plate were used. A concentration of 10,000 μg/plate was cytotoxic as noted by partial sparcity of background lawn. DMSO was used as a negative control. Reference mutagens included sodium azide, 2-aminoanthracene, 2-nitrofluorene, and 9-aminoacridine. Control cultures were incubated without the addition of any chemicals. There was no evidence of mutagenicity in any strain

either with or without S9. The study was conducted according to GLP standards.

Strength/Weaknesses: This study provides information of genetic toxicity in relevant strains of bacteria. The study was well conducted and used techniques for exposure to vapors. There are no perceived weaknesses.

Utility (Adequacy) for CERHR Evaluation Process: The study provides additional evidence that 1-BP does not induce mutations with or without metabolic activation. It is of interest that mutagenic events were not observed in strains TA1535 and TA100 in contrast with the results of Barber et al (*59*).

Kim et al. (*34*) examined the mutagenicity of 1-BP in *Salmonella* strains TA98, TA100, TA1535, and TA1537 and *E coli* strain Wp2uvrA with and without S9 (from male Sprague-Dawley rats induced with Aroclor 1254) metabolic activation. **[It was not specified if the protocol employed a closed incubation system designed to test volatile compounds].** Five concentrations ranging from 313 to 5,000 μg/plate were tested. Reference mutagens included sodium azide, 2-aminoanthracene, 9-aminoacridine, and 2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide. **[A negative control was also examined but the solvent used was not specified.]** 1-BP treatment did not increase the frequency of mutations at any dose studied. **[Cytotoxicity was not reported by the study authors.]**

Strengths/Weaknesses: The tests used appropriate strains of bacteria and employed positive and negative control chemicals. The failure to describe if a closed incubation system was used interjects some uncertainty in the interpretation of the negative results.

Utility (Adequacy) for CERHR Evaluation Process: This study provides a third source of data where 1-BP was tested in an *in vitro* microbial system.

Elf Atochem (*63*) examined the mutagenicity of 1-BP in L5178Y mouse lymphoma cells. The cells were treated for 3 hours with 125–1,500 mg/L 1-BP (99.3% purity) in the absence of metabolic activation or 125–2,500 mg/L 1-BP with S9 (from rats treated with Aroclor 1254) activation. The vehicle, DMSO, was used as a negative control. Methylmethane sulfonate and cyclophosphamide were used as reference mutagens. The highest concentration (2,500 mg/L) produced 100% cytolethality while the 2,000 mg/L concentration produced ~40–90% cytolethality, as assessed by relative cloning efficiency. A reproducible two-fold increase in mutation frequency compared to the concurrent control and/or evidence of a dose relationship were considered indicative of a positive response. Two separate experiments were conducted. In the absence of metabolic activation, a reproducible increase in mutation frequency was observed in cells treated with 1,000–1,500 mg/L 1-BP in both experiments. No increase in mutation frequency was observed in the first experiment with S9 activated cells. However, in the second experiment with S9 activated cells, an increase in mutation frequency was noted at 1,500–2,000 mg/L 1-BP. Study authors concluded that this study demonstrated mutagenic activity, especially in the absence of S9 activation.

Strengths/Weaknesses: This is a well conducted study to evaluate the potential of 1-BP to cause mutations in mammalian cells. The study was conducted according to current guidelines and accepted practices. There are no perceived weaknesses.

Utility (Adequacy) For CERHR Evaluation Process: These data provide evidence of mutagenic activity in a mammalian cell line. In order to draw conclusions concerning the

genotoxicity of 1-BP, these data must be viewed with other genetic toxicity data and metabolism data.

Elf Atochem (*64*) conducted a micronucleus study of 1-BP in bone marrow of mice. In the initial study, male and female Swiss OF1/ICO:OF1 (IOPS Caw) mice from Iffa Credo were treated twice with 0, 100, 400, or 800 mg/kg 1-BP (99.3%) in corn oil by ip injection. Cyclophosphamide was used as a reference clastogen. At least 5 animals/sex/group were used. Animals were killed 24 hours after the last treatment. The initial toxicity study indicated that 800 mg/kg would be a suitable high dose, and a second study was conducted with 0 and 800 mg/kg 1-BP. Mortality in males during the second study prompted a third study using an additional dose level of 600 mg/kg for males. Only the 600 mg/kg males and 800 mg/kg females were evaluated because the polychromatic/normochromatic erythrocyte (PE/NE) ratio for the controls from the initial attempt (100, 400, 800 mg/kg) were outside of the historic range and the test was considered invalid. No increase in micronucleated erythrocytes in bone marrow was observed in males treated with 600 mg/kg or in females treated with 800 mg/kg. The group treated with cyclophosphamide demonstrated a significant increase in micronucleated erythrocytes.

Strength/Weaknesses: This study provides information of the lack of 1-BP genetic toxicity *in vivo*. The study was well conducted and there are no perceived weaknesses.

Utility (Adequacy) for CERHR Evaluation Process: The study indicates that parenteral injection of 1-BP in mice failed to induce clastogenicity.

Kim et al. (*34*) conducted a micronucleus assay by exposing 10 Sprague-Dawley rats/sex/group to 0, 50, 300, or 1,800 ppm **[0, 252, 1,509, or 9,055 mg/m^3]** 1-BP vapors for 6 hours/day, 5 days/week, for 8 weeks. After treatment was complete, the rats were sacrificed and bone marrow was examined to determine the frequency of micronucleated polychromatic erythrocytes. 1-BP treatment did not increase the frequency of micronucleated polychromatic erythrocytes. The rats used in this experiment were apparently from the study described in Kim et al. (*44*). In that study, toxicity was observed at the highest dose (1,800 ppm) and consisted of decreased bodyweight and ataxia.

Strengths/Weaknesses: This is a study of appropriate design and was adequately reported.

Utility (Adequacy) for CERHR Evaluation Process: The study is of significant utility given that the route of exposure is directly relevant to human health risk assessment. The Kim et al. (*34*) results enhance confidence in the negative finding in the Elf Atochem (*64*) study where 1-BP was administered parenterally.

2.4 Carcinogenicity

No bioassays for carcinogenicity of 1-BP were identified.

2.5 Potentially Sensitive Subpopulations

There are no data available to evaluate the sensitivity of populations based on gender, age, or genotype.

2.6 Summary of General Toxicology and Biological Effects

Toxicokinetics

No information concerning the toxicokinetics of 1-BP in humans was found. Evidence from animal data indicates that 1-BP can be absorbed into the systemic circulation following inhalation exposure. The blood:air partition coefficient indicates that 1-BP is readily soluble in blood (*30*). However, a major portion of absorbed 1-BP is exhaled (excreted in the expired air) unchanged (*38*). Metabolism of 1-BP can occur through the mixed function oxidase (MFO) system (*17*) and via conjugation with glutathione (*31, 37, 38*). The available data suggest that metabolism via MFO enzymes is slow and may be easily saturable. Conjugation with glutathione can occur either enzymatically or non-enzymatically producing several cysteine conjugates that are excreted in the urine. Whether glutathione S-transferases are involved in the activation of 1-BP to a reactive species is unclear, although the data from mutagenicity tests suggests that such activation can occur (*59-61*). This suggests that conjugation with glutathione and glutathione S-transferases may play a role in the toxicity of 1-BP.

General Toxicity

Limited human data were found. One case report indicated peripheral neuropathy in a worker exposed to a degreasing and cleaning solvent containing 95.5% 1-BP (*39*). This study was considered unusable. NIOSH conducted a survey of workers exposed to 1-BP dividing them into groups of 'low' (117 ppm, **[585 mg/m^3]**), 'medium' (170 ppm, **[850 mg/m^3]**), or 'high' (197 ppm, **[985 mg/m^3]**) exposure (*40*). The authors suggested that no adverse health effects were associated with repeated occupational exposures at these concentrations. **[The Expert Panel considered the data to be inconclusive.]**

Data in Wistar rats indicate that the acutely lethal concentration is >30,200 mg/m^3 **[6,003 ppm]** (*43*). There may be a difference in the LC_{50} for Wistar rats compared with Sprague-Dawley rats (*44*) suggesting intraspecies variability. Hepatocyte vacuolation around the central vein was observed in animals exposed for one 4-hour period (*44*). Pulmonary edema was observed following acute exposure to lethal concentrations (>30,200 mg/m^3 **[6,003 ppm]**) (*43*). Repeated exposure to concentrations of ≥400 ppm **[2,012 mg/m^3]** result in adverse effects to the peripheral nervous system, possibly striated muscle, and liver (*52, 57*). Peripheral nervous system and muscular effects are associated with ataxia, altered gait, and decreased grip strength. One study also identified lesions in the brain (gray and white matter vacuolation) following 28 days of exposure to relatively high concentrations (*45*). These lesions were not observed in other studies of longer duration and lower concentration (*46, 58*). The Expert Panel concluded that the method of fixation used in the 13-week study (*46*) was not optimal for evaluation of neurohistopathology. Liver effects are defined by minimal to mild centrilobular hepatocyte vacuolation in male rats, but with little other evidence of adverse effect. This lesion is considered to be reversible, and in the absence of other signs of hepatotoxicity was considered to be adaptive. No effect levels for systemic toxicity of ~100–400 ppm (~500–2,000 mg/m^3) have been reported in repeat-dose studies of rats. Table 2-1 summarizes NOEC values and effects observed in animal general toxicity studies. Testicular and ovarian toxicity has been reported and are discussed in the section on Reproductive Toxicity.

Genetic Toxicity

The genetic toxicity of 1-BP has been tested in *S. typhimirium* strains TA98, TA100, TA1535, TA1537, and TA1538 (*34, 59, 62*). Positive results were reported only for TA100 and TA1535 in one study (*59*), but no increase in revertants was observed in two other studies (*34, 62*). The TA100 and TA1535 strains are known to possess GST activity that may result in the metabolism

of 1-BP to a reactive metabolite (*60, 61*). Because direct evidence of such a reactive metabolite is not available, this hypothesis is speculative. A mouse micronucleus test (*64*) and rat micronucleus test (*34*) of 1-BP were negative. Positive results were obtained in a mutagenicity assay in cultured L5178Y mouse lymphoma cells (*63*); however, the increase in mutation frequency was noted at cytotoxic concentrations.

Carcinogenicity

There are no data available on the potential carcinogenicity of 1-BP in humans or animals.

Sensitive Subpopulations

There are no data available to evaluate the sensitivity of populations based on gender, age, or genotype.

Table 2-1. Summary of General Toxicity Effects in Inhalation Studies

Concentration in ppm (mg/m^3)	Exposure Regimen	Species/ strain/ sex	Concentration: Effect	Reference
6,003 (30,200) 6,879 (34, 600) 6,997 (35,100) 7,355 (37,000) 8,448 (42,500)	4h/1d; nose-only	Wistar rat, M & F	**NOEC = 6,003 ppm (30,200 mg/m^3).** **6,879 ppm (34,600 mg/m^3):** Mortality in 3/10. **6,997 ppm (35,100 mg/m^3):** Mortality in 7/10. **7,355 ppm (37,000 mg/m^3):** Mortality in 10/10.	Elf Atochem (*43*)
11,000 (55,337) 13,000 (65,398) 15,000 (75,460) 17,000 (85,521)	4h/1d; whole-body	Sprague-Dawley rat, M & F	**NOEC = 11,000 ppm (55, 337 mg/m^3).** **17,000 ppm (85,521 mg/m^3):** Mortality in 10/10; number of deaths dose-related at lower concentrations.	Kim et al. (*44*)
398 (2,000) 993 (5,000) 1,590 (8,000)	6h/5d/4wk; whole-body	Sprague-Dawley rat, M & F	**398 ppm (2,000 mg/m^3):** Vacuolation of the brain (1/20 gray matter; 9/20 white matter). **993 ppm (5,000 mg/m^3):** ↓RBC, hemoglobin, hematocrit; ↑ relative liver, spleen, thyroid/parathyroid, and kidney weights; vacuolation of the brain (11/20 white and 20/20 gray matter). **1590 ppm (8,000 mg/m^3):** Mortality (8/10 M; 3/10 F), ataxia and hypotonic gait; vacuolation of brain (11/20 white and 20/20 gray matter) and spinal cord; kidney lesions; atrophic changes in testis.	ClinTrials (*45*)
50 (252) 300 (1,509) 1,800 (9,055)	6h/5d/8wk; whole-body	Sprague-Dawley rat, M & F	**NOAEC = 300 ppm (1,509 mg/m^3) .** **1,800 ppm (9,055 mg/m^3):** Ataxia, ↓ activity, ↓ bodyweight gain; renal tubular casts.	Kim et al. (*44*)
99 (500) 199 (1,000) 397 (2,000) 596 (3,000)	6h/5d/13wk; whole-body	Sprague-Dawley rat, M & F	**NOEC = 199 ppm (1,000 mg/m^3).** **397 ppm (2,000 mg/m^3):** slight centrilobular vacuolation of the liver. **596 ppm (3,000 mg/m^3):** ↑ relative liver weight (M) and slight to mild centrilobular vacuolation of the liver.	ClinTrials (*46*)
1,000 (5,031)	8h/7d/7wk; whole-body	Wistar rat, M	Hind-limb paralysis, paddle-like gait, ↓ creatine kinase activity, degeneration of myelin sheath and peripheral nerve, axonal swelling of gracilis of the spinal cord; ↓ MCV.	Yu et al. (*49, 51*)

Concentration in ppm (mg/m^3)	Exposure Regimen	Species/ strain/ sex	Concentration: Effect	Reference
200 (1,006) 400 (2,012) 800 (4,025)	8h/7d/12wk; whole-body,	Wistar rat, M	**NOAEC = 200 ppm (1,006 mg/m^3).*** **400 (2,012 mg/m^3):** ↓ Bodyweight; hind-limb grip strength; ↓ creatinine phospho-kinase activity; ↑ relative liver weight. **800 ppm (4,025 mg/m^3):** ↓ Bodyweight; ↓ fore-limb and hind-limb grip strength; ↓ motor nerve conduction velocity; ↑ distal latency; ↑ relative and absolute liver weight, ↓ spleen weight; ↓ creatinine phosphokinase activity; ovoid or bubble-like debris in myelin sheaths of peripheral nerves, swelling of preterminal axons of the gracile nucleus, and irregular banding of soleus muscle fibers; cytoplasmic spots in liver.	Ichihara et al. (*52, 57*)
100 (503) 250 (1,257) 500 (2,514) 750 (3,771) (F_0 only)	6h/7d/10 wk prior to mating and during gestation and lactation. Whole body.	Sprague-Dawley Rat, M & F	**NOEC = 100 ppm (503 mg/m^3) *** **250 ppm (1,257 mg/m^3):** No clinical signs of toxicity (F_0 or F_1 generations). ↓ in absolute but not relative brain weight (F_1 males); ↑ absolute thymus weights F_1 males (no lesions reported); centrilobular hepatocellular vacuolation (M); ↑ liver glycogen (F); ↑ renal pelvic mineralization (Male and Female F_0, Female F_1); ↑ hemosiderin in spleen (M&F). **500 ppm (2,514 mg/m^3):** No clinical signs of toxicity (F_0 or F_1 generations); ↓ in weight gain (F_1 males and F_0 and F_1 females during gestation and lactation); ↓ in absolute but not relative brain weight (M); ↑ relative liver weight (M&F); ↑ absolute thymus weights F_1 M (no lesions reported); centrilobular hepatocellular vacuolation (M&F); ↑ liver glycogen (F); ↑ renal pelvic mineralization (M&F); ↑ hemosiderin in spleen (Male and Female F_0, Female F_1). **750 ppm (3,771 mg/m^3):** No clinical signs of toxicity; ↓ weight gain (M&F); ↓ in absolute but not relative brain weight (M&F); ↑ relative liver weight (M&F); ↑ absolute thymus weights F_1 males (no lesions reported); centrilobular hepatocellular vacuolation (M&F); ↑ liver glycogen (F); ↑ renal pelvic mineralization (M&F); ↑ hemosiderin in spleen (M&F).	WIL Research Laboratories (*58*)

↑=Increased Effect; ↓=Decreased Effect; M=Males; F=Females; h=hours; d=days; wk=week; RBC=Red blood cell; MCV=Maximum motor nerve conduction velocity

* See Table 4-3 for effect levels based on reproductive effects.

3.0 DEVELOPMENTAL TOXICITY DATA

3.1 Human Data

No case report or epidemiological data were available for any aspect of potential developmental toxicity induced by exposure to 1-BP.

3.2 Experimental Animal Toxicity

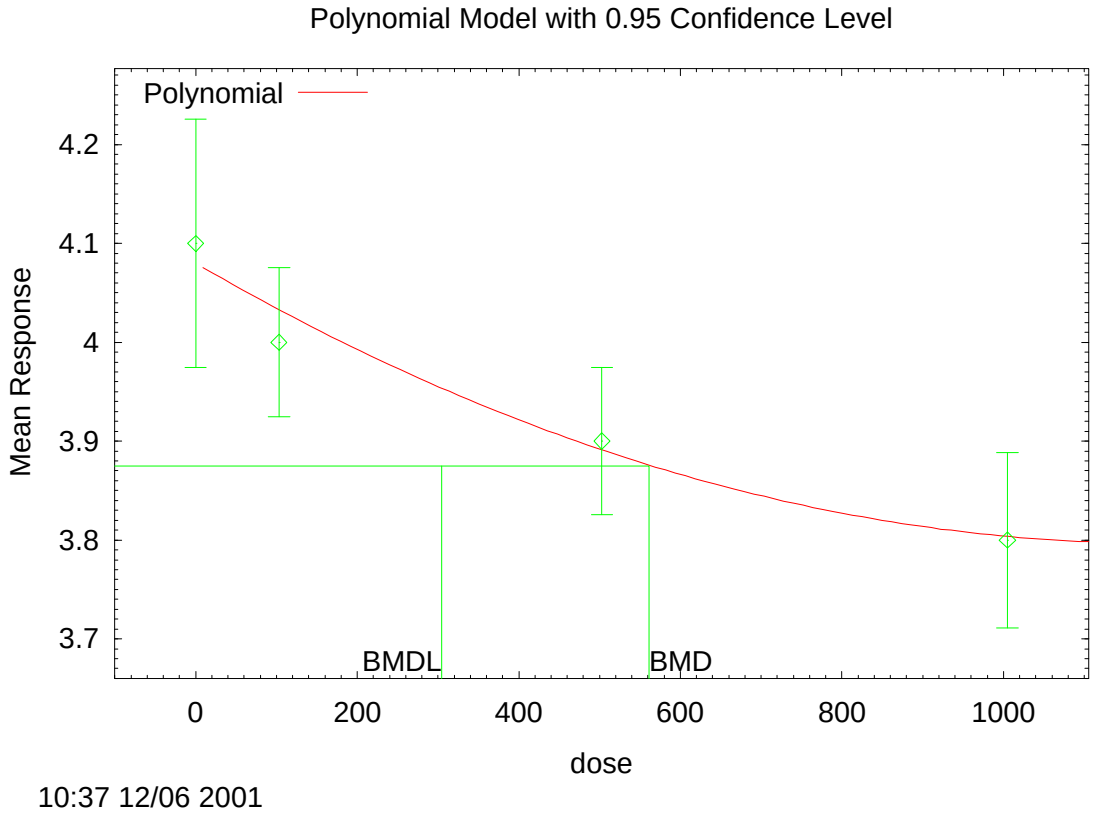
The BSOC sponsored a standard developmental toxicity study using Crl: CD (SD) IGS BR Sprague-Dawley rats (*18*). Pregnant animals (25/group) were exposed to actual vapor concentrations of 0, 520, 2,530, or 5,060 mg/m^3 **[0, 103, 503, or 1,005 ppm]** 1-BP (99.9% purity) for 6 hours/day from gd 6–19 (day of conception=day 0). Exposures were conducted in whole-body chambers under dynamic conditions. Concentrations were monitored by infrared (IR) spectrometry. Nominal chamber concentrations were selected to produce a gradation of effects from the lowest to the highest dose. Pregnancy was terminated on gd 20 and the fetuses removed by cesarean section. The uterine contents were weighed and one-half the fetuses preserved in Bouin's fluid for soft-tissue evaluation, while the other half were eviscerated and processed for skeletal evaluation using Alizarin Red-S and Alcian Blue. Continuous data were analyzed by ANOVA, Dunnett's test, and/or the Kruskal-Wallis test and incidence data were analyzed by a Fisher Exact Test with Bonferonni correction. The study was conducted according to GLP. Results of this study are summarized in Table 3-1. There was no effect on pregnancy rate. One animal from the 1,005 ppm (5,060 mg/m^3) group was sacrificed moribund. Examination of this animal indicated extramedullary hematopoiesis, hepatocellular necrosis, hepatocellular inflammation, and lymphoid cell hyperplasia of the spleen. These findings were not considered to be treatment related. Lacrimation and salivation were observed in animals exposed to 1,005 ppm (5,060 mg/m^3). Mean maternal bodyweight and bodyweight corrected for gravid uterus weight in the 503 ppm (2,530 mg/m^3) and 1,005 ppm (5,060 mg/m^3) groups were significantly reduced compared to the concurrent controls; maternal bodyweight gain and food consumption were also significantly reduced in these two groups. No signs of embryotoxicity were observed, and no treatment-related visceral or skeletal anomalies were noted. Fetal bodyweight was significantly reduced in all treated groups. A significant treatment-related increase in the litter incidence of bent ribs was seen in the 1,005 ppm (5,060 mg/m^3) group, but the authors considered this condition reversible and frequently observed in untreated rats. **[The Panel noted that bent ribs (also referred to as undulating, angulated, bowed or wavy rib (*65, 66*)) is a term applied to congenital undulations of several ribs and these changes are considered a fetal aberration (deviation) as contrast to a frank malformation.]** A slight (but not significant) increase in the incidence of wavy ribs was observed in litters exposed to 503 ppm (2,530 mg/m^3) 1-BP. No fetuses with wavy ribs were found in either control litters or in those recovered from dams inhaling 103 ppm (520 mg/m^3). **[The incidence of 'wavy' ribs in control rat fetuses is generally low (0 to 2.7%), is bilateral and the condition resolves without sequelae (*65, 67*). Bent or wavy ribs are associated with reduced local alkaline phosphatase activity and reduced calcium deposition and are thought to be the result of opposing cervical and abdominal muscular forces acting upon incompletely ossified ribs (*65*).]** Reduced skull ossification was observed at 503 and 1,005 ppm (2,530 and 5,060 mg/m^3), and was associated with maternal toxicity and reduced fetal bodyweight by authors. Thus, reduced ossification of the fetal rat skull occurred after 1-BP exposures less than those required to retard ossification of the ribs (*18*). The authors identify 103 ppm (520 mg/m^3) as a NOEC for maternal and fetal toxicity, and 1,005 ppm (5,060 mg/m^3) for teratogenicity.

The Expert Panel noted that Huntingdon Life Sciences (*18*) did not consider reduced fetal weight at the lowest dose to be treatment-related. Huntingdon Life Sciences (*18*) suggested that the practice of holding "1 or 2" control dams "until the end of the daily cesarean section period" resulted in "many control group fetuses weighing ~0.2 g heavier in bodyweight versus the laboratories' usual 3.9 gram fetuses" (*68*). Huntingdon Life Sciences (*18*) speculated that this practice resulted in apparent bodyweight reductions among treated as compared to concurrent control groups when considered for individual male and female fetuses. There is no question that normal fetal rodent bodyweights increase rapidly near term. However, 23–25 dams/group and their litters were examined (*18*). Therefore, the Panel questioned whether holding one dam/group (from 23-25 total litters) until the end of the workday could result in a statistical distortion of the data that was not related to exposure history.

The Expert Panel addressed the question of whether reduced fetal bodyweights at the 103 ppm (520 mg/m^3) concentration were due to 1-BP treatment by calculating a benchmark dose (BMD). The EPA BMD Software program (BMDS Version 1.3) was used. Initial attempts to model the data indicated that none of the models fit the data adequately. Examination of the raw data suggested that a single litter in the 103 ppm (520 mg/m^3) group was aberrantly low (i.e., an outlier): the mean for this litter was 3.2 grams, approximately three SD lower than the mean of 3.9 grams. Therefore, this litter was excluded from subsequent analyses. Doing this changed the mean and SD for this group from 3.9 + 0.23 to 4.0 + 0.17 grams. More importantly, it made the data amenable to dose-response modeling using the BMDS software.

The polynomial model provided the best data fit (Figure 3-1). The BMD was calculated as the concentration at which fetal weight was reduced 5% from the concurrent control mean. This provided a central estimate for the BMD of 561 ppm, and a 95th percentile lower confidence limit (BMDL) of 305 ppm. The Expert Panel noted that the BMD is consistent with the LOAEC for skeletal variations.

Figure 3-1. Benchmark Dose Analysis of Fetal CD Rat Bodyweight Following *In Utero* Exposure to 1-BP (*18*)



Strength/Weaknesses: The Huntingdon Life Sciences (*18*) bioassay is a well-conducted, GLP study performed in accord with current regulatory guidelines and standard practices using appropriate numbers of animals. Chamber concentrations were determined by weighing the 1-BP vapor generation apparatus prior to and following cessation of exposure, then dividing by the duration and airflow. The purity of the test material was determined "using a modified method provided by the sponsor" and was stated as 99.87%. The chamber air concentrations were measured using a Miran air analyzer, but specific details of that infrared method were not provided. Fetuses were evaluated for signs of developmental toxicity using appropriate methods.

Utility (Adequacy) for CERHR Evaluation Process: The Huntingdon Life Sciences (*18*) rat data are directly applicable to the evaluation process in that the protocol conformed to that expected from a standard inhalation bioassay carried out under GLP. It is noteworthy that only rats were included in the protocols available to date. No data for other common laboratory species (e.g., mice, rabbits) as required for standard developmental toxicity risk assessments were found. No pharmacokinetic, disposition, or transplacental transfer data were collected that could be applied in quantitative interspecies extrapolation of dose.

Table 3-1. Major Effects Observed in a Prenatal Toxicity Study by Huntingdon Life Sciences (*18*)

Number[a]	Dose in ppm (mg/m^3)	Maternal Effects	Fetal Effects
25/23	0		
25/23	103 (520)	NOEC	↓ Fetal weight (4.8%).*
25/25	503 (2,530)	↓ Weight gain and food intake.	↓ Fetal weight (4.8%).* ↑ Litters with reduced skull ossification (17 vs 4%).
25/24	1,005 (5,060)	↓ Weight gain and food intake. Clinical signs.	↓ Fetal weight (7.3%).* ↑ Litters with reduced skull ossification (18 vs 4%). ↑ Litters with bent ribs (13 vs 0%). ***[BMDs for 5% reduction in fetal weight were 561 ppm (central estimate) and 305 ppm (95th percentile lower confidence interval).]*** No increases in prenatal mortality, sex distribution, or external, skeletal, or visceral malformations.

Protocol: CD rats were exposed to 1-BP on gd 6–19. Dams were sacrificed on gd 20 for evaluation of prenatal toxicity.
Notes: ↑,↓=Statistically significant increase, decrease.
[a]Number of pregnant dams/litters evaluated.

Limited information about developmental toxicity associated with exposure to 1-BP is also available from a two-generation reproductive toxicity study in which Crl:CD(SD) IGS BR rats were exposed to 0, 100, 250, 500, or 750 ppm **[0, 503, 1,257, 2,514, 3,771 mg/m^3]** 1-BP vapors during premating, mating, gestation, and lactation (pnd 5–21) (*58*). Complete details of the WIL Research Laboratories (*58*) study are included in Section 4. Statistically significant reductions in live litter size were observed in F_0 and F_1 females exposed to 500 ppm and no offspring were observed in F_0 females exposed to 750 ppm. Given that there were proportionate decreases in implantation sites in the F_0 dams, the Panel noted the plausible explanation of an effect on fertility rather than adverse effects on development. Significant reductions in neonatal weight gain during nursing occurred in F_1 males and F_2 males and females of the 500 ppm group. There were no treatment-related effects on postnatal survival in either F_1 or F_2 litters. The authors stated that skeletal examinations would be conducted according to the Dawson method if external abnormalities were observed. There were no reports of external malformations in offspring. **[The Expert Panel identified a developmental NOEC of 250 ppm.]**

Strength/Weaknesses: This is a well-conducted GLP study performed according to standard practices and guidelines. Adequate numbers of animals were used in the evaluation and all the appropriate endpoints for reproductive toxicity were examined. One limitation is that

developmental effects may have been missed because animals were allowed to give birth, which may prevent detection of malformed or otherwise abnormal fetuses.

Utility (Adequacy) for CERHR Evaluation Process: This two generation study provides convincing evidence that adverse effects on rat reproductive performance associated with inhaled 1-BP were due to reduced fertility; no evidence of developmental toxicity was found in pregnant females (through 500 ppm groups). This study provides useful indirect evidence that inhaled 1-BP is not a developmental toxicant in rats at up to 500 ppm.

Limited information about potential developmental effects is available from a range-finding one-generation GLP study conducted by Huntingdon Life Sciences (*69*). Ten individually housed groups of Crl: CD (SD) IGS BR rats were randomly assigned and exposed (whole body) to HEPA-filtered air or 1-BP vapors (99.9% purity) in nitrogen at concentrations of 100, 199, 598, or 996 ppm **[503, 1,001, 3,008, 5,010 mg/m^3]** on gd 6–19 for 6 hours/day. Dams delivered and were exposed to 1-BP together with their litters on pnd 4–20. Concentrations in dynamic inhalation chambers were verified using an unstated infrared method. At birth, pups from 7–9 litters/group were sexed, weighed, and examined for viability and external abnormalities. Pup growth and survival were monitored from birth through weaning. At weaning, 1 pup/sex/litter was randomly selected for a post-weaning growth study and exposed to 1-BP on pnd 22–28. Hematology and clinical chemistry analyses and organ weight measurements were conducted in dams at the end of the lactation period and offspring from the pnd 22–28 day post-weaning study on pnd 29. Data were analyzed by ANOVA, Dunnett's test, and/or the Kruskal-Wallis test. Results in this study are summarized in Table 3-2. Dams in the 996 ppm group experienced lacrimation and increased salivation. Maternal bodyweight gain was reduced during treatment in the 199, 598, and 996 ppm groups but did not reach statistical significance. Food intake was not affected by treatment. Significant organ weight changes in dams included increases in relative weights (to bodyweight) of the liver and kidneys in the 598 and 996 groups. The authors did not consider any of the changes in maternal hematology or clinical chemistry parameters to be toxicologically significant. No external abnormalities or reduced birth weight were reported. During the period from birth to weaning, no increased pup mortality was observed; pup bodyweights were slightly, but not significantly, reduced in the 996 ppm group. Bodyweight gain during the post-weaning period (pnd 22–29) was significantly lower for males in the 598 and 996 groups and females in the 996 group. Significant organ weight changes in male offspring included increased absolute adrenal (100 and 199 ppm) and reduced brain weight (996 ppm) and increased relative adrenal weight (100, 199, and 996 ppm). In female offspring, absolute brain weight was significantly reduced in the 996 ppm group. The only hematological and biochemical effects in offspring that were considered treatment-related by authors included statistically significant reductions in platelet count in 598 and 996 ppm females and 996 ppm males, elevations in gamma-glutamyl transferase levels in 996 ppm males and females, and reduced circulating glucose levels in the 996 ppm females and in all treated males (significant only at high dose for males). Authors identified a maternal NOEC of 100 ppm but did not identify a developmental NOEC. **[The Expert Panel noted that exposure to 1-BP during the post-weaning period reduced bodyweight gain and may have targeted adrenals, platelets and the liver.]**

Strength/Weaknesses: One deficiency noted concerned 1-BP purity and stability in that a [**unstated]** "modified method provided by the study sponsor" was utilized in those analyses. Chamber nominal concentrations were determined by weighing the 1-BP vapor generation apparatus prior to and following cessation of exposure, then dividing by the duration and airflow. Huntingdon Life Sciences (*69*) indicated that chamber air was collected at four time points over the 6-hour exposures and evaluated using a 'Miran air analyzer.' The report neither presented the

details of chamber air sampling and infrared quantification, provided references to published or standardized methods for 1-BP measurement nor was it clear whether the calculated nominal concentrations were confirmed using conventional GC techniques.

Utility (Adequacy) for CERHR Evaluation Process: While the protocol is of little utility in hazard identification for teratogens, the investigation is valuable inasmuch as exposures were conducted throughout organogenesis, through neonatal life, and infancy. A rat LOAEC for developmental toxicity of 100 ppm can be identified based on the significant increase in absolute and relative adrenal weights for the F_1 males. After exposure to 598 or 996 ppm, adrenal to bodyweight ratios were also increased for the males, but not for the female offspring. Huntingdon Life Sciences (*69*) identified a maternal NOEC of 100 ppm based on reduced maternal bodyweight gain after exposure to 199, 598, and 996 ppm.

Table 3-2. Major Effects Observed in a Developmental Range-Finding Study by Huntingdon Life Sciences (*69*)

Number[a]	Dose in ppm (mg/m^3)	Maternal Effects	Offspring Effects
10/8	0		
10/9	100 (503)	NOEC.	↑ Relative adrenal weight (M).
10/8	199 (1,001)	↓ Bodyweight gain.[b]	↑ Relative adrenal weight (M).
10/7	598 (3,008)	↓ Bodyweight gain.[b] ↑ Relative liver and kidney weight.	↓ Bodyweight gain on pnd 22–25(M). ↓Platelets (F).
10/10	996 (5,010)	↓ Bodyweight gain.[b] ↑ Relative liver and kidney weight. Clinical signs. No toxicologically significant effects on hematology or blood chemistry	↓ Bodyweight gain on pnd 22–29 (M) and 22–25 (F). ↑ Relative adrenal weight (M) ↓Absolute brain weight. ↓ Platelets. ↓ Glucose levels. ↑Gamma-glutamyl transferase. No reduced birth weight, external abnormalities or increased mortality.

Protocol: CD rats were exposed to 1-BP on gd 6–19. Dams delivered and were then exposed to 1-BP with litters on pnd 4–20. One offspring/sex/litter was exposed on pnd 22–28.
Notes: ↑,↓=significant increase, decrease. M,F=Males, Females only.
[a]Number of pregnant dams/litters evaluated.
[b]Although not statistically significant, bodyweight effects were considered by authors in selection of NOEC.

3.3 Utility of Data

No data are available to evaluate potential developmental toxicity of 1-BP exposures in humans.

In rats, appropriate methods were used to evaluate teratogenicity following exposure on gd 6-19 (*18*). Postnatal growth and survival were evaluated in a two-generation reproductive toxicity assay (*58*) and in a range-finding reproductive toxicity assay (*69*). Dams in the two-generation study were exposed throughout the entire gestation period and from pnd 5 to 21, while dams in the screening study were exposed on gd 6–19 and pnd 4–20. All studies were conducted according to GLP. The data were adequate to evaluate developmental toxicity in rats. No data were available for other common laboratory species such as mice and rabbits. In addition, there are no pharmacokinetic, disposition, or transplacental data that could be applied to quantitative interspecies extrapolation.

3.4 Summary of Developmental Toxicity

There were no studies located that address potential developmental toxicity in humans exposed to 1-BP.

The data are sufficient to indicate that inhalation exposure to 1-BP in rats can induce signs of developmental toxicity. A prenatal inhalation developmental toxicity study in rats observed reduced ossification of the skull at ≥503 ppm (≥2,530 mg/m^3) and increased bent ribs at 1,005 ppm (5,060 mg/m^3); decreased maternal bodyweight gain and food consumption also occurred at these concentrations (*18*). Significant reductions in fetal bodyweight were observed at ≥103 ppm (520 mg/m^3). No evidence of embryotoxicity (lethality/terata) was seen at concentrations up to 1,005 ppm (5,060 mg/m^3) 1-BP on gd 6–19.

There was no NOAEC for fetal weight decrease in the 1-BP developmental toxicity study. The authors of the study speculated on non-treatment-related reasons for the statistically significant effect at the lowest exposure concentration (103 ppm) and suggested that the true LOAEC was the next higher concentration level, 503 ppm. The Expert Panel addressed the question by calculating a BMD. The EPA BMD Software program (BMDS Version 1.3) was used as described in Section 3.2. The BMD was calculated as the concentration at which fetal weight was decreased by 5% from the control mean. This provided a central estimate for the BMD of 561 ppm, and a 95th percentile lower confidence limit (BMDL) of 305 ppm. The Expert Panel noted that the BMD is consistent with the LOAEC for skeletal variations.

Two studies examined postnatal growth in rat pups whose dams were exposed to 1-BP during gd 6–19 and pnd 4–20 (*69*) or throughout the entire gestation and majority of the lactation period (pnd 5–21) (*58*). Whereas reduced fetal bodyweights were seen at day 20 after dams inhaled 103 ppm 1-BP from days 6–19 (*18*), no such changes were observed at birth (day 21) in male and female CD neonatal rats born to dams inhaling 100 ppm 1-BP from days 6–19 (*69*). Postnatal pup bodyweight gain was reduced in litters from dams exposed to ≥598 ppm (3,008 mg/m^3) (*69*). F_1 and F_2 pup weight gain was reduced during the nursing period at 500 ppm (2,514 mg/m^3) in a two-generation study in (*58*). Additional relevant effects are listed in Table 3-3.

The Panel concluded there is sufficient evidence in rats that inhalation exposure to 1-BP causes developmental toxicity in the form of skeletal variations, consistent with developmental delay, following inhalation at ≥503 ppm, 6 hours/day, gd 6–19. There was also a concentration-related reduction in fetal bodyweight consistent with developmental delay. The data are assumed relevant to consideration of potential risk to human health.

There is insufficient evidence in humans that 1-BP causes developmental toxicity, due to an absence of data.

Table 3-3. Summary of Developmental Toxicity in Inhalation Studies

Analytical Concentration in ppm (mg/m^3)	Exposure Regimen	Species/ Strain	Concentration: Effect	Reference
103 (520) 503 (2,530) 1,005 (5,060)	6h/d gd 6–19	CD (SD) IGS BR Rat	**Dams:** **Maternal NOEC=103 ppm (520 mg/m^3)** **503 ppm (2,530 mg/m^3):** ↓ Weight gain and food intake. **1,005 ppm (5,060 mg/m^3):** ↓ Weight gain and food intake; lacrimation, excessive salivation. **Fetuses:** **103 ppm (520 mg/m^3):** ↓ Bodyweight **503 ppm (2,530 mg/m^3)**: ↓ Bodyweight; ↓skull ossification. **1,005 ppm (5,060 mg/m^3)**: ↓ Bodyweight; ↓skull ossification;↑bent ribs. **[BMDs for fetal bodyweight: 561 ppm (central estimate); 305 ppm (95th percentile lower confidence limit).]**	Huntingdon Life Sciences (*18*)
100 (503) 199 (1,001) 598 (3,008) 996 (5,010)	6h/d gd 6–19 and pnd 4–20	CD Rat	**Dams:** **Maternal NOEC=100 ppm (503 mg/m^3)** **199 ppm (1,001 mg/m^3)**: ↓ Bodyweight gain. **598 ppm (3,008 mg/m^3)**: ↓ Bodyweight gain; ↑ relative liver and kidney weight. **996 ppm (5,010 mg/m^3)**: ↓ Bodyweight gain; ↑ Relative liver and kidney weight; clinical signs. **Pups:** **100 ppm (503 mg/m^3)**: ↑ Relative adrenal weight (M). **199 ppm (1,001 mg/m^3)**: ↑ Relative adrenal weight (M). **598 ppm (3,008 mg/m^3)**: ↓ Bodyweight gain (M; pnd 22–25): ↓ platelets (F). **996 ppm (5,010 mg/m^3)**: ↓ Bodyweight gain (M: pnd 22–29, F: pnd 22–25); ↓ Absolute brain weight (M,F), ↑ relative adrenal weight (M); ↓ platelets (M,F), ↑ gamma-glutamyl transferase (M,F); ↓ glucose (M,F).	Huntingdon Life Sciences (*69*)
100 (503) 250 (1,257) 500 (2,514)	6h/7d/wk for gestation and most of lactation. Whole body.	CD Rat	**Dam:** See Table 4-3 in Section 4. **Pup:** **Developmental NOEC=250 ppm (1,257 mg/m^3)** **500 ppm (2,514 mg/m^3):** ↓ Weight gain during lactation period.	WIL Research Laboratories (*58*)[a]

[a]Reproductive effects for this study are summarized in Section 4.
↑=Increased Effect; ↓=Decreased Effect; M=Male, F=Female.
h = hours; d = days; wk = week

4.0 REPRODUCTIVE TOXICITY

4.1 Human Data

In 1998, NIOSH conducted a health hazard evaluation at a plant where a 1-BP-containing spray adhesive was used in the manufacture of seat cushions (*40*). Forty-three employees (34 females and 9 males), whose exposure levels were classified as 'low' (117 ppm **[585 mg/m^3]**), 'medium' (170 ppm **[850 mg/m^3]**), or 'high' (197 ppm **[985 mg/m^3]**), were asked about reproductive problems. One employee (sex not specified) in the low exposure group reported seeing a doctor for reproductive/fertility problems and two males and one female in the low or mid exposure groups said they could not have a child after attempting to conceive for 1 year. NIOSH noted that their ability to detect reproductive or fertility problems was limited by the small sample size and personal nature of the questions asked. An analysis of blood samples for complete blood count was also conducted and is discussed in Section 2.

Strength/Weaknesses: The NIOSH (*40*) case report is very limited in content. The survey analysis was based on only 43 of 70 workers. According to the National Center for Health Statistics (*70*), about 10% of couples in the US seek medical attention for infertility. Therefore, 3 of 42 workers reporting possible fertility problems is not unexpected.

Utility (Adequacy) for CERHR Evaluation Process: The study is not useful except to point out the need for a well-designed human study with adequate exposure information and adequate power to detect an effect, i.e., one that monitors menstrual cycles and examines semen quality and serum hormones. A well-designed study would also include identification and analysis of potentially confounding factors.

4.2 Experimental Animal Toxicity

In a study sponsored by the BSOC, WIL Research Laboratories (*58*) evaluated the potential adverse effects of 1-BP whole-body inhalation exposure in F_0 and F_1 parental rats; reproductive capabilities were examined in the F_0 and F_1 generations and neonatal survival, growth and development were evaluated in F_1 and F_2 offspring. In this two-generation reproductive toxicity study, groups of 25 male and female Crl:CD(SD)IGS BR rats were exposed to filtered air or 100, 250, 500, or 750 ppm **[0, 503, 1,257, 2,514, 3,771 mg/m^3]** 1-BP vapors (99.8% purity) for 6 hours/day, 7 days/week. Exposure concentrations within each chamber were measured 9–10 times during each exposure period by a validated GC method. Exposure of F_0 rats commenced at 7 weeks of age and F_1 rats began direct exposure at weaning. Exposures were conducted for at least 70 days prior to mating. Females were not exposed on pnd 0–4 and only they, not their litters, were exposed during pnd 5–21. Therefore, offspring (litters) were indirectly exposed to the test chemical *in utero* and through nursing. In addition, the F_1 pups selected randomly for propagation of F_2 litters were directly exposed from pnd 22 forward. Results in treated animals were compared to both air control and historical control data from WIL Research Laboratories. Statistical analyses were stated to generally be conducted using two-tailed tests for a minimum significance of p=0.05. Most data were analyzed by one-way ANOVA with Dunnett's test. Exceptions were Chi-square test with Yates correction factor for parental mating and fertility indices; Kruskall-Wallis test with Mann-Whitney U-test for sperm motility, % normal sperm, pup sex at birth, and proportional postnatal survival; and Fisher's Exact test for histopathological findings. The study was stated to have been conducted in compliance with GLP.

Evidence of general toxicity was observed in the higher dosage groups and is discussed under Section 2.

Reproductive effects are outlined in Table 4-1. Prior to mating, the F_0 female rats exhibited increased estrous cycle length. While this effect appeared to be dose-related, statistical analysis of the data was not conducted, in part because several animals in each of the high dose groups did not cycle at all. However, the study authors considered values for the 500 and 750 ppm groups to be test agent related since they exceed the range of their historic control data for this end point (4.1–5.1 days). Reproductive performance was impaired in the higher dosage F_0 groups as evidenced by significant decreases in male/female mating index in the 750 ppm group, and in the male/female fertility index in the 500 and 750 ppm groups. An increased time to coitus in the F_0 500 and 750 ppm groups was not statistically significant but was considered test agent related since it exceeded historical control values**.** None of the females in the F_0 750 ppm group became pregnant. In contrast, 1-BP treatment had no effect on gestation length or complications during delivery. However, numbers of implantation sites and pups born to F_0 females were significantly reduced in the 500 ppm group.

At necropsy, significant reductions in F_0 absolute reproductive organ weights were observed for ovary (750 ppm), cauda epididymis (500 and 750 ppm), prostate (≥250 ppm, but did not decrease with increasing dose), seminal vesicles (750 ppm), and pituitary (750 ppm). Significant decreases in relative weights of these organs were only observed in the 750 ppm group for caudae epididymides and ovaries. Ovarian histologic analysis in F_0 rats in the 750 ppm group revealed a significant increase in the incidence of ovaries with reduced numbers of corpora lutea and with follicular luteinized cysts. In males, a slightly increased incidence of seminiferous tubule degeneration was not considered treatment related by the study authors since lesions in 4 of 6 affected rats were of minimal severity. Also, testicular sperm counts (absolute or per gram testis) were not significantly altered by treatment. An analysis of cauda epididymal spermatozoa from F_0 rats revealed significant reductions in morphologically normal sperm at ≥ 250 ppm. However the decrease from 99.7% normal sperm in controls to 99.3% at 250 ppm was not considered by the authors to be treatment related because this value is above historical control value of 99.0%. Cauda epididymal sperm numbers were significantly reduced at 750 ppm and the percentage of motile sperm was significantly reduced at 500 and 750 ppm. **[The Panel concurred with the authors' conclusions discussed in this paragraph.]**

A statistically significant decrease in implantation sites and in the number of offspring at birth was seen at the 500 ppm dose in both generations. The F_1 rats were evaluated for postnatal growth, development, and survival. A slight, but significant, reduction in pup viability on pnd 14–21 in the F_1 500 ppm group (97.7% vs. 100% in controls) was not considered of sufficient magnitude to be treatment related, especially because postnatal survival calculated from pnd 4 to pnd 21 was not different by treatment. Therefore, the authors concluded that there were no effects on pup survival. **[The Expert Panel agrees with this interpretation of the data.]** Mean offspring weights (litter as experimental unit) were lower at the 500 ppm dose in both generations. Significant reductions in F_1 litter weight gain were found in males of the 250 ppm group (pnd 21–28) and 500 ppm group (pnd 4–7, 7–14, and 21–28). A significant reduction in F_1 female weight gain was only noted in the 500 ppm group on pnd 21–28. The age of balanopreputial separation was significantly increased in the F_1 500 ppm group but authors attributed that effect as secondary to reduced weight gain in that group. The age at which female offspring attained of vaginal patency was not significantly different in treated F_1 offspring.

1-BP exposure in the F_1 animals was initiated on pnd 22. Twenty-five rats/sex/group in control and 100–500 ppm treatment groups were selected for mating. The mating experiment was

conducted as described for the F_0 rats. Increased estrous cycle lengths in the 250 and 500 ppm F_1 groups (4.9 and 5.1 days) were within ranges of historical controls (4.1–5.1) but were nevertheless attributed by the authors to be related to 1-BP treatment. This judgement was based on the fact that 3 and 4 animals, in the 250 and 500 ppm groups, respectively, had no complete estrous cycles (versus only 1 each in the control and 100 ppm groups). Again, no statistical analysis was performed for this endpoint. No significant effects were noted for F_1 fertility or mating indices, days to mating, gestation length, or birthing complications. However, authors noted that non-significant and non-dose-related reductions in fertility indices in the F_1 100, 250, and 500 ppm groups (68, 64, 72%, respectively) were below fertility indices of historical controls (~90%). Mean numbers of implantation sites were reduced in the F_1 dams in the 250 and 500 ppm groups with statistical significance achieved at the higher dose level. Live litter size was significantly decreased at 500 ppm. Apparent increases in the incidence of ovarian follicular cysts and interstitial cell hyperplasia (mild) in F_1 females in the 500 ppm group were not statistically significant. Absolute (but not relative) epididymis and pituitary weights were significantly reduced in the F_1 500 ppm males. Lesions observed in testes were considered minimal and their incidence was not altered significantly by treatment, although there appeared to be a trend. Other male reproductive organs were histologically normal. The percentage of motile sperm was slightly, but significantly, reduced in the F_1 males (from 89% in controls to 85%) at 250 ppm. The study authors did not consider this treatment-related since this value exceeds that of historic controls. However, the percentage of motile sperm was further (and significantly) reduced to 74% in the 500 ppm group. The percentages of morphologically normal sperm were significantly reduced at 500 ppm. A slight but statistically significant reduction from 99.5% normal sperm in controls to 98.9% in the 100 ppm group was not considered by the study authors to be test article related because the difference was very small, and no significant changes were seen in the 250 ppm group. **[The Expert Panel agreed with this interpretation.]** F_2 rats were only evaluated for postnatal growth and survival to pnd 21. Postnatal weight gain in males and females was significantly reduced in the F_2 500 ppm group. Survival was unaffected.

[The Expert Panel identified 100 ppm as a NOAEC in this study, and 250 ppm as a LOAEC, based on decreased prostate weight in the F_0 males and increased estrous cycle length in the F_1 female offspring. From the perspective of the LOAECs observed, both sexes are equally sensitive to 1-BP. Alterations in male and female reproductive outcomes at 500 ppm may contribute to the altered fertility and reduced litter size seen at this concentration, and the infertility seen at 750 ppm.]

Strength/Weaknesses: This is a comprehensive study conducted under GLP and it meets specifications of EPA's harmonized reproductive test guidelines. It includes indices of puberty as measures for reproductive development, and sperm measures as indices of testicular and epididymal function. This allows effects on reproductive organ function to be detected in the absence of an effect on reproductive performance at lower doses. Results provide convincing evidence that 1-BP is a reproductive toxicant in both male and female rats, with neither sex being obviously more sensitive than the other.

Adverse effects on litter size and sperm measures at 500 and 750 ppm were consistent across generations, suggesting a lack of a transgeneration effect, or increased susceptibility during perinatal or pubertal stages. Apparent increase in age at balanopreputial separation appears to be related to reduced bodyweights in offspring in the highest dosage group rather than to direct effects of the test agent on puberty. Despite significant (though not dramatic) reductions in epididymal weight, sperm morphology, sperm motility, and epididymal sperm counts, there were no effects on testicular histology or testicular sperm counts. Likewise, in the F_0 females, alterations in estrous cyclicity and litter size were found in the absence of significant decreases in

ovarian weight or significantly abnormal ovarian histology at 500 ppm.

Criteria for scoring histology were not provided (p. 55 of study). Some animals at 500 and 750 ppm were apparently more than "minimally" affected, especially as the testes contained at least some tubules with "Sertoli cell only." One might expect to see histologic evidence of abnormal spermatogenesis based on significant reduction of epididymal sperm counts in the 750 ppm group. The Panel suggested that study authors may want to reconsider the statistical analyses for testicular pathology.

The report has a section titled "Discussion and Conclusions" but it is a summary, with no rigorous discussion of the data or significance of the findings. For example, decreased weights of epididymis, prostate, and seminal vesicle could be indicative of lower weight gain in offspring, or could be indicative of an endocrine effect

Utility (Adequacy) for CERHR Evaluation Process: This is an excellent study for hazard identification and is adequate for the CERHR evaluation process. The wide array of endpoints provides a comprehensive picture of alterations in both the male and female reproductive system that together appear to account for the subfertility at 500 ppm and infertility at 750 ppm. Effects on many endpoints at 500 ppm, in the absence of significantly decreased bodyweight or other pathology, provide strong evidence for specificity of the reproductive toxicity.

Table 4.1. Major Effects Observed in a Two-Generation Reproductive Toxicity Study in Sprague Dawley Rats by WIL Research Laboratories (*58*).

Number[a]	Dose in ppm (mg/m^3)	Effects in F_0 Parents[d]	Effects in F_1 Offspring [F_2 Offspring][d]
25	0		
25	100 (503)	NOAEC.	NOAEC.
25	250 (1,257)	↓Prostate weight	↓F_1 weight gain on pnd 21–28 (M). ↑Estrous cycle length. (4.9 vs 4.5 days).[c]
25	500 (2,514)	↑Precoital interval (4.3 vs. 3.4 days).[b] ↑Estrous cycle length (5.5 vs 4.2 days).[c] ↓Fertility (52 vs 92%). ↓Implantation sites (9.0 vs 15.3). ↓Litter size (n=8.3 vs 14.4). ↓Normal sperm (98.2 vs 99.7%). ↓ Sperm motility (72 vs 87%). ↓ Cauda epididymis and prostate weights. No effects on gestation length or parturition, testicular weight or sperm counts, ovarian weight.	↓F_1 weight gain through pnd 28 (M) and pnd 21–28 (F). ↑Estrous cycle length (5.1 vs 4.5 days).[c] ↓Implantation sites (9.8 vs 15.5). ↓Litter size (8.6 vs 14.5). ↓Normal sperm (95.3 vs 99.5%). ↓Sperm motility (74 vs 89%). ↓ F_1 cauda epididymis and pituitary weight. [↓F_2 postnatal weight gain on pnd 4–21] No effect on F_1 or F_2 postnatal survival, F_1 age at vaginal patency, F_1 age at balanopreputial separation, mating indices, gestation length, parturition, or testicular lesions.
25	750 (3,771)	↓ Weight gain (M). ↑ Estrous cycle length (5.6 vs 4.2 days).[c] ↓ Mating (68 vs 96%). ↑ Pre-coital interval (4.8 vs 3.4 days).[b] No conceptions. ↓ Ovary weight. ↓ Corpora lutea. ↑ Ovarian cysts. ↓ Normal sperm (90.6 vs 99.7%). ↓ Sperm motility (53 vs 87%). ↓ Epididymal sperm count (370 vs $472x10^6$/gram tissue). ↓Epididymis, prostate, seminal vesicle, and pituitary weight.	No F_1 rats available due to complete infertility in F_0 rats.

Protocol: Inhalation exposure to 1-BP from 70 days prior to mating, during gestation and most of lactation in F_0 and F_1. Reproductive function evaluated in F_0 and F_1; postnatal mortality and growth evaluated in F_1 and F_2 litters.

Notes: M=Male; F=Female; ↑,↓=Statistically significant increase, decrease.

[a]Number of F_0 and F_1 male and female pairs, except that no F_1 offspring were available at 750 ppm.

[b]Not statistically significant but above historical control value.

[c]No statistical analyses conducted, but considered test article related (see text).

[d]See synopses for details about systemic effects.

A study by Ichihara et al. (*57*) examined the dose response of 1-BP-induced testicular toxicity including sperm measures (motility/morphology) and detailed testicular histology (testes fixed in Bouin's and stained with period acid Schiff's reagent). In the examination of testicular histology, subtle changes in seminiferous tubule cell associations, similar to those recommended by Creasy (*71*), were evaluated. These included enumeration of spermatogenic cells in stage VII tubules and elongated spermatids retained in stage IX–XI tubules (normally released at stage VIII). The rationale for this study included the increased use of 1-BP in industry and the previously reported reproductive toxicity induced by its isomer, 2-BP. Eight-to-nine, 10-week-old male Wistar rats (from the Shizuoka Laboratory Animal Center) were exposed to air or 200, 400, or 800 ppm **[1,006, 2,012, or 4,025 mg/m^3]** 1-BP vapors (99.81% purity) for 8 hours/day for 12 weeks. The maximum dose in this study was selected based on observations in previous studies that exposure to 1,000 ppm resulted in debilitation. Chamber concentrations of 1-BP were measured by GC and reported. At the end of the exposure period the rats were sacrificed and necropsied. Data were evaluated by one-way ANOVA followed by Dunnett's method. Reproductive effects are discussed here while other systemic effects are discussed in Section 2. Table 4-2 lists findings of this study. Significant reductions in absolute organ weights were observed for seminal vesicles (≥200 ppm), epididymides and pituitary (≥400 ppm), and prostate (800 ppm). Significant reductions in relative organ weights were noted in seminal vesicles (≥200 ppm) and epididymides (800 ppm). Bodyweight gain was reduced in the 400 and 800 ppm groups. Histopathological changes were observed in the epididymides, prostate, and seminal vesicles of the 800 ppm group. Epididymides had reduced duct cavity diameter, wider interstitial space, increased epithelial cell height and contained neutrophils or degenerated epithelial cells. Prostate and seminal vesicles had reduced alveoli size and degenerated cells were observed in the seminal vesicle cavity. Histological evaluation of testes revealed vacuolated seminiferous epithelium in 2 of 9 rats of the 800 ppm group. The numbers of retained elongated spermatids in stages IX, X, and XI were significantly increased in 400 and 800 ppm groups and a significant increase in degenerating spermatocytes in stage VII was seen in the 800 ppm group. Sperm quality was also affected as observed by significant reductions in sperm count and motility and increases in tailless sperm at ≥400 ppm. At 800 ppm a significant increase in sperm with abnormal heads (banana-like or straight) was observed. Table 4-2 includes values for sperm parameters. Plasma testosterone level was significantly reduced in the 800 ppm group, but there were no changes in follicle stimulating hormone (FSH) or luteinizing hormone (LH) levels. The presence of retained elongated spermatid during the postspermiation periods (stages IX–XI) led authors to conclude that the likely mode of 1-BP toxicity results in failure of spermiation. Authors stated that this pattern of toxicity differs from that of 2-BP which has been reported to target spermatogonia.

Strength/Weaknesses: A strength of this study is the thorough evaluation of testicular effects of 1-BP including detailed histology, sperm measures, and serum hormones. The exposure period is sufficiently long to see effects on all spermatogenic stages, and the range of doses is sufficiently wide to determine a no effect level and begin to see systemic effects on bodyweight. Enumeration of spermatogenic cell types in seminiferous tubule cross sections allowed conclusions about sensitive cell types and/or stages. The conclusion that the main effect in testis is spermatid retention beyond Stage VIII is consistent with a possible effect on Sertoli cell function and/or possible effect on the endocrine support of spermatogenesis. Decreased testosterone levels in the high-dose group coupled with decreased weights of testosterone-dependent organs (most consistently the seminal vesicles) are consistent with the latter hypothesis, as is observed decrease in sperm quality (motility/morphology). Retained spermatids may account for the decreased numbers of sperm in the epididymides.

A weakness of the study is that relatively low numbers of animals per group (9–10) limits the power of the study to detect an effect. For example, lower and more variable serum testosterone level might obtain statistical significance if more animals were assessed. Also, the significance of the adverse effects on testicular and sperm measures is hard to interpret without fertility data.

Utility (Adequacy) for CERHR Evaluation Process: This study is particularly useful for characterizing effects of 1-BP in males since it includes detailed histology with quantification of germ cells and serum hormones. It has limited usefulness for hazard identification since it does not include a fertility assessment, but is a valuable adjunct to 1-BP weight of evidence considerations.

Table 4-2. Major Effects in Reproductive Toxicity Study in Wistar Rats by Ichihara et al. (*57*)

Number/ Dose	Dose in ppm (mg/m^3)	Effects
8	0	
9	200 (1,006)	↓ Absolute seminal vesicle weight. ↓ Relative seminal vesicle weight.
9	400 (2,012)	↓ Absolute seminal vesicle, epididymides, and pituitary weight. ↓ Relative seminal vesicle weight. ↑ Retained elongated spermatids (1.3 vs 0.49/tubule). ↓ Sperm count (588 vs $792x10^6$/g cauda). ↓ Motile sperm (67 vs 83%). ↑ Tailless sperm (18 vs 4%). ↓ Bodyweight gain. ↑ Relative liver weight. ↓ Mean corpuscular hemoglobin concentration.
9	800 (4,025)	↓ Absolute seminal vesicle, epididymides, pituitary, and prostate weight. ↓ Relative seminal vesicle and epididymides weight. ↑ Histological changes in epididymides, prostate, and seminal vesicles. ↑ Retained elongated spermatids (4.8 vs 0.49/tubule). ↑ Degenerating spermatocytes (0.6 vs 0.04/tubule). ↓ Sperm count (240 vs $792x10^6$/g cauda). ↓ Motile sperm (25 vs 83%). ↑ Tailless sperm (36 vs 4%). ↑ Abnormal sperm (100 vs 1%). Vacuolated seminiferous epithelium in 2/9 rats. ↓ Plasma testosterone (2.9 vs 4.5 ng/mL) with no change in LH or FSH. ↓ Bodyweight gain. ↑ Relative and absolute liver weight; ↓ absolute spleen weight. ↑ Histological changes in liver. ↑ Mean corpuscular volume. ↓ Mean corpuscular hemoglobin concentration.
Protocol: 10-week-old male rats exposed to 1-BP vapors for 8 hours/day for 12 weeks. **Notes**: ↑, ↓: Statistically significant increase, decrease.		

Kim et al. (*44*) and Yu et al. (*51*) examined testes microscopically and no adverse effects were reported. In the Kim et al. (*44*) study, Sprague-Dawley rats inhaled 1,800 ppm 1-BP for 6 hours/day, 5 days/week, for 8 weeks. Testes were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned and stained with hematoxylin-Eosin and/or PAS hematoxylin. In the Yu et al. (*51*) study, male Wistar rats were exposed to 1,000 ppm 1-BP vapors (99.4% purity) for 8/hours/day for 5 or 7 weeks. Kim et al. (*44*) reported an increase in relative weight of

ovaries, but no ovarian lesions were observed. Additional details of these two studies are included in Section 2.

Strength/Weaknesses: The experimental designs of the Kim et al. (*44*) and Yu et al. (*51*) studies could allow comparison of relative effects on gonads and blood. However, since there is no indication that testes (or ovaries) were examined for subtle effects such as retained spermatids or vacuolated Sertoli cells, it is doubtful that testes were evaluated in sufficient detail to detect changes seen in the other studies. Lack of effect could also be due to the shorter duration of exposure, but 7–8 weeks should be sufficient to detect changes in spermiation and sperm counts. Increased relative weights of testes and ovaries could simply be due to bodyweight depression without change in absolute gonad weights.

Utility (Adequacy) for CERHR Evaluation Process: These studies by Kim et al. (*44*) and Yu et al. (*51*) are not useful for evaluating reproductive effects. They may be useful for comparing blood measures with other studies.

Two unpublished general toxicity studies also included evaluation of the testes. In a 28-day inhalation study, testicular hypo/aspermatogenesis was seen in two surviving Sprague-Dawley rats after exposure to 8,000 mg/m^3 or about 1,600 ppm (*45*), but this effect could not be specifically related to the exposure due to systemic toxicity at this concentration. On the other hand, no testicular or ovarian lesions were observed in Sprague-Dawley rats exposed to up to 3,000 mg/m^3 (~700 ppm) 1-BP vapors for 13 weeks (*46*). This finding is consistent with the results of the multigeneration study described above. Complete details of these studies and a review of strengths, weaknesses, and utility is included in Section 2.

Saito-Suzuki et al. (*72*) conducted dominant lethal studies in rats to determine the structure-activity relationships of 5 halogenated propanes. In addition to 1-BP (>98% purity) the following compounds were examined: 1,2,3-tribromopropane, 1,2-dibromopropane, 1,2,3-trichloropropane, and 1-chloropropane. Eleven-week-old male Crl: Sprague Dawley rats (n=15/group) were gavaged with 10% of the acute lethal dose of each compound in olive oil for 5 days. 1-BP was administered at a dose of 400 mg/kg bw. Olive oil was the negative control and 1,2-dibromo-3-chloropropane was the positive control (n=15/group). At 1–8 weeks after treatment, the males were mated weekly with untreated females. Data were analyzed using Fisher's Exact Method and the Mann-Whitney U test. 1-BP treatment had no effect on male fertility. Females (n=15/time period) were sacrificed 13–14 days after mating and examined for corpora lutea, implants, live embryos, and early and late embryonic deaths. 1-BP treatment increased the number of mean dead implants at the 8-week mating but had no effect on the dominant lethal mutation index (live embryos per test female/live embryos per control females). The authors concluded that dominant lethal mutations were induced by propanes containing a bromine or chlorine atom on each carbon with bromine comprising two of the atoms.

Strength/Weaknesses: This is a classic dominant lethal protocol showing that a relatively high oral dose of 1-BP (~maximum tolerated dose) does not induce dominant lethality. Other halogenated propanes serve as controls in that they are effective at lower dosages.

Utility (Adequacy) for CERHR Evaluation Process: This paper is important since it eliminates 1-BP as a germ cell mutagen, and thereby rules out a mechanism of action exhibited by related halogenated propanes. The study also shows that short-term (5 day) exposure at high levels failed to produce adverse effects sufficient to affect fertility. The protocol neglected specific changes in testis/epididymis function.

An abstract is available that describes a reproductive study conducted in rats according to OECD Guideline 422 (*73*). While the abstract reported results similar to those observed by WIL Research Laboratories (*58*), the full study report was not available to the Expert Panel during the present review of 1-BP.

4.3 Utility of Data

The only pertinent information on humans comes from a Health Hazard Evaluation performed by NIOSH in 1998 (*40*). This study, which was based on questionnaire fertility data, was not of adequate sample size. Several studies provide convincing evidence that 1-BP is a reproductive toxicant in the rat. A two-generation study (*58*) demonstrated adverse reproductive effects associated with a range of concentrations of 1-BP. The consistency of effects across the two generations and lack of significant effects on pubertal indices suggests that 1-BP is an adult, but not a perinatal or juvenile toxicant with respect to adverse effects on reproduction. The Expert Panel considered this study relevant since it was conducted under GLP conditions, and protocols were consistent with U.S. EPA's harmonized Reproductive Test Guidelines. A second inhalation toxicity study by Ichihara et al. (*57*) provides complementary information about the male reproductive toxicity of 1-BP in rats that is consistent with the results of the WIL Research Laboratories study. These data are assumed relevant to judging hazard potential of 1-BP exposures in humans.

4.4 Summary of Reproductive Toxicity

There are insufficient data upon which to evaluate the reproductive toxicity of 1-BP in humans.

Reproductive studies, including a two-generation study, were conducted in rats. Major findings of these studies are included in Table 4-3.

The two-generation study provides sufficient data to indicate that repeated chronic inhalation exposure of female Sprague-Dawley rats to 1-BP at doses of 250 ppm (1,257 mg/m^3) and higher results in reproductive toxicity (*58*). Effects included a dose-related increase in estrous cycle length in F_1 females exposed to ≥ 250 ppm (1,257 mg/m^3) and F_0 females exposed to ≥ 500 ppm. Follicular cysts were seen in ovaries of F_0 females exposed to 750 ppm (3,771 mg/m^3) and were accompanied by decreased ovarian size and decreased numbers of corpora lutea (*58*). Reduced fertility and litter size were observed in the F_0 and F_1 generations at ≥500 ppm (2,514 mg/m^3), but the experimental design did not permit differentiation as to whether these effects were due to reduced female or male fertility, or both.

There are sufficient data to indicate that repeated inhalation exposure of male rats to 1-BP results in reproductive toxicity at doses of 200 ppm (1,006 mg/m^3) and higher. Effects in a two-generation study included decreased prostate weight in F_0 males at 250 ppm (1,257 mg/m^3), and dose-related decreases in percentages of normal sperm and motile sperm in F_0 and F_1 generations at ≥500 ppm (2,514 mg/m^3) (*58*). Decreased epididymal sperm count, epididymal weight, and seminal vesicle weight were observed at the 750 ppm (3,771 mg/m^3) dose. Reduced fertility and litter size were observed in the F_0 and F_1 generations but the experimental design did not permit differentiation as to whether these effects were due to reduced female or male fertility, or both. Testicular toxicity consistent with the above study was also characterized in a subchronic inhalation study (*57*). Decreased absolute and relative seminal vesicle weights were observed at 200 ppm (1,006 mg/m^3). Histopathological changes were observed in epididymides, prostate, and seminal vesicles at a dose of 800 ppm (4,025 mg/m^3). The presence of retained elongated

spermatids was increased at doses of 400 and 800 ppm (2,012 and 4,025 mg/m^3), and reductions in sperm count and motility were observed. Plasma testosterone levels were reduced at 800 ppm (4,025 mg/m^3) (*57*). The Expert Panel noted a conclusion by Ichihara et al. (*57*) that the main effect in testis is spermatid retention beyond Stage VIII. The Panel concludes that such effects are consistent with altered Sertoli cell function or impaired endocrine support of spermatogenesis.

The Expert Panel selected a NOAEC of 100 ppm (503 mg/m^3) for the two-generation reproductive toxicity study (*58*), and opined that reduced fertility in the two-generation study was due to reproductive toxicity in both males and females. This was based on the observation that exposure to 2,514 mg/m^3 (500 ppm) increased estrous cycle length and compromised sperm quality (as discussed above in separate summaries for male and female rats). Further, the Panel noted that the male and female reproductive systems may be equally sensitive since decreased prostate weight at 250 ppm (*58*) and decreased seminal vesicle weight at 200 ppm (*57*), as well as extended estrous cycles in F_1 females at 250 ppm occurred at similar concentrations. However, difficulties in analyzing the length of the estrous cycle when some of the animals were not cycling precluded a definitive statistical analysis on this last point. Lastly, the Expert Panel noted consistency of effects across the two generations and stated there was no evidence of increased sensitivity in developing rats exposed *in utero* and indirectly through mother's milk, or during pubertal development.

Table 4-3. Summary of Reproductive Toxicity Inhalation Studies

Concentration in ppm (mg/m^3)	Exposure Regimen	Species/ Strain	Concentration: Effect	Reference
100 (503) 250 (1,257) 500 (2,514) 750 (3,771) [F_0 only]	6h/7d/10 wk prior to mating and during gestation and most of lactation. Whole body.	Male and female CD Rat	**NOAEC= 100 ppm (503 mg/m^3** **250 ppm (1,257 mg/m^3):** ↑Estrous cycle length in F_1; ↓ prostate weight (F_0). **500 ppm (2,514 mg/m^3):** ↑Estrous cycle length; ↓ normal sperm and sperm motility; ↓ epididymis and prostate (F_0) weights;↓ fertility, implantation sites, and litter size; ↑ precoital interval. **750 ppm (3,771 mg/m^3):** ↑Estrous cycle length; ↑ ovarian follicular cysts and ↓ corpora lutea; ↓ sperm count, normal sperm and sperm motility; ↓ ovary weight and numbers of corpora lutea;↓ epididymis, prostate, seminal vesicle and pituitary weights;↓ mating, ↑ precoital interval, and complete infertility.	WIL Research Laboratories (*58*)
200 (1,006) 400 (2,012) 800 (4,025)	8h/12 wk whole body.	Male Wistar Rats	**200 ppm (1,006 mg/m^3):** ↓ Absolute and relative seminal vesicle weight. **400 ppm (2,012 mg/m^3):** ↑ Retained elongated spermatids; ↓ sperm count and motility and ↑ tailless sperm; ↓ absolute seminal vesicle, epididymides, and pituitary weight and relative seminal vesicle weight. **800 ppm (4,025 mg/m^3):** ↑ Retained elongated spermatids and degenerating spermatocytes; ↓ sperm count and motility and ↑ tailless sperm and abnormal sperm; vacuolated seminiferous epithelium in 2/9 rats; epididymis, prostate, and seminal vesicle lesions; ↓ testosterone; ↓ absolute seminal vesicle, epididymides, prostate, and pituitary weight and relative seminal vesicle and epididymides weight.	Ichihara et al. (*57*)

↑=Increased Effect; ↓=Decreased Effect; F_0=Effects observed only in F_0, F_1=Effects observed only in F_1.
h = hours; d = days; wk = week

Summary Statements

There is insufficient evidence in humans that 1-BP causes reproductive toxicity due to an absence of data.

There is sufficient evidence in female rats that exposure to 1-BP causes reproductive toxicity manifested as ovarian dysfunction following inhalation at ≥250–500 ppm daily for 6 h/d for 10 weeks. Subfertility is observed following inhalation at ≥ 500 ppm under the same conditions. These data are assumed relevant to consideration of human risk.

There is sufficient evidence in male rats that exposure to 1-BP causes reproductive toxicity manifested as decreased secondary sex organ weights following inhalation at ≥200–500 ppm daily for 6–8 h/day for 10–12 weeks. The data are assumed relevant to consideration of human risk.

5.0 SUMMARIES, CONCLUSIONS, AND CRITICAL DATA NEEDS

5.1 Summary and Conclusions of Reproductive and Developmental Hazards

Developmental Toxicity

Prenatal developmental toxicity was assessed in Crl:CD rats (*18*). The data are sufficient to conclude that 1-BP caused developmental toxicity, in the form of decreased fetal weight and increased incidence of skeletal variations, in rats exposed to the compound by inhalation on a daily basis during the period of *in utero* development. The skeletal effects are typical of those associated with developmental delay and are believed to be reversible. The skeletal effects occurred in pups whose dams were exposed 6 hours/day to concentrations of 503 ppm (2,530 mg/m^3) and higher; a benchmark analysis of the fetal weight data indicated a BMD that detected a 5% change was 561 ppm (central estimate) with a lower 95^{th} percent confidence limit of 305 ppm. These data are assumed relevant for assessing human hazard. No information was available on developmental outcome after 1-BP exposure in humans.

Reproductive Toxicity

Reproductive effects of 1-BP were observed in a two-generation inhalation study in Crl:CD rats (*58*). Decreased fertility, decreased numbers of implantation sites and litter size and increased precoital interval were observed after exposure at concentrations of 500 ppm (2,514 mg/m^3) and higher. These effects could be attributable to effects on either the male or female parent. Evaluation of other endpoints indicated adverse effects in both sexes. In males, prostate weight was decreased at concentrations of 250 ppm (1,257 mg/m^3) and higher, and there were effects on seminal vesicle weight and sperm quality at higher concentrations. Effects in females included an increase in ovarian follicular cysts at 750 ppm (3,771 mg/m^3). There was also an increase in estrous cycle length that was judged to be 1-BP-related at 250 ppm (1,257 mg/m^3) and higher. The NOAEC for this study was 100 ppm (503 mg/m^3).

A subchronic inhalation study in male Wistar rats confirms the effect on reproductive organ weights (*57*). These effects were observed at the lowest concentration tested, 200 ppm (1,006 mg/m^3). Histopathologic evidence of inhibited spermiation was also observed in this study at concentrations of 400 ppm (2,012 mg/m^3) and higher.

There is sufficient evidence to conclude that inhaled 1-BP causes reproductive toxicity in male and female rats. The NOAEC for these effects was 100 ppm (503 mg/m^3). These results are assumed relevant for human hazard assessment.

The human data on potential effects of 1-BP are too limited in content to conclude that 1-BP is a human reproductive or developmental toxicant.

5.2 Summary of Human Exposure

Within the United States, 1-BP is used as a solvent in spray adhesives (*16*), cold bath degreasing (*25*), and precision cleaning (*10*). 1-BP may also be used as a solvent for fats, waxes, or resins or as an intermediate in the synthesis of pharmaceuticals, insecticides, quaternary ammonium compounds, flavors or fragrances (*1*). In the future it is possible that 1-BP may be used as a substitute for hydrochlorofluorocarbons (HCFCs) (*20*), but current usage of 1-BP is less than 5

million pounds/year (*10*). No information was found that documents exposure of the public to 1-BP through contact with air, drinking water, food, or consumer products.

NIOSH collected 8-hour TWA personal breathing zone measurements for 1-BP in 3 plants where 1-BP-containing spray adhesives were used (n=99) and in 1 plant where 1-BP was used as a cold bath degreaser (n=20). In the plants where 1-BP was used as a solvent in spray adhesives, exposures ranged from 18 to 381 ppm (mean=142 ppm) (*26-28*). After ventilation control improvements had been implemented in two of the adhesives-using plants, NIOSH found that exposures had decreased to a range of 1.2–58 ppm (n=64; mean=19 ppm) (*16, 29*). These surveys demonstrated that exposures may be significantly reduced by ventilation control. In the plant where 1-BP was used in a cold bath degreaser that had been isolated in an enclosed room with local exhaust, only 7 of 20 workers who used the degreaser at least once a day had 8-hour personal TWA exposures that exceeded the minimal quantification limit of 0.02 ppm. Their exposures ranged from 0.04 to 0.63 ppm (*25*). Numerous additional exposure measurements have been collected by industry, but those data were not assessed by the Panel. The exposure measurements evaluated were from a few selected locations and cannot be considered to represent the full cross-section of exposure levels nationwide.

It is likely that worker exposures also occur through dermal contact with 1-BP. No studies have yet evaluated dermal exposure. Biological monitoring may be the best way to evaluate the contribution of dermal exposure to total absorbed dose.

5.3 Overall Conclusions

Available human data are insufficient to draw conclusions on the potential for reproductive or developmental toxicity. Available data are sufficient to conclude that 1-BP exposure can induce developmental and reproductive toxicity in rats. In evaluating the potential effects on human reproduction, the rat data are assumed to be relevant for humans. Accordingly, dose levels were identified from animal studies to use in this evaluation.

- A benchmark concentration 95th percentile lower confidence limit of 305 ppm (1,534 mg/m^3) was identified from a rat inhalation developmental toxicity.
- A LOAEC of 250 ppm (1,257 mg/m^3) for female reproduction (NOAEC=100 ppm [503 mg/m^3] was identified from an inhalation, two-generation reproductive toxicity study.
- A LOAEC of 200 ppm (1,006 mg/m^3) for male reproduction (NOAEC=100 ppm [503 mg/m^3] was identified from the Ichihara et al. (*57*) study and WIL Research Laboratories (*58*) study.

Available data in rats suggest that adverse effects on reproduction and development can occur independent of systemic toxicity; the mechanisms that lead to reproductive or developmental toxicity are unknown. In addition, there are no relevant kinetic or metabolism data for 1-BP to develop dosimetric comparisons. As a result, exposure concentrations from animal studies were used to compare directly to human exposure concentrations to ascertain levels of concern.

Limited occupational exposure data are available. NIOSH collected 8-hour TWA personal breathing zone measurements for 1-BP in 3 plants where 1-BP-containing spray adhesives were used (n=99) and in 1 plant where 1-BP was used as a cold-bath degreaser (n=20). In the plants where 1-BP was being used as a spray adhesive, exposures ranged from 18 to 381 ppm (mean=142). After ventilation control improvements had been implemented in two of the adhesives-using plants, NIOSH found that exposures had decreased to a range of 1.2–58 ppm (n=64; mean=19). In the plant where 1-BP was used as a cold-bath degreaser, 7 of 20 8-hour personal TWA exposures exceeded the minimal quantification limit (MQL) of 0.02 ppm. Of the 7 measurements with concentrations higher than the MQL, the values ranged from 0.04 to 0.63 ppm; the degreaser had recently been enclosed in a room with local exhaust ventilation installed to vent vapors outside the workplace. The exposure measurements evaluated were from a few selected locations and cannot be considered an accurate representation of occupational exposure levels nationwide. In addition, no data are available to quantify the contribution of occupational dermal exposure to total daily dose. Workplace air concentrations fall into a broad range of inhalation exposures. Furthermore, no data are available to estimate consumer or environmental exposure. Thus, the Expert Panel can only compare the reported range of workplace air concentrations to the critical concentrations identified in the animal studies.

Considering the workplace air concentrations summarized in the previous paragraph, and provided there is no additional exposure from other sources and routes:

- The Expert Panel expressed minimal concern for adverse effects on human reproduction and development in situations where exposures were intermittent and well-controlled, as in the example of the cold-bath degreaser.
- The Expert Panel expressed serious concern at the upper end of the exposure range, as in the example of the poorly controlled spray adhesive applications.
- The Expert Panel concluded that considerable uncertainty remains as to the safety of the intermediate range of exposure concentrations. The Panel was unable to assign a level of concern associated with such exposures.

5.4 Critical Data Needs

Critical data needs are defined as tests or experiments that could provide information to substantially improve an assessment of human reproductive risks. The items listed below under Exposure and Effects are considered by the Panel as critical data needs.

Exposure:

- Because of the limited data currently available, usage information in occupational settings and consumer products is needed. This would include data on the specific industries, operations, volumes and numbers of workers potentially exposed. For consumers, information on products containing 1-BP is needed.

- No data are currently available on dermal absorption of 1-BP. As this may be a significant route of human exposure, percutaneous absorption of 1-BP should be evaluated.

- Given concerns about multiple routes of exposure, the development of a validated method for determining total absorbed dose would significantly contribute to human risk evaluation.

Effect:

- A well conducted study of men and women occupationally exposed to 1-BP is urgently needed. At a minimum, such a study should include a thorough exposure assessment and comprehensive evaluation of neurological, hematopoietic, and reproductive endpoints. The study should have adequate statistical power and collect data on potential confounding factors.

Although not considered critical data needs, the following studies would provide information that would contribute to our understanding of the toxicity of 1-BP.

- Basis of Toxicity. Because 1-BP is structurally related to a group of haloalkanes with known reproductive toxicity, mechanistic studies evaluating these compounds would be useful to identify pathways of activation and targets.

- Metabolism. Because only very limited information is currently available, additional studies of the metabolism of 1-BP would be useful. In particular, the role of glutathione in 1-BP metabolism and the role of metabolic activation of 1-BP should be explored.

6.0 REFERENCES

1. HSDB. Hazardous Substances Data Bank. Bethesda (MD): National Institutes of Health. 2001. Available from: URL: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB.
2. Aldrich-Chemical. Material Safety Data Sheet for 1-bromopropane. 1996.
3. Factory Mutual. Flammability testing on Ensolv for Enviro Tech International, Inc. 1997.
4. Astro. Material Safety Data Sheet for Ensolv Precision Vapor Degreasing and Cleaning Solvent. 1997.
5. Fensterheim R. Letter from Brominated Solvents Committee to Ms. Christine Dibble, USEPA. 2000.
6. BSOC. Comments on 1-bromopropane (1-BP; CASRN: 106-94-5) CERHR review. Brominated Solvents Committee. 2001.
7. Fisher Scientific. Material Safety Data Sheet for 1-bromopropane. 2000.
8. OSHA. Nomination of 1-bromopropane (1-BP) and 2-bromopropane (2-bp) for testing by the National Toxicology Program. Directorate of Health Standards Programs, U.S. Occupational Safety and Health Administration; 1999.
9. ASTM. Standard specification for vapor-degreasing grade and general grade normal-propyl bromide. 2000.
10. EnviroTech. Response to NTP-CERHR Expert Panel Draft Report on Reproductive and Developmental Toxicity of 1-Bromopropane. EnviroTech International, Inc. 2001.
11. Amity International. Manufacturers Safety Data Sheet for LEKSOLTM. 2001.
12. Ecolink. Material Safety Data Sheet for HYPERSOLVE NPB. 2001.
13. M.G. Chemicals. Material Safety Data Sheet for Contact Cleaner - NPB Heavy Duty. 2000.
14. Petroferm Inc. Material Safety Data Sheet for LENIUM ES. 2001.
15. UNEP. Montreal protocol on substances that deplete the ozone layer -- report on the geographical market potential and estimated emissions of n-propyl bromide. 2001.
16. Reh C. HETA 98-0153. December 21, 2000. Mooresville (NC): Custom Products, Inc.; 2000.
17. Kim K-W, Kim HY, Park SS, et al. Gender differences in activity and induction of hepatic microsomal cytochrome P-450 by 1-bromopropane in Sprague-Dawley rats. Biochem Molec Biol 1999;32:232-238.
18. Huntingdon Life Sciences. A developmental toxicity study in rat via whole body inhalation exposure. Study No. 98-4141. Study Director, D. Rodwell. East Millstone (NJ): Study sponsored by Brominated Solvents Committee (BSOC); 2001.
19. ATOFINA. Confirmation of ATOFINA's position relating to potential health risks. 2001.
20. EPA. Protection of stratospheric ozone: Notice 14 for Significant New Alternatives Policy Program. Fed Reg 2000;65:78977-78989.
21. O'Malley N. Albemarle comments on CERHR review of 1-bromopropane. 2001.
22. Schwarzenbach RP, Giger W, Schaffner C, Wanner O. Groundwater contamination by volatile halogenated alkanes abiotic formation of volatile sulfur compounds under anaerobic conditions. Environ Sci Technol 1985;19:322-327.
23. Wuebbles DJ, Patten KO, Johnson MT, Kotamarathi. New methodology for ozone depletion potentials of short-lived compounds: n-propyl bromide as an example. J Geophys Res 2001;106:14,551-14,571.
24. Doull J, Rozman KK. Derivation of an Occupational Exposure Limit for *n*-propyl bromide. Sponsored by EnviroTech International; 2001.
25. Reh CM, Nemhauser JB. HETA 2000-0233-2845. Indianapolis (IN): Trilithic, Inc.; 2001.
26. Reh C, Mortimer V. HETA 98-0153. May 21, 1999. Mooresville (NC): Custom Products, Inc.; 1999.

27. Reh C. HETA 99-0260. January 30, 2000. Sawmills (NC): Marx Industries, Inc.; 2000.
28. Reh C. HETA 2000-0410. March 7, 2001. Thomasville (NC): STN Cushion Company; 2001.
29. Harney J. HETA 2000-0410. September 12, 2001. Thomasville (NC): STN Cushion Company; 2001.
30. Meulenberg CJ, Vijverberg HP. Empirical Relations Predicting Human and Rat Tissue:Air Partition Coefficients of Volatile Organic Compounds. Toxicol Appl Pharmacol 2000;165:206-216.
31. Tachizawa H, Macdonald TL, Neal RA. Rat liver microsomal metabolism of propyl halides. Mol Pharmacol 1982;22:745-751.
32. Neal R. Studies on the metabolism of diethyl 4-nitrophenyl phosphorotionate (Parathion) in vitro. Biochem J 1967;103:183-191.
33. Kim K-W. Correspondence with CERHR. 2001.
34. Kim H, Chung J, Chung Y, et al. Toxicological Studies on Inhalation of 1-Bromopropane Using Rats. Report submitted to the Industrial Health Research Institute -- Korea Industrial Safety Corporation; 1998.
35. Kaneko T, Kim HY, Wang PY, Sato A. Partition Coefficients and Hepatic Metabolism in Vitro of 1-and 2-Bromopropanes. J Occup Health 1997;39:341-342.
36. Khan S, O'Brien PJ. 1-Bromoalkanes as new potent nontoxic glutathione depletors in isolated rat hepatocytes. Biochem Biophys Res Commun 1991;179:436-441.
37. Barnsley EA, Grenby TH, Young L. Biochemical studies of toxic agents, the metabolism of 1- and 2-bromopropane in rats. Biochem J 1966;100:282-288.
38. Jones AR, Walsh DA. The oxidative metabolism of 1-bromopropane in the rat. Xenobiotica 1979;9:763-772.
39. Sclar G. Encephalomyeloradiculoneuropathy following exposure to an industrial solvent. Clin Neurol Neurosurg 1999;101:199-202.
40. Trout D. HETA 98-0153. December 1, 1999. Mooresville (NC): Custom Products, Inc.; 1999.
41. Elf Atochem. Acute oral toxicity in rats. N-propyl bromide. Study No. 10611 Tar. Study Director, Jack Clouzeau. Miserey, France: Centre International de Toxicologie; 1993.
42. Elf Atochem. Acute dermal toxicity in rats. N-propyl bromide. Study No. 13113 Tar. Study Director, Stephane de Jouffrey. Miserey, France: Centre International de Toxicologie; 1995.
43. Elf Atochem. Study of acute toxicity on n-propyl bromide administered to rats by vapour inhalation. Determination of the 50% lethal concentration. Study No. 95122. Study Director, F. Schorsch. Verneuil-en-Halatte, France: Laboratoire d'Etudes de Toxicologie Experimentale; 1997.
44. Kim HY, Chung YH, Jeong JH, Lee YM, S SG, Kang JK. Acute and repeated inhalation toxicity of 1-bromopropane in SD rats. J Occup Health 1999;41:121-128.
45. ClinTrials. A 28 day inhalation study of a vapor formulation of ALBTAI in the albino rat. Report No. 91189. Study director, R. Labbe. Senneville, Quebec: Bio-Research Laboratories. Study sponsored by Albemarle Corporation; 1997.
46. ClinTrials. A 13 week inhalation study of a vapor formulation of ALBTAI in the albino rat. Report No. 91190. Study director, R. Labbe. Senneville, Quebec: Bio-Research Laboratories. Study sponsored by Albemarle Corporation; 1997.
47. O'Malley N. Personal communication from Albemarle Corporation. 2001.
48. Binnington B. Memo to M. Adamo, "Evaluation of brain and cervical spinal cord - Project Nos. 91189, 91190". ClinTrials BioResearch Ltd. 1997.
49. Yu X, Ichihara G, Kitoh J, et al. Preliminary report on the neurotoxicity of 1-bromopropane, an alternative solvent for chlorofluorocarbons. J Occup Health 1998;40:234-235.

50. Yu X. Personal Correspondence to CERHR. 2001.
51. Yu X, Ichihara G, Kitoh J, et al. Neurotoxicity of 2-bromopropane and 1-bromopropane, alternative solvents for chlorofluorocarbons. Environ Res 2001;85:48-52.
52. Ichihara G, Kitoh J, Yu X, et al. 1-Bromopropane, an alternative to ozone layer depleting solvents, is dose-dependently neurotoxic to rats in long-term inhalation exposure. Toxicol Sci 2000;55:116-123.
53. Zhao W, Aoki K, Xie T, Misumi J. Electrophysiological changes induced by different doses of 1-bromopropane and 2-bromopropane. J Occup Health 1999;41:1-7.
54. Mauderly JL, Tesarek JE, Sifford LJ, Sifford LJ. Respiratory measurements of unsedated small laboratory mammals using nonrebreathing valve. Lab Anim Sci 1979;29:323-9.
55. Fueta Y, Ishidao T, Kasai T, Hori H, Arashidani K. Decreased Paired-Pulse Inhibition in the Dentate Gyrus of the Brain in Rats Exposed to 1-Bromopropane Vapor. J Occup Health 2000;42:149-151.
56. Ohnishi A, Ishidao T, Kasai T, Arashidani K, Hori H. Neurotoxicity of 1-bromopropane in rats. JUOEH 1999;21:23-28.
57. Ichihara G, Yu X, Kitoh J, et al. Reproductive toxicity of 1-bromopropane, a newly introduced alternative to ozone layer depleting solvents, in male rats. Toxicol Sci 2000;54:416-23.
58. WIL Research Laboratories. An inhalation two-generation reproductive toxicity study of 1-bromopropane in rats. Study No. WIL-380001. Study Director, D. Stump. Ashland (OH): Study sponsored by Brominated Solvents Committee (BSOC); 2001.
59. Barber E, Donish WH, Mueller KR. A procedure for the quantitative measurement of the mutagenicity of volatile liquids in the Ames Salmonella/microsome assay. Mutat Res 1981;90:31-48.
60. Graves RJ, Callander RD, Green T. The role of formaldehyde and S-chloromethylglutathione in the bacterial mutagenicity of methylene chloride. Mutat Res 1994;320:235-43.
61. Thier R, Taylor JB, Pemble SE, et al. Expression of mammalian glutathione S-transferase 5-5 in Salmonella typhimurium TA1535 leads to base-pair mutations upon exposure to dihalomethanes. Proc Natl Acad Sci USA 1993;90:8576-80.
62. Elf Atochem. Ames test--reverse mutation assay on *Salmonella typhimurium*. n-Propyl bromide. HIS1005/1005A. Study performed by Sanofi Recherche. Service de Toxicologie; 1994.
63. Elf Atochem. *In vitro* mammalian cell gene mutation test in L5178Y TK+/- mouse lymphoma cells of *n*-propyl bromide. Study No. 13293. Study director, B. Molinier. Miserey, France: Centre International de Toxicologie; 1996.
64. Elf Atochem. Micronucleus test by intraperitoneal route in mice. N-propyl bromide. Study No. 12122 MAS. Study Directo, Brigitte Molinier. Miserey, France: Centre International de Toxicologie; 1995.
65. Khera KS. Common fetal aberrations and their teratologic significance: a review. Fundam Appl Toxicol 1981;1:13-8.
66. Wise LD, Beck SL, Beltrame D, et al. Terminology of developmental abnormalities in common laboratory mammals (version 1). Teratology 1997;55:249-92.
67. Nishimura M, Iizuka M, Iwaki S, Kast A. Repairability of drug-induced "wavy ribs" in rat offspring. Arzneimittelforschung 1982;32:1518-22.
68. Rodwell D, Thornton S, Agajanova T, Wilson D, Carman A, Malandro L. The effect of time on cesarean section on fetal body weights in rats on developmental toxicity studies. Toxicologist 2000;54:297.
69. Huntingdon Life Sciences. A range-finding developmental/reproductive study of 1-bromopropane in rats via whole body inhalation exposure. Final. Study No. 98-4140.

Study Director, D. Rodwell. East Millstone (NJ): Study sponsored by Brominated Solvents Committee (BSOC); 1999.
70. NCHS. Fertility, family planning, and women's health: new data from the 1995 national survey of family growth. Vital and Health Statistics 1997;23.
71. Creasy DM. Evaluation of testicular toxicity in safety evaluation studies: The appropriate use of spermatogenic staging. Toxicol Pathol 1997;25:119-131.
72. Saito-Suziki R, Teramoto S, Shirasu Y. Dominant lethal studies in rats with 1,2-dibromo-3-chloropropane and its structurally related compounds. Mutat Res 1982;101:321-327.
73. Takeuchi T, Okuda H, Nagano K, et al. Reproduction and developmental toxicity of 1-bromopropane in rats. J Toxicol Sci 2001;26:222.