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**CRITERIA FOR A RECOMMENDED STANDARD:  
OCCUPATIONAL EXPOSURE TO 1-BROMOPROPANE**

Do Not Cite - Draft

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

Centers for Disease Control and Prevention  
National Institute for Occupational Safety and Health

**January 2016**  
*External Review Draft*

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1 **FOREWORD**

2 When the U.S. Congress passed the Occupational Safety and Health Act of 1970 (Public  
3 Law 91-596), it established the National Institute for Occupational Safety and Health  
4 (NIOSH). Through the Act, Congress charged NIOSH with recommending occupational  
5 safety and health standards and describing exposure limits that are safe for various  
6 periods of employment. These recommendations include but are not limited to the  
7 exposures at which no worker will suffer diminished health, functional capacity, or life  
8 expectancy because of his or her work experience. Through criteria documents, NIOSH  
9 communicates these recommended standards to regulatory agencies (including the  
10 Occupational Safety and Health Administration [OSHA]), health professionals in  
11 academic institutions, industry, organized labor, public interest groups, and others in the  
12 occupational safety and health community. Criteria documents contain a critical review  
13 of the scientific and technical information about the prevalence of hazards, the existence  
14 of safety and health risks, and the adequacy of control methods.

15  
16 This criteria document reflects a NIOSH literature-based critical review of information  
17 from human and animal studies relevant to occupational exposure to 1-bromopropane  
18 (1-BP; CAS Number 106-94-5). It describes the potential health effects of occupational  
19 exposure to this substance. 1-BP is a brominated alkane identified as an alternative to  
20 ozone-depleting substances and other compounds with known adverse health effects.  
21 Available human data indicate an association between occupational exposures to 1-BP  
22 and neurological effects. The results of a 2-year bioassay conducted by the National  
23 Toxicology Program (NTP) provide evidence of the ability of 1-BP to cause neoplastic  
24 lesions in the lungs, gastrointestinal tract and skin of rodents. Experimental animal  
25 studies provide additional evidence of the onset of a wide spectrum of non-cancer  
26 adverse health outcomes, including neurological, reproductive, developmental, and  
27 hepatological effects, following subchronic and chronic inhalation exposures to 1-BP.

28  
29 Based on its evaluation of the available scientific information about 1-BP, NIOSH has  
30 proposed a recommended exposure limit (REL) of 0.3 parts per million (ppm) (1.5

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1 milligrams per cubic meter [mg/m<sup>3</sup>] of air) as an 8-hour time-weighted average (TWA)  
2 concentration during a 40-hour workweek. The intent of the NIOSH REL is to reduce  
3 workers' risk of lung cancer associated with a 45-year working lifetime of occupational  
4 exposure to 1-BP. Preventing the most sensitive adverse health effect, i.e., lung cancer,  
5 serves as the basis of the REL. The REL is anticipated to reduce the risk of other  
6 adverse health outcomes observed in humans or animals exposed to 1-BP, including  
7 other cancers (gastrointestinal cancer and skin tumors) and non-cancer endpoints  
8 (including neurological, reproductive, and developmental toxicity). Limiting airborne 1-  
9 BP exposures to below 0.3 ppm is anticipated to reduce the risk of carcinogenic and  
10 noncarcinogenic effects. However, because there is residual risk of cancer at the REL,  
11 efforts should be made to reduce exposures to less than 0.3 ppm. Available data also  
12 indicate the ability of 1-BP to cause skin irritation and potentially be dermally absorbed  
13 under certain conditions. The hierarchy of controls—including elimination, substitution,  
14 isolation, and engineering controls; administrative controls; and use of personal  
15 protective equipment—should be implemented to minimize worker inhalation exposures  
16 and skin contact with 1-BP.

17  
18 NIOSH urges employers to disseminate this information to workers and customers and  
19 requests that professional and trade associations and labor organizations inform their  
20 members about the hazards of exposure to 1-BP.

21  
22  
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25 Centers for Disease Control and Prevention  
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1 **EXECUTIVE SUMMARY**

2 1-Bromopropane (1-BP; CAS #106-94-5) is an organic solvent used in commercial and  
3 industrial applications, such as vapor degreasing operations and dry cleaning facilities.

4 Peer-reviewed studies have raised concerns about the potential occupational health  
5 risks associated with exposure to 1-BP [Sclar 1999; Ichihara et al. 2002, 2004a, 2004b;  
6 Majersik et al. 2007; Raymond and Ford 2007; CDC 2008]. For this reason, the National  
7 Institute for Occupational Safety and Health (NIOSH) has conducted an analysis of the  
8 scientific information available on the human health and toxicological effects of 1-BP.

9 This criteria document presents these results of the NIOSH assessment: (1) the salient  
10 facts on occupational exposures to 1-BP and the toxicity of 1-BP, (2) the rationale and  
11 justification for a NIOSH recommended exposure limit (REL) for 1-BP, derived with  
12 current quantitative risk assessment methodology, and (3) recommendations for  
13 eliminating or reducing workplace risks of exposure.

14  
15 Since the late 20th century, 1-BP has received increased global attention as an  
16 alternative to ozone-depleting substances and other regulated chemicals [EPA 2003a].  
17 In part, this is because 1-BP is reported to not persist in the upper regions of the  
18 atmosphere (that is, the stratosphere) for more than 15 days; also, 1-BP exhibits low  
19 potential for acting as a greenhouse gas [Nelson et al. 1997]. The use of 1-BP in multiple  
20 industrial and commercial processes in the United States and other countries is  
21 documented in peer-reviewed studies and exposure assessments. The number of  
22 workers exposed to 1-BP is unknown, but 1-BP has been identified as a high production  
23 volume (HPV) substance; at least 1 million pounds is used annually in the United States  
24 [EPA 2012; NTP 2014].

25  
26 Case studies, exposure assessments, and investigations provide evidence of 1-BP  
27 exposure in the workplace and the onset of adverse neurological effects attributed to 1-  
28 BP [Sclar 1999; Ichihara et al. 2002, 2004a, 2004b; Majersik et al. 2007; Raymond and  
29 Ford 2007; CDC 2008; Blando et al. 2010; Li et al. 2010a; Samukawa et al. 2012].

30 NIOSH has conducted several health hazard evaluations (HHEs) intended to assess

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1 occupational exposures to 1-BP in industrial and commercial settings where the  
2 substance is used during foam cushion and furniture fabrication, precision cleaning and  
3 vapor degreasing of electronics, and dry cleaning [NIOSH 2000, 2002a, 2002b, 2003b,  
4 2010]. The results of these investigations provide evidence of workers' exposure to 1-BP  
5 in multiple workplace settings.

6  
7 The scientific literature provides limited data regarding the absorption, metabolism, and  
8 disposition of 1-BP in animals and humans. The findings of experimental animal studies,  
9 in addition to investigations of occupational exposures to 1-BP, support the conclusion  
10 that 1-BP is absorbed and made systemically available by both inhalation and dermal  
11 exposures. Evidence of the systemic uptake of 1-BP via oral ingestion has also been  
12 reported [Lee et al. 2005, 2007]. Depending on species, sex, and activity levels, 30% to  
13 70% of the absorbed dose is eliminated unchanged in exhaled breath [Jones and Walsh  
14 1979; Garner et al. 2006]. The remaining absorbed dose has been reported to be  
15 eliminated unchanged in the urine of humans [Kawai et al. 2001] or transformed into  
16 metabolites eliminated via urine and exhaled breath of all species. The metabolism of 1-  
17 BP has been demonstrated to vary on the basis of species and sex [Garner and Yu  
18 2014]. The metabolism and elimination of 1-BP occurs via two pathways, mediated by  
19 either glutathione (GSH) conjugation or cytochrome P450 (CYP450) oxidation [Garner et  
20 al. 2006; Garner and Yu 2014]. It is unclear how these different metabolic pathways  
21 directly impact the manifestation of systemic and organ-specific toxicity in humans or  
22 animals following exposures to 1-BP.

23  
24 Experimental animal toxicity studies provide sufficient evidence of the ability of 1-BP to  
25 induce a wide spectrum of non-cancer health endpoints following acute, subchronic, and  
26 chronic inhalation exposures. These health endpoints include systemic and organ-  
27 specific toxicity such as (1) neurotoxicity, (2) reproductive toxicity, (3) blood toxicity, (4)  
28 hepatotoxicity, and (5) immunotoxicity. In addition, 1-BP has been identified by the  
29 National Toxicology Program Report on Carcinogens [2013] as *reasonably anticipated to*  
30 *be a human carcinogen*.

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1 Adverse changes in the male reproductive system of rats have been reported [ClinTrials  
2 BioResearch 1997a; Ichihara et al. 2001a; WIL Research Laboratories 2001; Furuhashi  
3 et al. 2006; Banu et al. 2007; Liu et al. 2009; NTP 2011]. Significant changes have also  
4 occurred in the reproductive systems of female rodents [WIL Research Laboratories  
5 2001; NTP 2011]. Other noted adverse outcomes of exposure to 1-BP in animal studies  
6 included decreased numbers of offspring, reduced offspring survival rates, and  
7 increased incidence of malformations in offspring [Huntingdon Life Sciences 2001; WIL  
8 Research Laboratories 2001; Furuhashi et al. 2006]. Adverse effects in the central  
9 nervous system (CNS) and peripheral nervous system (PNS) of animals have been  
10 reported, including movement disorders; biochemical, electrophysiological, and  
11 histopathological changes; and altered behavior [ClinTrials BioResearch 1997a; Yu et al.  
12 1998, 2001; Ohnishi et al. 1999; Fueta et al. 2000; Banu et al. 2007; Ueno et al. 2007;  
13 Suda et al. 2008]. Hematotoxicity attributed to 1-BP exposures has also been  
14 documented [ClinTrials BioResearch 1997a, 1997b; Kim et al. 1999b; Huntingdon Life  
15 Sciences 1999]. Specific effects noted in these studies included reduced red blood cell  
16 (RBC) and white blood cell (WBC) counts, in addition to changes in numerous blood  
17 chemistry parameters. A single study provides evidence of the ability of 1-BP to induce  
18 significant immunological effects in both mice and rats following short-term whole-body  
19 inhalation exposure at occupationally relevant concentrations [Anderson et al. 2010].

20  
21 The results of a 2-year inhalation bioassay conducted by the National Toxicology  
22 Program (NTP) [2011] provide evidence of the ability of 1-BP to cause neoplastic lesions  
23 in multiple organ systems of rats and mice. More specifically, NTP [2011] concluded that  
24 the carcinogenicity of 1-BP was clearly evident in female F344/N rats from increased  
25 incidences of adenoma of the large intestine and in female B6C3F1 mice from increased  
26 incidences of alveolar/bronchiolar (lung) neoplasms. NTP [2011, 2013] concluded that  
27 the occurrence of rare adenomas of the large intestine and increased incidences of  
28 neoplasms of the skin provided evidence of carcinogenic activity of 1-BP in male F344/N  
29 rats. The 13<sup>th</sup> Report of Carcinogens identified 1-BP as "Reasonably anticipated to be a  
30 human carcinogen" [NTP 2014].

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1 Exposure to 1-BP has been associated with mutagenicity and DNA damage in *in vitro*  
2 studies and with DNA damage in occupationally exposed workers. 1-BP did not induce  
3 micronuclei induction and dominant lethal mutations in *in vivo* studies. Several metabolites  
4 of 1-BP have been shown to increase DNA adducts, mutations, DNA damage, and  
5 chromosomal damage in *in vitro*, *in vivo*, and epidemiology studies. NTP critically reviewed  
6 all available 1-BP genotoxic data and summarized that the available data provided some  
7 support that 1-BP is genotoxic. Although the genotoxicity results are mixed, 1-BP is  
8 considered a potential genotoxicant on the basis of the overall weight of evidence.

9  
10 No confirmed mode of action (MOA) has been established for non-cancer health  
11 endpoints or cancers associated with exposures to 1-BP. The available data allow for  
12 multiple potential MOAs for both non-cancer health endpoints and cancers associated  
13 with 1-BP exposures, but they are insufficient to identify the key biological events that  
14 result in the onset of these adverse outcomes. Potential MOAs associated with the  
15 onset of non-cancer health endpoints and tumor (cancer) formation include oxidative  
16 stress from (1) GSH depletion, (2) immunosuppression, (3) chronic inflammation, (4)  
17 gamma-aminobutyric acid (GABA) dysfunction, and (5) bioactive metabolites [NTP  
18 2013].

19  
20 NIOSH assessed the qualitative and quantitative information on the human health and  
21 toxicological impacts of 1-BP. The results of the analysis serve as the basis of the  
22 recommendations presented in this criteria document. NIOSH recommends that  
23 occupational exposures to airborne 1-BP be limited to 0.3 ppm (1.5 milligrams per cubic  
24 meter [mg/m<sup>3</sup>] of air) as an 8-hour time-weighted average (TWA) concentration during a  
25 40-hour workweek. The proposed NIOSH recommended exposure limit (REL) of 0.3  
26 ppm corresponds with an excess working lifetime risk of lung cancer of 1 per 1,000  
27 workers. The proposed REL is based on the results of a quantitative assessment of  
28 cancer risks (described in Chapter 7). Data on lung tumors in female mice were selected  
29 as the basis of the REL for 1-BP because lung cancer was identified as the most  
30 sensitive health endpoint [NTP 2011]. Maintaining airborne concentrations below 0.3

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1 ppm is intended to reduce the risk of lung cancers associated with exposure to 1-BP in  
2 the workplace. It is expected that maintaining occupational exposures to airborne  
3 concentrations of 1-BP below the REL should also reduce other health effects  
4 associated with 1-BP exposure, including neurotoxicity, reproductive toxicity,  
5 developmental effects, and hepatotoxicity. This assumption is based on the results of the  
6 quantitative risk assessment focusing on non-cancer health endpoints summarized in  
7 Appendix B.

8  
9 The REL of 0.3 ppm represents the maximum 8-hour TWA concentration of 1-BP to  
10 which a worker may be exposed and corresponds to the 95% lower confidence limit of 1  
11 in 1,000 risk estimate. Keeping exposures within the risk limit of 1 in 1,000 is the  
12 minimum practical level of protection. NIOSH does not consider an exposure limit set at  
13 a risk level of 1 in 1,000 to be a safe level of exposure for workers because of the  
14 residual risk of lung cancer and other health effects at the REL. Therefore, exposures  
15 should always be kept below a risk level of 1 in 1,000. NIOSH recommends that all  
16 reasonable efforts be made to further reduce risks from worker exposures to 1-BP to  
17 levels significantly below the REL through the use of the hierarchy of controls, including  
18 elimination, substitution, engineering controls and, when those methods do not  
19 adequately reduce exposures, personal protective equipment. NIOSH also recommends  
20 that a comprehensive safety and health program be implemented that includes worker  
21 education and training, hazard communication and exposure monitoring. The REL for 1-  
22 BP of 0.3 ppm is quantifiable by NIOSH method 1025 and Occupational Safety and  
23 Health Administration (OSHA) method PV2061.

24  
25 Insufficient exposure data are available to assess the extent to which the REL of 0.3 for  
26 1-BP is achievable in various workplaces. The hierarchy of controls (described in the  
27 next paragraph) has been applied to effectively lower airborne concentration of other  
28 organic solvents—with physiochemical properties similar to those of 1-BP—in dry  
29 cleaning and vapor degreasing operations [Earnest 2002; NIOSH 2002 c,d,e,f; EPA  
30 2004]. These results suggest that airborne concentrations of 1-BP can be effectively

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1 lowered by applying technology and the hierarchy of controls. The REL is intended to  
2 promote effective use of existing control technologies and to encourage the research  
3 and development of new control technologies where needed, in order to control  
4 workplace 1-BP exposures.

5  
6 NIOSH recommends the development of a comprehensive occupational safety and  
7 health program to prevent workplace exposures to 1-BP or reduce them to levels below  
8 the REL of 0.3 ppm. Efforts should emphasize application of the hierarchy of controls  
9 and good workplace practices. The hierarchy of controls has been used as a means of  
10 determining how to implement feasible and effective controls and comprises the  
11 following primary components:

- 12 • Elimination or substitution
- 13 • Engineering controls
- 14 • Administrative and work practice controls
- 15 • Personal protective equipment (PPE)

16 Specific recommendations presented in this criteria document focus on two operations  
17 that commonly employ 1-BP: dry cleaning and vapor degreasing. In both operations, risk  
18 of exposure can come from (1) direct contact with the solvent or (2) contact with and/or  
19 inhalation of solvent vapor. Engineering techniques such as process isolation,  
20 ventilation, filtration, closed systems, and vapor condensers are widely accepted for  
21 controlling solvent contact and solvent vapor exposures. NIOSH encourages the  
22 application of these same techniques to operations that employ 1-BP as the working  
23 solvent. NIOSH also provides generic PPE recommendations relevant to all industries,  
24 operations, and tasks where 1-BP is produced, used, or stored. These PPE  
25 recommendations include information on the selection of appropriate respirators and  
26 chemical protective clothing (CPC).

27  
28 NIOSH recommends that employers implement additional measures under a  
29 comprehensive safety and health program. This program should include exposure  
30 monitoring, hazard communication, respiratory protection programs, and medical

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1 monitoring. These elements, in combination with efforts to maintain airborne 1-BP  
2 concentrations below the REL and to prevent exposures of the skin to the substance, will  
3 further protect the health of workers.

4  
5 In 2012, OSHA revised the Hazard Communication Standard (HCS) to align with the  
6 United Nations Globally Harmonized System of Classification and Labeling of Chemicals  
7 (GHS). This revision provides detailed criteria for hazard classification as well as new  
8 label elements (pictograms, signal words, hazard statements, and precautionary  
9 statements). On the basis of the revised HCS [OSHA 2013] and available  
10 epidemiological and toxicological data, NIOSH has developed GHS designations for 1-  
11 BP. These designations characterize the health endpoints contained in the revised HCS  
12 and GHS relevant to protecting workers and improving occupational safety and health  
13 programs.

14  
15 A strategy to monitor exposure should be developed and implemented for each specific  
16 process and group of workers potentially exposed to 1-BP. The goal of the exposure  
17 monitoring program is to ensure a more healthful work environment where worker  
18 exposure does not exceed the REL for 1-BP of 0.3 ppm. Such a program should include  
19 routine area and personal monitoring of airborne concentrations to assess the  
20 effectiveness of engineering controls, work practices, PPE, training, and other factors in  
21 controlling airborne concentrations of 1-BP. The monitoring program can identify specific  
22 work areas or job tasks where worker exposures exceed the REL and therefore require  
23 additional efforts or changes in processes to reduce them. Supplemental factors such  
24 as the number of workers in the group, variability in their exposure, level of workplace  
25 controls, and environmental conditions must be considered during development of the  
26 exposure monitoring program.

27  
28 Numerous biological monitoring approaches have been developed to identify and  
29 quantify potential biomarkers for 1-BP [Kawai et al. 2001; B'Hymer and Cheever 2004;  
30 Hanley et al. 2006, 2009, 2010; Valentine et al. 2007; Cheever et al. 2009; Mathias et al.

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1 2012]. When biomonitoring indices for 1-BP and its metabolites are developed that allow  
2 for the interpretation of quantitative data, use of these approaches could enhance  
3 exposure assessments by allowing for characterization of scenarios involving multiple  
4 exposure routes (such as inhalation and dermal contact) or assessing temporal patterns  
5 of exposure.  
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1 **ABBREVIATIONS**

2	1-BP	1-bromopropane
3	2-BP	2-bromopropane
4	ABT	1-aminobenzotriazole
5	ACGIH	American Conference of Governmental Industrial Hygienists
6	AcPrCys	<i>N</i> -acetyl- <i>S</i> -( <i>n</i> -propyl)-L-cysteine
7	AcPrCys <sub>cr</sub>	AcPrCys level adjusted for creatine
8	AEL	acceptable exposure limit
9	AIC	Akaike information criterion
10	AIHA	American Industrial Hygiene Association
11	AL	action level
12	ALT	alanine aminotransferase
13	APR	air-purifying respirator
14	As <sup>+</sup>	arsenic
15	ATSDR	Agency for Toxic Substances and Disease Registry
16	BDNF	brain-derived neurotrophic factors
17	BMC	benchmark concentration
18	BMCL	benchmark concentration lower-bound confidence limit
19	BMD	benchmark dose
20	BMR	benchmark response
21	Br <sup>-</sup>	bromide
22	BSC	Brominated Solvents Consortium
23	°C	degrees Celsius
24	CA1	cornu ammonis area 1
25	CA DHS	California Department of Health Services
26	CA EPA	California Environmental Protection Agency
27	CAS	Chemical Abstract Service
28	CIB	Current Intelligence Bulletin
29	CAA	Clean Air Act of 1990

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1	CERHR	Center for the Evaluation of Risks to Human Reproduction
2	cfm	cubic feet per minute
3	CFCs	chlorofluorocarbons
4	Cl <sup>-</sup>	chloride
5	cm <sup>2</sup>	square centimeter(s)
6	cm/hr	centimeter(s) per hour
7	cm/s	centimeter(s) per second
8	CNS	central nervous system
9	CS <sub>2</sub>	carbon disulfide
10	CYP	cytochrome enzyme
11	CYP2E1	cytochrome P450 enzyme 2E1
12	CYP450	cytochrome P450 enzyme
13	DG	dentate gyrus
14	DL	distal latency
15	DNA	deoxyribonucleic acid
16	DNEL	derived no effect level
17	EC	European Commission
18	<i>E. coli</i>	<i>Escherichia coli</i>
19	ESI-MS	electrospray ionization mass spectrometry
20	F344	Fischer 344 rats
21	EPA	U.S. Environmental Protection Agency
22	fEPSP	field excitatory postsynaptic potential
23	FR	Federal Register
24	GABA	gamma-aminobutyric acid
25	GABA <sub>A</sub>	GABA type A
26	GC	gas chromatography
27	GD	gestation day(s)
28	GESTIS	Institute of Occupational Safety and Health of the German Social
29		Accident Insurance

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1	GHS	Globally Harmonized System of Classification and Labeling of
2		Chemicals
3	GM	geometric mean
4	GR	glucocorticoid receptor
5	GSH	glutathione
6	GSP	S-propyl glutathione
7	GSSG	glutathione disulfide, oxidized form of glutathione
8	GST	glutathione-S-transferase
9	GSTM1	glutathione-S-transferase M1
10	GSTT1	glutathione-S-transferase T1
11	HAP	hazardous air pollutant
12	HCFCs	hydrochlorofluorocarbons
13	HETAB	Hazard Evaluations and Technical Assistance Branch
14	HHA	health hazard alert
15	HHE	health hazard evaluation
16	HPLC	high performance liquid chromatography
17	HO-1	heme oxygenase-1
18	IARC	International Agency for Research on Cancer
19	IDLH	immediately dangerous to life or health
20	Ig	immunoglobulin
21	(IRR)	subnotation of SK:DIR indicating the potential for a chemical to be
22		a skin irritant following exposure of the skin
23	kg	kilogram(s)
24	L	liter(s)
25	L/min	liter(s) per minute
26	lb	pound(s)
27	LC	lethal concentration
28	LC <sub>LO</sub>	lowest concentration of a chemical that caused death in humans
29		or animals; lethal concentration low

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1	LC <sub>50</sub>	lethal concentration that causes the death of 50% (one half) of a
2		group of test animals; median lethal concentration
3	LCL	lower confidence limit
4	LD <sub>LO</sub>	lowest dose of a chemical that caused death in humans or
5		animals; lethal dose low
6	LD <sub>50</sub>	lethal dose that causes the death of 50% (one-half) of a group of
7		test animals; median lethal dose
8	LOD	limit of detection
9	LOQ	limit of quantification
10	MA	model averaging
11	MBP	myelin basis protein
12	MCV	motor nerve conduction velocity
13	mEq/L	milliequivalent(s) per liter
14	mg	milligram(s)
15	mg/cm <sup>2</sup>	milligram(s) per square centimeter
16	mg/kg	milligram(s) per kilogram of body weight
17	mg/kg-day	milligram(s) per kilogram of body weight per day
18	mg/dL	milligram(s) per deciliter
19	mg/L	milligram(s) per liter
20	m <sup>3</sup> /min	cubic meter(s) per minute
21	ml	milliliter(s)
22	ML	motor latency
23	ml/kg	milliliter(s) per kilogram
24	mmol/L	millimole(s) per liter
25	MOA	mode of action
26	MRI	magnetic resonance imaging
27	MSDS	Material Safety Data Sheet
28	m/min	meter(s) per minute
29	MS	mass spectrometry
30	NADPH	nicotinamide adenine dinucleotide phosphate

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1	ND	nondetectable
2	NIOSH	National Institute for Occupational Safety and Health
3	NJDEP	New Jersey Department of Environmental Protection
4	NJDHSS	New Jersey Department of Health and Senior Services
5	NK	natural killer (cells)
6	NOEL	No Observed Effect Level
7	NQO1	NAD(P)H:quinone oxidoreductase
8	NTP	National Toxicology Program
9	ODSs	ozone-depleting substances
10	OECD	Organisation for Economic Co-operation and Development
11	OEL	occupational exposure limit
12	OSH	occupational safety and health
13	OSHA	Occupational Safety and Health Administration
14	OV	organic vapor
15	<i>P. aeruginosa</i>	<i>Pseudomonas aeruginosa</i>
16	PAPR	powered air-purifying respirator
17	PBZ	personal breathing zone
18	PCR	polymerase chain reaction
19	PEL	permissible exposure limit
20	PERC	perchloroethylene
21	PID	photoionization detector
22	PND	postnatal day
23	PNS	peripheral nervous system
24	PPE	personal protective equipment
25	ppm	parts per million
26	PrCYS	globin S-propyl cysteine
27	RCRA	Resource Conservation and Recovery Act
28	REACH	Registration, Evaluation, Authorization, and restriction of
29		CHemical substances
30	REL	recommended exposure limit

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1	ROS	reactive oxygen species
2	R-Phrase	risk phrase
3	S9	supernatant fraction 9
4	SAR	supplied-air respirator
5	SCBA	self-contained breathing apparatus
6	SD	Sprague-Dawley rats
7	SDS	safety data sheet
8	SLA	spontaneous locomotor activity
9	S-Phrase	safety phrase
10	SNAP	significant new alternative policy
11	SRBC	sheep red blood cells
12	STEL	short-term exposure limit
13	<i>S. typhimurium</i>	<i>Salmonella typhimurium</i>
14	TCA	1,1,1-trichloroethane
15	TEAP	Technology and Economic Assessment Panel
16	TLV	threshold limit value
17	TWA	time-weighted average
18	UF	uncertainty factor
19	UN	United Nations
20	U.S.	United States
21	VOC	volatile organic compound
22	WT	wild-type
23	µg	microgram(s)
24	µg/cm <sup>2</sup>	microgram(s) per square centimeter
25	µg/cm <sup>2</sup> /hr	microgram(s) per square centimeter per hour
26	µg/g	microgram(s) per gram
27	µg/L	microgram(s) per liter
28	µL	microliter(s)
29	µmol	micromole(s)
30		

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1 **GLOSSARY**

2 **Adenoma:** an epithelial tumor of glandular origin and structure

3

4 **Amenorrhea:** abnormal absence or suppression of menstruation

5

6 **Ataxia:** an inability to coordinate voluntary muscular movements, symptomatic of some  
7 nervous disorders

8

9 **Carcinoma:** a malignant tumor derived from epithelial tissue

10

11 **Clastogenic:** a specific mutagenic process that gives rise to, induces disruption, or  
12 results in breakages in chromosomes

13

14 **Diaphoresis:** profuse perspiration

15

16 **Demyelination:** the state resulting from the loss or destruction of myelin

17

18 **Dysphagia:** difficulty in swallowing

19

20 **Dysesthesia:** impairment of sensitivity, especially to touch

21

22 **Hemiparesis:** muscular weakness or partial paralysis restricted to one side of the body

23

24 **Hyperreflexia:** overactivity of physiological reflexes

25

26 **Immediately dangerous to life or health (IDLH) value:** a maximum (airborne  
27 concentration) level above which only a highly reliable breathing apparatus providing  
28 maximum worker protection is permitted [NIOSH 2004, 2013]. IDLH values are based on  
29 a 30-minute exposure duration.

30

31 **Myalgia:** pain in one or more muscles

32

33 **Neurogenesis:** development of nerves, nervous tissue, or the nervous system

34

35 **N95 filtering facepiece respirators:** a term that describes the class of respirators that  
36 uses N95 filters to remove particles from the air that is breathed through them. An N95  
37 filter removes at least 95% of airborne particles in NIOSH “worst case” testing with  
38 particles of “most-penetrating” size.

39

40 **NIOSH recommended exposure limit (REL):** an 8- or 10-hour time-weighted average  
41 or ceiling exposure concentration recommended by NIOSH on the basis of an evaluation  
42 of the health effects data

43

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1 **Occupational exposure limit:** levels of exposure that most employees may be exposed  
2 to for up to 10 hours per day, 40 hours per week, for a working lifetime, without  
3 experiencing adverse health effects.

4  
5 **OSHA permissible exposure limit (PEL):** regulatory limit on the amount or  
6 concentration of a substance in the air. OSHA PELs are based on an 8-hour time-  
7 weighted average exposure.

8  
9 **Organic vapor cartridge:** device used in respirators to remove organic vapors from the  
10 air

11  
12 **Paraparesis:** partial paralysis affecting the lower limbs

13  
14 **Paresthesia:** a sensation of pricking, tingling, or creeping on the skin having no  
15 objective cause and usually associated with injury or irritation of a sensory nerve or  
16 nerve root

17  
18 **Personal protective equipment:** respirators, work gloves, work boots, and other  
19 equipment that reduces or eliminates worker exposure to hazards

20  
21 **Polyneuropathy:** a noninflammatory degenerative disease of nerves, usually caused by  
22 toxicants

23  
24 **Purkinje neurons:** a class of GABAergic neurons that are found in the cortex of the  
25 cerebellum and are critical in the control of motor movement

26  
27 **Pyknosis/pyknotic:** a degenerative condition of a cell nucleus, marked by irreversible  
28 condensation of the chromatin during apoptosis

29  
30 **Splendore-Hoepli material (bodies):** star-like asteroid or club-shaped eosinophilic  
31 material around infections and non-infectious agents; may represent the deposition of  
32 immunoglobulins, major basic proteins and debris from the host inflammatory cells and  
33 is seen amid wide areas of degeneration and necrosis [Hussein 2008]

34  
35 **Supplied-air respirator system:** an atmosphere-supplying respirator for which the  
36 source of breathing air is not carried by the user

37  
38 **Teratogenicity:** having the ability to induce or increase abnormal prenatal development

39  
40 **Time-weighted average:** the average exposure during a normal 8- to 10-hour workday.

41  
42 **Volatile organic compound (VOC):** an organic chemical compound with high vapor  
43 pressure and low boiling point

44

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1 **CHAPTER 1: INTRODUCTION**

2 **1.1 PURPOSE**

3 This document presents the criteria and components of a recommended standard to  
4 reduce or eliminate significant risk of health impairment from exposure to 1-  
5 bromopropane (1-BP) (Chemical Abstract Service [CAS] number 106–94–5). This  
6 document was developed in accordance with the Occupational Safety and Health Act of  
7 1970 [29 U.S.C. 669(a)(3); 29 U.S.C. 671 (c)(1)]. The Act charges the National Institute  
8 for Occupational Safety and Health (NIOSH) with recommending occupational safety  
9 and health (OSH) standards and developing criteria for toxic materials. These criteria are  
10 to describe exposures that are safe for various periods of employment, including but not  
11 limited to the exposures at which no worker will suffer diminished health, functional  
12 capacity, or life expectancy because of his or her work experience.

13  
14 The purpose of the criteria document is to evaluate and analyze the scientific literature  
15 concerning potential health effects, toxicology, risk assessment, engineering controls,  
16 work practices, personal protective equipment (PPE), and recommendations pertaining  
17 to 1-BP. The focus is on data most relevant to occupational settings, with an emphasis  
18 on inhalation and dermal exposures. The criteria document provides the basis for the  
19 recommended exposure limit (REL) for 1-BP, although compliance with this  
20 recommended standard is not the sole objective. The intended outcome of the document  
21 is to reduce occupational exposures to 1-BP and thereby prevent adverse health effects  
22 associated with 1-BP exposure through hazard guidance implementation. In its entirety,  
23 the REL and accompanying guidance should help employers develop a more healthful  
24 work environment. The REL and guidance will also provide useful information to help  
25 workers actively participate in their own protection.

26  
27

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1 1.2 SCOPE

2 This criteria document presents (1) the salient facts on occupational exposures to 1-BP  
3 and the toxicity of 1-BP, (2) the rationale and justification for a REL for 1-BP, derived by  
4 means of current quantitative risk assessment methodology, and (3) recommendations  
5 for controls to prevent or limit worker exposures to 1-BP. The recommendations made in  
6 this document should assist in protecting the safety and health of workers. Observance  
7 of these recommendations should prevent or reduce the risks of adverse health effects  
8 associated with workers' exposure to 1-BP.

9

10 Literature published through December 2014 was utilized and extracted from databases  
11 including but not limited to PubMed, NIOSHTIC-2, and Chemical Abstracts Service. The  
12 literature search identified critical scientific data on topics including physical and  
13 chemical properties, human health effects, laboratory testing, chemical toxicokinetics,  
14 toxicity, engineering controls, PPE use and function, risk management, and modeling  
15 systems that are relevant to workplace exposure to 1-BP. Search terms specific to each  
16 scientific discipline were used and yielded information in peer-reviewed journal articles,  
17 government publications, peer-reviewed data sources, and professional practice  
18 manuals. Data identified in the comprehensive literature search were evaluated if the  
19 following considerations were met:

- 20 • the studies were peer-reviewed
- 21 • the data were generated with standardized protocols
- 22 • the exposure conditions were described in detail.

23 Chapter 2 characterizes the findings of human studies and exposure assessments,  
24 including the health effects observed in workers exposed to 1-BP. Chapter 3 illustrates  
25 the potential metabolic pathways of 1-BP. Chapter 4 presents experimental toxicological  
26 data on non-cancer endpoints. Chapter 5 provides a summary of experimental data on  
27 genotoxicity and cancer. Chapter 6 describes the potential modes of action (MOAs) for  
28 non-cancer health endpoints and cancer. Chapter 7 presents the results of the  
29 quantitative risk assessment based on cancer data from animals. Chapter 8 outlines the

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1 basis of the REL, along with supplemental authoritative recommendations. Chapter 9  
2 summarizes hazard prevention and control measures to reduce workplace exposure to  
3 1-BP, including the risk management practices intended to prevent or reduce workplace  
4 exposure to 1-BP. Chapter 10 highlights guidance on medical monitoring and  
5 surveillance, in addition to biological monitoring options for 1-BP. Chapter 11  
6 summarizes exposure monitoring for 1-BP in the workplace. Chapter 12 discusses the  
7 research needed to better characterize and control workplace exposure to 1-BP and to  
8 delineate the health effects of 1-BP. Appendix A contains the NIOSH analytical method  
9 (1025) for 1-BP. Appendix B presents the results of a quantitative risk assessment  
10 based on numerous non-cancer health endpoints.

### 12 1.3 BACKGROUND

13 Bromopropane is a saturated brominated aliphatic hydrocarbon that exists in two isomer  
14 forms, 1-BP and 2-bromopropane (2-BP; CAS number 75-26-30), used as substitutes  
15 for ozone-depleting substances (ODSs) and other regulated compounds with recognized  
16 health effects. Studies of workers exposed to 1-BP and 2-BP have raised concerns,  
17 beginning with the sentinel reports describing adverse reproductive and hematological  
18 health effects in workers exposed to 2-BP in a Korean electronics factory [Kim et al.  
19 1996; Park et al. 1997; Ichihara 2005]. Since these initial reports, human studies have  
20 revealed neurological, reproductive, and hematological effects associated with  
21 occupational exposures to 1-BP [Sclar 1999; Ichihara et al. 2002, 2004a, 2004b, 2005;  
22 Raymond and Ford 2007; Majersik et al. 2007; CDC 2008; Li et al. 2010a]. Neurotoxic  
23 effects, along with reproductive and developmental toxicity, have been reported in  
24 experimental animal studies [Yu et al. 1998, 2001; Oshinishi et al. 1999; Ichihara et al.  
25 2000a, 2000b, 2005; WIL Laboratories 2001; Wang et al. 2002, 2003; Banu et al. 2007;  
26 Ueno et al. 2007; Suda et al. 2008; Liu et al. 2009]. The Center for the Evaluation of  
27 Risks to Human Reproduction (CERHR) of the National Toxicology Program (NTP) has  
28 concluded that there is sufficient evidence of developmental and reproductive toxicity in  
29 animals exposed to 1-BP and 2-BP [Boekelheide et al. 2004; NTP 2003a, 2003b, 2004].  
30 On the basis of results of a 2-year bioassay, NTP [2011] reported clear evidence of the

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1 carcinogenic activity of 1-BP, due to significantly increased incidences of adenoma of  
2 the large intestine of female rats and increased incidences of alveolar/bronchiolar  
3 neoplasms in female mice.

4  
5 Since the reporting of the sentinel cases that signaled the potential health hazards of 1-  
6 BP and 2-BP, use of 2-BP has declined domestically and internationally. In the United  
7 States, 2-BP is not intentionally produced, and it is found almost exclusively as a  
8 contaminant (<0.1% by volume) of 1-BP [Boekelheide et al. 2004]. By comparison, the  
9 volume of 1-BP manufactured and used in the United States is much greater. For this  
10 reason, the focus of this criteria document is occupational exposure to 1-BP; only limited  
11 information is included on 2-BP.

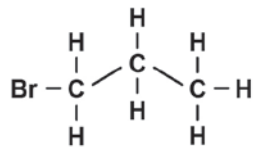
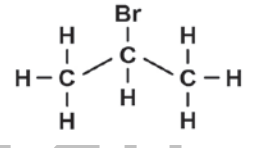
## 12 1.4 CHEMICAL AND PHYSICAL PROPERTIES

13 1-BP and 2-BP are saturated brominated aliphatic hydrocarbons (also known as alkanes  
14 and paraffins) that are colorless to light-yellow liquids with a strong, sweet aroma. 1-BP  
15 is less flammable than other halogenated alkanes at room temperature [NTP 2011,  
16 2013], but the Institute of Occupational Safety and Health of the German Social Accident  
17 Insurance (GESTIS) [2012] identifies it as a highly flammable liquid and vapor on the  
18 basis of the guidelines established via the Globally Harmonized System (GHS) of  
19 Classification and Labeling of Chemicals. 1-BP is insoluble in water but can interact with  
20 water to form acids. Both isomers of bromopropane are soluble in acetone, ethanol,  
21 alcohol, and carbon sulfide. Table 1-1 lists the physical and chemical properties of 1-BP  
22 and 2-BP.

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1 **TABLE 1-1 – PHYSICAL AND CHEMICAL PROPERTIES OF 1-BP AND 2-BP**  
2

Characteristic	1-BP	2-BP
Synonyms	n-propyl bromide, propyl bromide	isopropyl bromide, 2-propyl bromide, sec-propyl bromide
CAS Registry Number	106-94-5	75-26-3
Molecular weight	122.99	122.99
Molecular formula	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> Br	(CH <sub>3</sub> ) <sub>2</sub> CHBr
Molecular structure		
Appearance	Colorless to light-yellow liquid	Colorless to light-yellow liquid
Odor	Strong, sweet	Strong, sweet
Melting point	-110°C [NTP 2004]	-89°C [NTP 2003a]
Boiling point	71°C at 760 mmHg (1 atm) [NTP 2004]	59.38°C at 760 mmHg (1 atm) [NTP 2003a]
Flash point	25°C [OSHA 2014a]	19°C [NIOSH 2003a] (Continued)

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<b>Characteristic</b>	<b>1-BP</b>	<b>2-BP</b>
Vapor pressure	110.8 mmHg (0.146 atm) at 20°C [NTP 2004]	175 mmHg (0.230 atm) at 20°C [Lewis 1996]
Vapor density	1.45 at 20°C at STP [GESTIS 2012]	4.27 [Sax 1979]
Relative density of the vapor/air mixture	1.45 at 20°C [GESTIS 2012]	N/A
Saturated vapor pressure	N/A	230,263 ppm (23.03%) [Lewis 1996]
Specific gravity	1.353 at 20°C [NTP 2004]	1.31 at 20°C [NTP 2003a]
Water solubility	2,450 mg/L at 20°C [NTP 2004]	3,180 mg/L at 20°C [NTP 2003a]
Octanol-water partition coefficient (log K <sub>ow</sub> )	2.10 [NTP 2004]	2.14 [NTP 2003a]
Auto ignition temperature	490°C [GESTIS 2011]	N/A
Lower explosive limit in air	34,000 ppm (3.4% by volume) [GESTIS 2012]	46,000 ppm (4.6% by volume) [USCG 1996]
Upper explosive limit in air	91,000 ppm (9.1% by volume) [GESTIS 2012]	N/A

*(Continued)*

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Characteristic	1-BP	2-BP
Refractive index	1.4341 at 20°C [O'Neil 2001]	1.4251 at 20°C [O'Neil 2001]
Decomposition product (when heated)	Bromide (Br) [GESTIS 2012]	Bromide (Br) [Lewis 2000]
Conversion factors (at 25°C and 1 atm)	1 ppm = 5.03 mg/m <sup>3</sup> , 1 mg/m <sup>3</sup> = 0.2 ppm	1 ppm = 5.03 mg/m <sup>3</sup> , 1 mg/m <sup>3</sup> = 0.2 ppm

1  
2 **Abbreviations:** atm = standard atmosphere; 1-BP = 1-bromopropane; 2-BP = 2-bromopropane; °C = degrees Celsius; mg/m<sup>3</sup> =  
3 milligram(s) per cubic meter of air; mg/L = milligram per liter; mmHg = millimeters of mercury; N/A = not available; ppm = parts per  
4 million

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1 1.5 USE AND PRODUCTION IN THE UNITED STATES

2 1-BP has received increased global attention in recent years as a potential alternative to  
3 ODSs and other compounds with known adverse health effects, such as  
4 chlorofluorocarbons (CFCs), hydrochlorofluorocarbons (HCFCs), and methyl chloroform  
5 (also known as 1,1,1-trichloroethane, or TCA) [EPA 2003a]. 1-BP is reported to not  
6 persist in the upper regions of the atmosphere (that is, the stratosphere) for more than  
7 15 days, and it exhibits a low potential for acting as a greenhouse gas [Nelson et al.  
8 1997]. The perceived limited ecological impact associated with the release of 1-BP, in  
9 addition to both domestic and international pressures to eliminate the production and  
10 use of chemical substances that are damaging to the environment, have resulted in  
11 increased demand for the brominated solvent [EPA 2003a; UNEP 2006]. 1-BP is not  
12 classified as a hazardous air pollutant (HAP) by the U.S. Environmental Protection  
13 Agency (EPA) or as hazardous waste under the Resource Conservation and Recovery  
14 Act (RCRA) [EPA 2003a].

15  
16 The EPA identified 1-BP as a potential substitute for ODSs under authority granted by  
17 the Significant New Alternatives Policy (SNAP) Program, a 1990 amendment to the  
18 Clean Air Act (CAA). In 2003, a proposed SNAP ruling published in the Federal Register  
19 identified 1-BP as an acceptable alternative in several uses. These include using 1-BP  
20 as a substitute for CFC–113, methyl chloroform, and HCFC–141b in aerosol solvent and  
21 adhesive end uses, in addition to using it as a replacement for CFC–113 and methyl  
22 chloroform in general metals cleaning, electronics cleaning, and precision cleaning [EPA  
23 2003a]. Use of 1-BP in these settings was subject to the condition that formulations did  
24 not contain more than 0.05% 2-BP by weight before addition of stabilizers or other  
25 chemicals. In the final SNAP ruling, published in 2007, the EPA identified 1-BP as an  
26 acceptable alternative to CFC–113 and methyl chloroform in the solvent cleaning  
27 industry. This includes the cleaning of general metal and electronics, precision cleaning  
28 with vapor degreasers, in-line cleaning systems, and automated equipment used for  
29 cleaning below the boiling point [EPA 2007b]. The EPA updated its SNAP ruling for 1-BP

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1 in 2007. The update identified 1-BP as an unacceptable alternative to CFC–113, methyl  
2 chloroform, and HCFC–141b in aerosol solvent and adhesive end uses. The ruling was  
3 based, in part, on studies conducted by NIOSH [EPA 2007c]. NIOSH field investigations  
4 indicated that workers employed in foam cushion fabrication (see Section 2.3) were  
5 exposed to airborne concentrations of 1-BP that exceeded 17 to 30 parts per million  
6 (ppm), the range of exposure levels that the EPA considered potentially acceptable [EPA  
7 2007c].

8  
9 1-BP is used as a solvent in vapor degreasing and cold cleaning operations of metals  
10 and high-tech electronic components in the aerospace, military, and electronics  
11 industries [EPA 2003ba]. Additional primary applications of 1-BP include use as a  
12 solvent in adhesive and coatings spray applications, specifically during the production of  
13 polyurethane and foam products [EPA 2003a]. Secondary applications of 1-BP include  
14 use as a solvent of fats and resins and as a chemical intermediate in the synthesis of a  
15 wide range of products, including pharmaceuticals, insecticides, flavorings, and  
16 fragrances [NTP 2004, 2014].

17  
18 In some states, 1-BP is now being used as an alternative solvent in the dry cleaning  
19 industry, in response to the restricted use of perchloroethylene (PERC), also known as  
20 tetrachloroethylene [DLI 2007; Blando et al. 2010; NIOSH 2010a]. For example, an  
21 estimated 1,500 dry cleaning facilities in New Jersey may eventually convert to 1-BP  
22 because of a state-based ban on PERC [Blando et al. 2010]. 1-BP is the only identified  
23 PERC alternative that is usable in the original PERC-based dry cleaning equipment,  
24 following a conversion process that costs approximately \$4,000 per unit; in comparison,  
25 other PERC alternatives that use aliphatic hydrocarbon or silicone-based cleaners  
26 require new equipment that costs approximately \$50,000 [NIOSH 2010a]. Because of  
27 the cost difference, it is reasonable to anticipate that many dry cleaning facilities will  
28 choose to use 1-BP in place of PERC. A 2007 nationwide industry survey revealed that  
29 of those owners who were considering replacing their PERC systems, 24% would  
30 choose to convert to 1-BP [Murphy 2007; NIOSH 2010a]. Commercially available

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1 products used in dry cleaning operations contain ~90% 1-BP; advertisements identify  
2 these substances as nonhazardous, environmentally friendly, or “green” drop-in  
3 substitutes for PERC [DLI 2007; Blando et al. 2010].

4  
5 Major producers of 1-BP have historically been located in Asia and Europe, but limited  
6 volumes of the chemicals are manufactured in the United States [UNEP 2006]. 1-BP  
7 production primarily involves a process that reacts propanol with an excess of hydrogen  
8 bromide gas [NTP 2011]. This process yields 1-BP and small amounts of 2-BP, along  
9 with other byproducts. Reduction or removal of these contaminants occurs via  
10 modification of the production process and the distillation procedures [NTP 2014].

11  
12 In response to anticipated demands for 1-BP, several U.S. manufacturers increased its  
13 production in the late 20<sup>th</sup> century. The Brominated Solvents Consortium (BSC), a group  
14 of U.S.-based 1-BP manufacturers, reported between 1999 and 2000 an estimated 1.5  
15 million pounds of 1-BP was produced domestically and an additional 2.8 million pounds  
16 was imported [NTP 2004]. An estimated 8.2 million pounds of the brominated solvent  
17 was used in the United States in 2002 [NTP 2004, 2014]. The Technology and Economic  
18 Assessment Panel (TEAP) estimated a global production capacity of 44 to 132 million  
19 pounds of 1-BP by 2010, based on the potential replacement of substantial amounts of  
20 CFCs and chlorinated solvents by the brominated solvents industry [EPA 2003a; UNEP  
21 2006]. The EPA stated that the quantity of 1-BP needed to meet future demands would  
22 be much lower than the TEAP prediction, in part because many producers and  
23 secondary users of the brominated solvent would withdraw their products containing  
24 1-BP from commerce, owing to the reports of adverse health effects in exposed workers  
25 and animals [EPA 2003a]. NTP [2004] reported a current growth for 1-BP of <3.0%. The  
26 EPA reported that 15.4 million pounds of 1-Bp were produced or imported in 2011 [EPA,  
27 2013].

28 The production of 2-BP is unintentional in the United States; the chemical is found  
29 almost exclusively as a contaminant (<0.1% by volume) during production of 1-BP  
30 [Boekelheide et al. 2004]. The limited domestic quantity of 2-BP is almost exclusively

10

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1 used as a process agent in the production of pharmaceutical dyes and other organic  
2 chemicals, much like 1-BP. International applications of 2-BP include its use as a  
3 pesticide, a solvent, and a replacement for CFCs and other ODSs [Boekelheide et al.  
4 2004].

## 5 1.6 WORKER EXPOSURE

6 Exposure to workers has been increasing in the past few decades because of the  
7 introduction of 1-BP into several industrial and commercial sectors as a substitute for  
8 substances identified as causing severe health effects (such as cancer, reproductive  
9 toxicity, and development effects) or ozone depletion [EPA 2003a,b; Blando et al. 2010;  
10 NTP 2014]. Workers may be exposed via the inhalation of vapors or mists, in addition to  
11 dermal contact, during the production of 1-BP or commercial operations, such as  
12 adhesive spraying; degreasing or precision cleaning of metals, plastics, and electronic  
13 components; dry cleaning; aircraft maintenance; and asphalt production [Chalupka  
14 2014].

15  
16 EPA [2007a] estimated the number of businesses using 1-BP base do data collected  
17 from trade organizations and manufactures. This analysis indicated that 2,540 to 9,280  
18 businesses use 1-BP resulting in the potential for exposure in 3,320 to 69,100 workers.  
19 The largest use is as a vapor degreaser within 500 to 2,500 businesses [EPA, 2007a].  
20 The analysis indicated that 8,300 to 40,300 workers may be exposed to 1-BP in these  
21 businesses. The second largest use of 1-BP is as an adhesive in the manufacturing of  
22 foam cushions and laminates [EPA, 2007a]. The use of 1-BP as an adhesive occurs in  
23 100 to 280 foam manufacturers with the potential of 400 to 9,800 workers exposed to 1-  
24 BP.

25  
26

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## 1 1.7 OCCUPATIONAL EXPOSURE LIMITS AND HEALTH GUIDELINES

2 In the United States, numerous federal and state governmental agencies have  
3 developed recommendations for 1-BP. The Occupational Safety and Health  
4 Administration (OSHA) has not developed a permissible exposure limit (PEL) for 1-BP,  
5 but it coauthored a Hazard Alert with NIOSH that described the health concerns of  
6 workplace exposures to 1-BP [NIOSH 2013a].

7  
8 In the 2003 proposed SNAP ruling on 1-BP, the EPA recommended a voluntary  
9 acceptable exposure limit (AEL) of 25 ppm for an 8-hour time-weighted average (TWA)  
10 [EPA 2003a]. The intent of the proposed AEL was to protect workers from reproductive  
11 and developmental toxicity, neurotoxicity, and hepatotoxicity from inhalation exposures  
12 to 1-BP [EPA 2003a]. The EPA rescinded its proposed AEL for general metal and  
13 electronics cleaning and precision cleaning operations. The updated 2007 SNAP  
14 proposal did not contain a recommended AEL but stated that levels sufficient to protect  
15 against male reproductive effects would be in the range of 18 to 30 ppm, and those to  
16 protect against female reproductive effects would be in the range of 17 to 22 ppm [EPA  
17 2007c]. This ruling is applicable only to solvent cleaning operations and does not apply  
18 to 1-BP-containing aerosol solvent and adhesives used in certain operations such as  
19 foam cushion fabricating [EPA 2007c].

20  
21 The California Department of Industrial Relations (CA DIR) established a permissible  
22 exposure limit (PEL) for 1-BP. The CA DIR adopted an 8-hour TWA PEL of 5 ppm for 1-  
23 BP, based on reproductive effects in male and female rats, in addition to technological  
24 feasibility assessments from industry [CA DIR 2009]. CA DIR [2009] assigned 1-BP a  
25 skin notation to emphasize the importance of skin absorption.

26  
27 The American Conference of Governmental Industrial Hygienists (ACGIH) established a  
28 threshold limit value (TLV<sup>®</sup>) for 1-BP of 10 ppm as an 8-hour TWA, set to provide  
29 protection against the potential for neurotoxicity, hepatotoxicity, and reproductive and  
30 developmental toxicity in 1-BP-exposed workers [ACGIH 2005]. ACGIH has released a

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1 notice of intended change for the TLV–TWA for 1-BP, on the basis of data published  
2 since the development of the original 2005 TLV [ACGIH 2011]. The draft ACGIH  
3 documentation states, “A TLV–TWA of 0.1 ppm should provide protection against the  
4 potential for neurotoxicity, hepatotoxicity, and reproductive and developmental toxicity in  
5 1-BP-exposed workers” [ACGIH 2014].

6  
7 ICF Consulting Group [1998] proposed an 8-hour TWA OEL of 100 ppm for 1-BP, based  
8 on mild liver histopathology and decreased sperm motility in rats. Rozman and Doull  
9 [2002] identified neurotoxicity as the most sensitive endpoint for 1-BP and derived an 8-  
10 hour TWA OEL for 1-BP of 60 to 90 ppm, based on mild central nervous system (CNS)  
11 effects in the form of headaches in 1-BP-exposed workers. The California Department of  
12 Health Services (CA DHS) recommended that airborne concentrations of 1-BP be limited  
13 to about 1 ppm in order to protect against the reproductive and nerve toxicity of 1-BP  
14 [CA DHS 2003]. In addition, CA DHS recommended a skin notation to require protection  
15 against skin contact exposures. Maier et al. [2004] proposed an 8-hour TWA OEL of 20  
16 ppm for 1-BP, with live litter size being the toxicological endpoint. As part of the  
17 Registration, Evaluation, Authorization, and Restriction of Chemical substances  
18 (REACH) full dossier on 1-BP, derived no-effect levels (DNELs) intended for workplace  
19 settings have been established for 1-BP. These DNELs are as follows: (1) 870 ppm for  
20 acute/short-term exposure associated with systemic effects, (2) 479 ppm for acute/short-  
21 term exposure associated with local effects, and (3) 4 ppm for long-term exposure  
22 associated with systemic effects [ECHA 2010]. Table 1-2 summarizes the quantitative  
23 exposure recommendations for 1-BP.

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1 **TABLE 1-2 – QUANTITATIVE EXPOSURE RECOMMENDATIONS FOR 1-BP**

<b>Exposure recommendation</b>	<b>Airborne concentration</b>	<b>Adverse effects (species)</b>
AEL [EPA 2003a]	25 ppm 8-hour TWA*	Decreased sperm motility (rats)
AEL [EPA 2007b]	17–30 ppm 8-hour TWA†	Decreased sperm motility (rats)
OEL [ICF Consulting Group 1998]	100 ppm 8-hour TWA	Mild liver histopathology; decreased sperm motility (rats)
OEL [Rozman and Doull 2002]	60–90 ppm 8-hour TWA	Mild CNS effects (humans)
OEL [Maier et al. 2004]	20 ppm 8-hour TWA	Decreased live litter size (rats)
PEL [CA DIR 2009]	5 ppm 8-hour TWA; skin notation	Reproductive effects in both sexes (rats)
REACH DNEL [ECHA 2010]	870 ppm	Acute/short-term exposure—systemic effects; most sensitive endpoint
	479 ppm	Acute/short-term exposure—local effects; most sensitive endpoint
	4 ppm	Long-term exposure—systemic effects; most sensitive endpoint
TLV® [ACGIH 2005]	10 ppm 8-hour TWA	CNS toxicity; reproductive toxicity (male, female); developmental toxicity
TLV® [ACGIH 2014]	0.1 ppm 8-hour TWA	CNS toxicity; male and female reproductive toxicity; developmental toxicity

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2 **Abbreviations: AEL = acceptable exposure limit; CNS = central nervous system; DNEL =**  
 3 **derived no effect level; ppm = parts per million; OEL = occupational exposure limit;**  
 4 **REACH = Registration, Evaluation, Authorization, and Restriction of Chemical substances;**  
 5 **TLV® = threshold limit value; TWA = time-weighted average.**

6 \*Rescinded.

7 †Recommended exposure range.

8

9

10

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1 Numerous organizations have established qualitative exposure recommendations for 1-  
2 BP. The California Environmental Protection Agency (CA EPA) has classified 1-BP as a  
3 reproductive/developmental toxicant via the Safe Drinking Water and Toxic Enforcement  
4 Act of 1986, also known as Proposition 65 [CA EPA 2008]. The European Commission  
5 has, in the European Chemical Substance Information System [ECB 2010], designated  
6 1-BP and 2-BP as toxic agents with several Risk (R) and Safety (S) phrases. Table 1-3  
7 provides a summary of the qualitative exposure recommendations for 1-BP.

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1 **TABLE 1-3 – QUALITATIVE EXPOSURE RECOMMENDATIONS FOR 1-BP**

Reference	Classification	Hazard statement
CA EPA [2008]	Reproductive/developmental toxicant	None
ECB [2010]	R11 R36/37/38 R48/20  R60 R63 R67 S53 S45	Highly flammable Irritant to the eyes, respiratory system, and skin Harmful: Danger of serious damage to health by prolonged exposure through inhalation  May impair fertility Possible risk of harm to the unborn child Vapors may cause drowsiness and dizziness Avoid exposure—obtain special instructions before use In case of accident or if you feel unwell, seek medical advice immediately
ACGIH [2013]	A3 - Confirmed animal carcinogen with unknown relevance to humans	None

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2 **Abbreviations: H = hazard statement; R = risk phrase; S = safety phrase.**

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1 1.8 SUMMARY

2 1-BP is a brominated organic solvent used increasingly in industries such as precision  
3 cleaning, vapor degreasing, polyurethane and foam cushion fabricating, and dry  
4 cleaning. The chemical and physical properties of 1-BP make it a viable replacement for  
5 ODSs and other compounds with recognized adverse health effects. In the United  
6 States, 2-BP is found almost exclusively as a contaminant of 1-BP. The number of  
7 workers currently exposed to 1-BP cannot yet be estimated. Workers employed in  
8 industries replacing ODSs and other compounds with 1-BP are at elevated risk of  
9 exposure to the brominated solvent. Available information indicates that 1-BP may pose  
10 an occupational health risk for exposed workers.

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## CHAPTER 2: HUMAN STUDIES AND EXPOSURE ASSESSMENTS

Occupational exposure may occur through inhalation and dermal contact at workplaces during production, transportation, handling, or use of 1-BP. Data on the health effects of 1-BP exposure on workers are available from case reports, cross-sectional surveys, and NIOSH Health Hazard Evaluations (HHEs). Numerous case reports have been published describing workers who have experienced a wide spectrum of adverse health effects attributed to 1-BP. Section 2.1 provides an overview of the case reports, including a description of the signs and symptoms revealed by the study and exposure data; Table 2-1 summarizes these case studies. Section 2.2 describes the results of published cross-sectional surveys and exposure assessments, and Table 2-2 provides a summary of all reviewed studies. Section 2.3 describes the exposure and health data collected during the NIOSH HHEs conducted from 1999 through 2008 to investigate the use of 1-BP in numerous workplace settings. Tables 2-3 and 2-4 provide summaries of the health and exposure data reported in the NIOSH HHEs.

### 2.1 CASE REPORTS

Sclar [1999] presented the case of an ill 19-year-old male employed as a metal stripper for 2 months. The man had been using an industrial solvent as a degreasing and cleaning agent; the solvent was determined to contain 1-BP (>95.5%), 1,2 epoxy butane (<0.5%), 1,3 dioxolane (<2.5%), and nitromethane (<0.25%). The patient had numbness and mild, progressive weakness of his proximal lower extremities and right hand. Other adverse effects included transient dysphagia and urinary difficulties. The skin on the right hand darkened post exposure. Sclar [1999] indicated the absence of exposure data. The physician diagnosed a primary demyelinating condition, predominately affecting the patient's lower extremities. Magnetic resonance imaging (MRI) of the brain and spinal cord revealed evidence of possible CNS involvement. This included patchy areas of increased T2 signal in the periventricular white matter. Before the patient was lost to follow-up, his symptoms had started to resolve. Sclar [1999] theorized that exposure to 1-BP had been responsible for the described symptoms and the development of central and peripheral demyelination.

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2 Ichihara et al. [2002] reported on three female workers at a North Carolina cushion  
3 company who were identified as having neurological effects of exposure to 1-BP as a  
4 solvent in glue. Review of the Material Safety Data Sheet (MSDS) for the adhesive spray  
5 revealed that the compound consisted of 1-BP (55%), ethyl acetate (8%), and aliphatic  
6 petroleum distillates (2%). The patients were aged 35 (Patient 1), 30 (Patient 2), and 50  
7 (Patient 3). All three workers were exposed to 1-BP while using the adhesive spray in  
8 the fabrication of seat cushions. The workers sprayed the adhesive on polyurethane  
9 foam parts and then held them together with their hands until the parts bonded. These  
10 activities indicate that exposure to the adhesive containing 1-BP may have occurred via  
11 inhalation of the vapors and direct contact with the skin. Patient 1 had been spraying  
12 with 1-BP for approximately 11 months, and Patients 2 and 3 had been spraying 3–4  
13 months. Common neurological symptoms included staggering, numbness, a tingling,  
14 prickling, or other abnormal sensation in the skin (paresthesia/dysesthesia), a decrease  
15 in vibration sensitivity in the legs, and multiple symptoms in the CNS including memory  
16 loss, headaches, and mood changes. All three patients experienced diarrhea, urinary  
17 incontinence, and abnormal sweating. Ichihara et al. [2002] reported these as possible  
18 effects on the autonomic nervous system. Patients 1 and 2 experienced disruptions in  
19 their menstrual cycle. The exposure level of Patient 3 was estimated via passive  
20 samplers for organic solvents for eight hours during four separate workdays. The  
21 authors reported daily TWA concentrations ranging from 60 to 261 ppm. Ichihara et al.  
22 [2002] noted that the exposure estimates were obtained after improvement of the  
23 ventilation system.

24

25 Majersik et al. [2007] reported six cases of severe neurotoxicity in foam cushion gluers  
26 at a factory where an adhesive containing 1-BP was used to bind polyurethane pieces. A  
27 review of the adhesive's MSDS revealed the compound consisted of 1-BP (70%), 1, 2-  
28 epoxy butane (0.3%), styrene butadiene rubber (10%), and rosin ester (20%). The  
29 patients were a 29-year-old female (Patient 1), a 43-year-old female (Patient 2), a 28-  
30 year-old female (Patient 3), a 26-year-old female (Patient 4), a 46-year-old male (Patient

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1 5), and a 16-year-old male (Patient 6). Patients 1–5 had been employed at the factory  
2 for at least 3 years; Patient 6 worked at the facility for 3 months prior to the investigation.  
3 Patients 1–3 applied glue via a spray gun onto polyurethane foams pads, which were  
4 attached by hand to other foam pads or cloth. Patients 4–6 worked in close proximity to  
5 the glue sprayers. Thin latex gloves were worn by workers; no additional PPE was worn.  
6 The author reported that as workers sprayed the adhesive, it often splattered their faces.  
7 Therefore, inhalation and dermal exposures to the 1-BP-containing adhesive occurred.

8  
9 All six patients experienced subacute onset of lower-extremity pain or paresthesias  
10 [Majersik et al. 2007]. Five of the six patients experienced difficulty walking, spastic  
11 paraparesis, distal sensory loss, and hyperreflexia. Three of the patients experienced  
12 nausea and headache. Medical evaluations of the patients revealed serum bromide (Br<sup>-</sup>)  
13 concentrations ranging from 44 to 170 milligrams per deciliter (mg/dL) (reference, 0–40  
14 mg/dL) and serum chloride (Cl<sup>-</sup>) concentrations ranging from 105 to 139 millimoles per  
15 liter (mmol/L) (reference, 98–107 mmol/L) [Majersik et al. 2007].

16  
17 Three weeks after the identification of Patient 1, use of the 1-BP-containing adhesive at  
18 the factory was suspended [Majersik et al. 2007]. Prior to this suspension, Utah  
19 Occupational Safety and Health (UOSH) conducted an investigation of the factory,  
20 including the collection of personal breathing zone (PBZ) air samples for each gluer  
21 during the 7-hour workday. The mean 1-BP concentration was 130 ppm (range, 91–176  
22 ppm), with a TWA of 108 ppm (range, 92–127 ppm) [Majersik et al. 2007]. The  
23 investigation did not identify any other potential neurotoxicant at the factory. At a 2-year  
24 follow-up, five patients still had health problems attributed to occupational exposures to  
25 the adhesive containing 1-BP [Majersik et al. 2007]. Patients 1 and 2 had not recovered  
26 and were unable to return to work. Patient 5 still experienced headaches, spastic  
27 paraparesis, and lower-extremity sensory loss. Patients 3, 4, and 6 were lost to follow-  
28 up.

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1 Raymond and Ford [2007] reported on four furniture factory (i.e., foam cushion  
2 fabricator) workers who became ill following the use of a soft seam adhesive containing  
3 1-BP (70%), 1,2 epoxy butane (0.3%), styrene-butadiene-styrene copolymer (10%), and  
4 rosin ester (20%). The adhesive had been introduced at the factory in early 1999.  
5 Workers applied it as an aerosol spray and by hand and brush to bind leather and fabric  
6 coverings. No PPE was used during this process; skin exposure to 1-BP may have  
7 contributed to the onset of the reported health effects.

8  
9 The four workers presented for emergency care within 3 weeks of the introduction of the  
10 adhesive [Raymond and Ford 2007]. They were a 42-year-old female employed at the  
11 factory for 36 months (Patient 1), a 22-year-old female employed for 41 months (Patient  
12 2), a 29-year-old male employed for less than a month (Patient 3), and a 28-year-old  
13 female employed for 8 months (Patient 4). Patient 1 experienced flu-like illness,  
14 headache, weakness, sore throat, fever, lightheadedness, fatigue, nausea,  
15 unsteadiness, numbness in the feet, and insomnia. Patient 2 had ataxia, leg numbness,  
16 lightheadedness, nausea, loss of balance, unsteady gait, and dysesthesias. Patient 3  
17 suffered from weakness, staggering gait, dizziness, slowing of thinking and movements,  
18 auditory and visual hallucinations, chills, nervousness, transient right hemiparesis,  
19 diminished hand dexterity, hair loss, diaphoresis, cardiac irregularity, and esophageal  
20 reflux. Patient 4 had severe headache, myalgias, weakness, dizziness, nausea, blurred  
21 vision, and numbness in the extremities. None of the workers had a medical history of  
22 neurological problems prior to the introduction of the adhesive containing 1-BP.

23  
24  
25 NIOSH conducted a health hazard evaluation (HHE) at this facility 9 months after the  
26 patients became ill. The HHE included an in-depth investigation of the potential 1-BP  
27 exposure of the fabrication lines [NIOSH 2003b]. The geometric mean (GM) value of  
28 airborne 1-BP concentrations for full-shift PBZ air samples was 81 ppm (range, 18–254  
29 ppm). Additional information on the findings of the HHE can be found in Section 2.3.

30

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1 Raymond and Ford [2007] reported that at a 2-year follow-up, only Patients 1 and 2 were  
2 available for further evaluation. Patients 3 and 4 were lost to follow-up. Two years after  
3 the initial diagnosis, Patient 1 was still weak, and she was unsteady when asked to  
4 stand with her eyes closed. At an 8-year follow-up, Patient 1 was experiencing recurring  
5 headaches, sleep disturbances, unsteady gait, numbness, and paresthesias below the  
6 knees. At a 5-year follow-up, Patient 2 was still experiencing residual lower-extremity  
7 pain; at her 8-year follow-up evaluation she no longer had pain but was still suffering  
8 from numbness and dysesthesias. The authors stated that because of confounding  
9 factors, in the form of elevated urinary As<sup>+</sup> levels, a conclusive diagnosis linking 1-BP to  
10 the neurological disorders in Patients 1 and 2 was not possible.

11  
12 CDC [2008] described two independent cases of neurological abnormalities in workers  
13 employed at facilities where 1-BP was used. The first case, in 2007, was of a 50-year-  
14 old male who had worked at an electronics plant in Pennsylvania for 8 years. For the  
15 past 3 years, the man had used a 1-BP vapor and immersion degreaser to clean circuit  
16 boards. He would submerge and spray circuit boards and then drain, clean, and charge  
17 the bath tank. Typically, no PPE was used, and ventilation was reported to be poor. He  
18 suffered from confusion, dysarthria, dizziness, paresthesias, and ataxia. Neurological  
19 examination found he had slowed mentation (mental activity) and mild confusion. His  
20 gait was wide-based, ataxic, and sensory in nature. The worker also suffered from mild  
21 sensory neuropathy in his extremities. Short-term area air sampling revealed a  
22 concentration of 178 ppm 1-BP. Serum Br<sup>-</sup> concentration obtained 2 weeks after  
23 presentation was 48 milligrams/deciliter (mg/dL) (ref. range 0–10 mg/dL). The worker  
24 continued to have peripheral neuropathy, trouble maintaining mental focus, and ataxia  
25 for a year after initial presentation.

26  
27 Case 2, in early 2008, was a 43-year-old male who became ill after using a cleaning  
28 solvent containing 1-BP, at his dry cleaning facility [CDC 2008]. Six weeks prior to  
29 becoming ill, the patient had stopped using PERC and started using a dry cleaning  
30 solvent that was greater than 95% by weight 1-BP. He reported manually charging his

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1 dry cleaning machine with approximately 50–60 gallons of the solvent while wearing no  
2 PPE. Over the next 2 days of use, he experienced unusual fatigue, headaches, nausea,  
3 arthralgias, visual disturbances, paresthesias, and muscular twitching. The patient  
4 underwent multiple medical evaluations. Computed tomography and physical  
5 examination yielded unremarkable findings. A fine tremor in his upper extremities was  
6 noted. Serum tests were normal [CDC 2008]. The results of exposure monitoring  
7 revealed high peak concentrations (75 to 250 times background levels) of 1-BP during  
8 the unloading and handling of clothes. An investigation of this incident revealed that the  
9 patient had not adjusted the temperature and pressure settings of the dry cleaning  
10 machine to account for the difference in physical properties of 1-BP and PERC.

11  
12 Samukawa et al. [2012] reported a case of 1-BP-induced neurotoxicity in a 43-year-old  
13 male worker employed as a metal cleaner. The patient reported using 1-BP as a  
14 cleaning agent for 8.5-9.5 hours/day for 5-6 days/week for 18 months. Daily tasks  
15 focused on the immersion of metal parts in a wash tank (assumed to contain  
16 undisclosed 1-BP solution) for 15 seconds, in addition to their subsequent removal and  
17 wiping down with an ethanol solution. The patient also cleaned the wash tank monthly.  
18 Samukawa et al. [2012] noted that local ventilation was not used in the facility and that  
19 the patient reported wearing cloth gloves, which the authors noted, may have increased  
20 dermal exposures to 1-BP. Samukawa et al. [2012] stated that the patient did not use a  
21 protective mask prior to using 1-BP as a cleaning agent. The patient did start wearing an  
22 unspecified protective mask for about 5 months before admission. Air sampling data  
23 collected via passive samplers revealed 1-BP concentrations ranging from 353-663 ppm  
24 with a mean TWA concentration of 553 ppm.

25 The patient experienced numbness and pain of his extremities, in addition to mild  
26 weakness and gait disturbances [Samukawa et al. 2012]. Two months after the onset of  
27 these symptoms the patient was admitted for medical care. Neurological examination  
28 revealed: (1) mild weakness in the distal extremities; (2) pain and temperature sensation  
29 decreased in the distal lower extremities; and (3) symmetrically decreased vibration  
30 sense in the distal lower extremities. In addition, the patient exhibited cognitive

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1 impairment and difficulty walking attributed to severe ataxia caused by uncoordinated  
2 movements of lower extremities. Routine blood screenings and cerebrospinal fluid  
3 examination revealed no abnormal findings. A MRI revealed mild brain atrophy with no  
4 focal lesions. Samukawa et al. [2012] reported prolonged distal latency and decreased  
5 conduction velocity in all examined nerves. In addition, a biopsy of the sural nerve  
6 revealed histological changes including axonal damage. Serum Br- level at 2 months  
7 after cessation of exposure was 58 µg/ml (normal range: < 5 µg/ml).

8

9 Samukawa et al. [2012] reported notable improvement of the patient's condition after the  
10 cessation of exposure to 1-BP. Four months after his last exposure, the patient was able  
11 to walk with the assistance of a cane, and his serum Br- level had decreased to 20  
12 µg/ml. After seven months, the patient was able to ride a bicycle and had a normal  
13 serum Br- level. The results of the case study indicate that 1-BP induced peripheral  
14 neuropathy in the patient, following repeated exposures for 18 months in an  
15 occupational setting.

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1 **TABLE 2-1 – SUMMARY OF CASE REPORTS ON WORKPLACE EXPOSURES TO SOLVENTS CONTAINING 1-BP**

<b>Reference</b>	<b>Facility type</b>	<b>Total number (sex)</b>	<b>Solvent components (%)</b>	<b>Reported symptoms</b>
Sclar [1999]	Metal stripping— degreasing	1 (male)	1-BP (> 95.5), 1,2 epoxy butane (< 0.5), 1,2-dioxolane (< 2.5), nitromethane (< 0.25)	Numbness, discolored skin, urinary problems, dysphagia, weakness in the extremities; elongated in distal latency of lower extremities; decreased sensory nerve conduction velocity
Ichihara et al. [2002]	Polyurethane foam cushion fabricating	3 (female)	1-BP (55), ethyl acetate (8), aliphatic petroleum distillates (2)	Difficulty walking, numbness, tingling, abnormal skin sensation, dizziness, headache, decreased vibration sense in lower extremities
Majersik et al. [2007]	Foam cushion fabricator	6 (2 male, 4 female)	Unspecified	Lower extremity pain, difficulty walking, spastic paraparesis, distal sensory loss, hyperreflexia, nausea, headaches, poor balance, dizziness, numbness
Raymond and Ford [2007]	Foam cushion fabricator	4 (1 male, 3 female)	1-BP (70), 1,2 epoxy butane (0.3), styrene-butadiene-styrene copolymer (10), rosin ester (20)	Headache, weakness, sore throat, fever, lightheadedness, fatigue, nausea, unsteadiness, numbness in feet, insomnia, ataxia, dysesthesias, dizziness, hallucinations, chills, nervousness, diminished hand dexterity, hair loss, blurred vision, diaphoresis, depression
CDC [2008]	Electronics—not specified (Case report 1)	1 (male)	Unspecified	Confusion, dysarthria, dizziness, paresthesias, ataxia
CDC [2008]	Dry cleaning (Case report 2)	1 (male)	1-BP (> 95)	Headache, nausea, dizziness, malaise, arthralgias, difficulty focusing, paresthesias, muscular twitching

*(Continued)*

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Reference	Facility type	Total number (sex)	Solvent components (%)	Reported symptoms
Samukawa et al. [2012]	Metal cleaning operation	1 (male)	Unspecified	Numbness and pain in the extremities, mild weakness in the distal extremities, gait disturbances and difficulty walking attributed to severe ataxia, cognitive impairment

---

1 Abbreviation: 1-BP = 1-bromopropane.

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## 2.2 CROSS-SECTIONAL STUDIES AND EXPOSURE ASSESSMENTS

Limited human or exposure data are available to aid in characterizing the hazards of workplace exposures to 1-BP. This section reviews the data collected in workplace settings. Table 2-2 provides a summary of all reviewed studies.

Ichihara et al. [2004a] examined 24 female and 13 male workers for adverse health effects at a 1-BP and 2-BP production facility in Yixing City, Jiangsu Province, China. This was a follow-up to an earlier study [Ichihara et al. 1999] at the same facility in 1996. The original study investigated workers' exposure to 2-BP; however, the facility, which had been producing 2-BP in 1996, began producing 1-BP in 1999. Ichihara et al. [2004a] reported that the purity of 1-BP produced there was 96.74%; contaminants included di-n-propyl ether (1.02%), 2-BP (0.83%), 1,2-dibromopropane (0.4%), 1,2-dibromoethane (0.26%), and an unknown substance (0.75%).

Worker symptoms included eye and upper respiratory tract irritation, headaches, dizziness, and feelings of heavy headedness, which related to damage in the CNS [Ichihara et al. 2004a]. The authors suggest that the sore throats observed as the dominant clinical feature may have been the result of previous 2-BP exposure. Three female workers had amenorrhea, and one had irregular menstruation. Nine female and four male workers experienced mild anemia. Ichihara et al. [2004a] stated that an iron deficiency partially contributed to the anemia. The authors did not make any conclusions on the role of 1-BP, but did report experiencing nasal and conjunctival irritation following visits to the facility.

Workers' personal exposures were assessed with passive air samplers [Ichihara et al. 2004a]. The full-shift, 12-hour PBZ TWA for 1-BP exposure ranged from nondetectable (ND) to 170.5 ppm, much higher than the range of ND to 16.18 ppm for 8-hour PBZ TWA 2-BP exposure observed in 1996 [Ichihara et al. 1999]. As part of this investigation, Ichihara et al. [2004a] examined the use of urinary 1-BP levels as a potential biomarker

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1 of exposure. A comparison of the urinary 1-BP levels to individual airborne 1-BP  
2 concentrations revealed that the two were significantly correlated. The results of this  
3 study indicate that urinary 1-BP may be a good indicator of occupational exposure to  
4 airborne 1-BP.

5  
6 In a second study, Ichihara et al. [2004b] surveyed 27 female workers in a 1-BP  
7 production factory in Yixing City, Jiangsu Province, China, to assess neurological effects  
8 in exposed workers and to correlate the observed effects with exposure levels. Prior to  
9 1999, the production factory had produced 2-BP, and therefore workers hired prior to  
10 that year had been exposed to 2-BP in addition to 1-BP. The surveyed workers were all  
11 female, on average  $36.2 \pm 5.7$  years old, and had held their jobs for  $27 \pm 31$  months. For  
12 comparison purposes, 23 age-matched ( $\pm 2$  years) women were selected from 202  
13 female workers in a beer factory in the same city. These control workers lived in the  
14 same areas as the 1-BP case workers. Medical examinations, electrophysiologic  
15 studies, blood tests, neurobehavioral tests (forward and backward digit span; Benton  
16 visual memory test; pursuit aiming test; and Profile of Mood States test, which includes  
17 tension, depression, anxiety, fatigue, and confusion), postural sway, and assessment of  
18 exposure to 1-BP were conducted as part of the study.

19  
20 Medical examinations determined that none of the case subjects had a history of  
21 diabetes mellitus, which could be a cause of polyneuropathy [Ichihara et al. 2004b].  
22 Electrophysiological studies found that in comparison with the beer factory workers, the  
23 workers exposed to 1-BP had significantly longer (by approximately 35%) distal latency  
24 (DL) in the tibial nerve and 16% lower sensory nerve conduction velocity (NCV). There  
25 were also numerous exposed workers with delayed vibration sensation in toes or fingers;  
26 none of the controls had delayed sensation.

27  
28 Reduced vibration sensation occurred in 15 of the 1-BP workers but none of the  
29 controls. The results of neurobehavioral and mood tests revealed significant changes in  
30 1-BP exposed workers compared to controls. These findings indicate a reduction in the

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1 function of the CNS. One of the co-variables tested, exposure either from 1991 or from  
2 1999 until study completion, also did not affect the various test outcomes in an obvious  
3 fashion (this differentiation was made because of the facility's gradual switch from  
4 producing 2-BP [since 1991] to producing 1-BP, between 1996 and 1999). Few  
5 significant changes were observed in the posture sway tests. When test results were  
6 stratified by exposure levels,  $\leq 2.64$  or  $\geq 8.84$  ppm, significant differences in NCV values  
7 were detected. Laboratory tests showed significantly lower levels of vitamin B1 and  
8 lower WBC counts in 1-BP workers versus controls, but the authors reported that neither  
9 diabetes nor vitamin B1 deficiency confounded the findings. The full-shift, 8-hour PBZ  
10 TWA concentration obtained from passive samplers ranged from 0.34 to 49.2 ppm, with  
11 the median at 1.61 ppm and the GM at 2.92 ppm [Ichihara et al. 2004b].

12  
13 Ichihara et al. [2004b] acknowledged that the limited number of participants in their study  
14 limited its statistical power, in particular with respect to long-term effects from previous 2-  
15 BP exposure. The conclusions of the study indicate that 1-BP may induce adverse  
16 effects in the CNS, in addition to PNS, in the peripheral sensory and motor nerves.

17  
18 Hanley et al. [2006] evaluated 30 workers at two foam-fabricating plants to determine  
19 occupational exposures to 1-BP during the manufacturing of polyurethane seat cushions  
20 and to assess the feasibility of using urinary Br<sup>-</sup> concentrations as a biomarker of 1-BP  
21 exposure. The evaluated workers included 13 adhesive sprayers (1 man, 12 women)  
22 and 17 non-sprayers (4 men, 13 women). The ages of sprayers ranged from 18 to 57  
23 years (average, 35.5 years). The ages of non-sprayers ranged from 24 to 54 years  
24 (average, 36.1 yrs). Hanley et al. [2006] collected PBZ air samples for two consecutive  
25 days. In addition, all workers' urine voids were collected for the same 48-hour period for  
26 comparison with exposure data.

27 The sprayers' TWA full-shift exposures to 1-BP ranged from 45 to 200 ppm, with a GM  
28 of 92 ppm [Hanley et al. 2006]. The TWA full-shift exposures for non-sprayers ranged  
29 from 0.6 to 60 ppm, with a GM of 11 ppm. The GM values for daily urinary Br<sup>-</sup> excretion  
30 were four times higher for sprayers than for non-sprayers. One- and 2-day urinary Br<sup>-</sup>

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1 concentrations for sprayers significantly correlated with airborne concentrations of 1-BP  
2 measured via PBZ air samples. Hanley et al. [2006] reported that the 48-hour urinary Br<sup>-</sup>  
3 concentrations correlated well with the subjects' average TWA exposure to 1-BP ( $r^2 =$   
4 0.89), indicating that urinary Br<sup>-</sup> may be a useful index of exposure to 1-BP. When the  
5 data were stratified by jobs, the correlation between urinary Br<sup>-</sup> concentration and TWA  
6 for airborne 1-BP concentrations for sprayers was lower. However, this may be due to  
7 sprayers' handling of the wet adhesive with bare hands, causing additional skin  
8 exposure to 1-BP. Hanley et al. [2006] concluded that urinary Br<sup>-</sup> appears to be a  
9 reasonable index for 1-BP exposure.

10  
11 Hanley et al. [2009] investigated the use of *N*-acetyl-*S*-(*n*-propyl)-L-cysteine (AcPrCys),  
12 a mercapturic acid conjugate, as a biomarker of exposure for 1-BP in the same  
13 population of foam-fabricating workers. AcPrCys is a metabolite of 1-BP and is theorized  
14 to be a more specific biomarker of exposure than urinary Br<sup>-</sup> because of the limited  
15 potential of interference from nonoccupational exposures. Using aliquots of the urine  
16 collected and analyzed in the previous study [Hanley et al. 2006], the authors analyzed  
17 samples by a method that applied high-performance liquid chromatography (HPLC)  
18 coupled with electrospray ionization mass spectrometry (ESI-MS) [Cheever et al. 2009].  
19 Airborne TWA 1-BP concentrations and urinary AcPrCys levels were compared for both  
20 sprayers and non-sprayers.

21  
22 Sprayers exhibited higher levels of the urinary AcPrCys than non-sprayers, which  
23 correlated with PBZ TWA 1-BP concentrations. Urinary AcPrCys and Br<sup>-</sup> levels were  
24 found to be highly correlated, and although AcPrCys was proportional to 1-BP exposure  
25 in air, the correlation was significant but weak, reflecting patterns of exposure not  
26 measured by TWA sampling. Hanley et al. [2009] reported a statistically significant  
27 association between urinary AcPrCys levels adjusted for creatinine (AcPrCys<sub>cr</sub>) and 1-  
28 BP TWA air concentrations for both sprayers and non-sprayers. GM AcPrCys<sub>cr</sub> levels  
29 were two orders of magnitude greater for sprayers and ~25 times greater for non-

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1 sprayers compared to controls. Hanley et al. [2009] concluded that urinary AcPrCys is  
2 an effective biomarker for workers exposed to high concentrations of 1-BP.

3  
4 In a follow-up study, Hanley et al. [2010] continued to investigate the use of urinary Br-  
5 and AcPrCys as valid biomarkers of exposures to low 1-BP airborne concentrations in  
6 occupational settings. Urine samples were collected over a 48-hour period from workers  
7 employed at five facilities, four of which used 1-BP in vapor degreasing operations; the  
8 fifth used 1-BP in the manufacture of adhesives. Workers were divided into groups  
9 depending on their proximity to the vapor degreasers or whether they had direct contact  
10 with 1-BP in the adhesive manufacturing facility. Urinary concentrations of the 1-BP  
11 metabolites were correlated with PBZ air samples collected during the same study  
12 period.

13  
14 Hanley et al. [2010] reported that the PBZ TWA GM concentration of 1-BP was 2.6 ppm  
15 (GSD = 3.05) for workers located near the vapor degreasers and 0.308 ppm (GSD =  
16 2.98) for workers located away from the vapor degreaser. In the adhesive manufacturing  
17 facility, for workers with direct exposure to 1-BP, the TWA GM breathing zone  
18 concentration of 1-BP was 3.79 ppm (GSD = 5.04), whereas for workers with indirect  
19 exposure the concentration was 0.325 ppm (GSD = 2.44). The authors reported that the  
20 urinary Br- levels were three times higher than for workers located away from the  
21 degreasing operations, and AcPrCys levels were 14 times higher. Similar trends were  
22 observed in the adhesive manufacturing facility. Hanley et al. [2010] concluded that both  
23 metabolites are important excretion pathways for 1-BP metabolism and should be  
24 considered effective biomarkers for monitoring low-level exposures to 1-BP.

25  
26 Li et al. [2010a] investigated the dose-dependent effects associated with exposure to 1-  
27 BP in 60 female and 26 male workers employed at three independent 1-BP production  
28 factories in China. Study participants were interviewed and the questionnaire included  
29 items that consisted of basic demographics information and their medical and  
30 occupational histories. The health status of the study participants was assessed via

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1 electrophysiological studies, neurological indexes (i.e., vibration sense, reflex, and  
2 muscle strength), neurobehavioral tests, and blood tests. PBZ samples were collected  
3 using passive samplers to quantify workers' exposure to 1-BP and 2-BP in each facility.  
4 Area air samples were also collected using detection tubes to determine the total  
5 combined ambient concentration of 1-BP and 2-BP. The results of the PBZ samples  
6 were used to classify workers into low, medium, or high exposures.

7  
8 Analysis via gas chromatography–mass spectrometry of the 1-BP product used at the  
9 three independent production facilities revealed 96–99% pure 1-BP; the remaining  
10 component of the 1-BP product contained impurities that included di-n-propyl ether, 2-  
11 BP, 1,2-dibromopropane, 1,2-dibromoethane, and an unknown substance [Li et al.  
12 2010a]. The reported PBZ TWA concentrations of 1-BP collected during 8- or 12-hour  
13 shifts ranged from 0.07 to 106.4 ppm for women and from 0.06 to 114.8 ppm for men.  
14 PBZ TWA concentrations of 2-BP ranged from 0.01 to 14.9 ppm for women and from  
15 0.004 to 5.4 for men. Workers were grouped into low, medium, and high exposure  
16 groups based on the results of the PBZ samples. The area air samples revealed varying  
17 concentrations of the brominated solvent that ranged by an order of magnitude in the  
18 individual facilities on the basis of their placement. Overall, the area samples trended  
19 toward being higher at the raw product collection sites than at the reaction pot sites.

20  
21 Li et al. [2010a] reported dose-dependent neurological and hematological changes in  
22 female workers, attributed to occupational exposures to 1-BP. The dose-dependent  
23 neurological effects included electrophysiological changes in the form of tibial DL and  
24 decreased sural nerve conduction velocity (SNCV), decreased vibration sense in toes,  
25 and reduced score on Benton cognitive testing. Significant changes in the blood  
26 chemistry of exposed women, including decreased RBC count and increased  
27 concentrations of lactate dehydrogenase (LDH), thyroid-stimulating hormone (TSH), and  
28 fructosamine (FSH), were observed to occur in a dose-response manner. A lowest  
29 observed adverse effect level (LOAEL) of 1.28 ppm was identified for the female workers  
30 on the basis of the decreased vibration sense in the toes and decreased RBC count.

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1 Male workers appeared to experience fewer effects associated with occupational  
2 exposures to 1-BP. The authors stated that workers were exposed to “trace”  
3 concentrations of 2-BP, which were documented by PBZ sampling. Exposure to 2-BP is  
4 a confounding factor that may have contributed to the onset of the hematological effects  
5 [Li et al. 2010a].

6  
7 Blando et al. [2010] investigated occupational exposures to 1-BP in dry cleaning facilities  
8 in New Jersey. Because of a ban on PERC by the New Jersey Department of  
9 Environmental Protection (NJDEP), these dry cleaning facilities converted their  
10 equipment from using PERC to using 1-BP. A total of 11 facilities were identified that  
11 were using 1-BP, and four participated in the study. PBZ samples were collected in three  
12 facilities, and area air samples were collected at specific locations in all four facilities. In  
13 addition, the authors characterized a single dry cleaning machine operator’s exposure to  
14 organic vapors over the course of a workday, by using a real-time direct-reading organic  
15 vapor monitor with a photoionization detector (PID). Video exposure monitoring was  
16 conducted to coordinate the real-time results with specific workplace activities.

17  
18 Blando et al. [2010] collected a total of 14 PBZ samples and 12 area air samples. The  
19 PBZ 8-hour TWA concentrations of 1-BP ranged from ND to 54.5 ppm. Dry cleaning  
20 machine operators experienced the highest concentrations of 1-BP, which ranged from  
21 ND to 54.5 ppm. Clerks encountered 1-BP concentrations that ranged from 0.65 to 21.9  
22 ppm. The highest estimated PBZ 8-hour TWA of 2-BP was 0.02 ppm. Area air samples  
23 were collected for 95 to 504 minutes; TWA concentrations were determined only for the  
24 time during which actual work activities were conducted. The ambient levels of 1-BP  
25 varied throughout the facilities, depending on proximity to the dry cleaning equipment  
26 and other factors. The measurements, collected by real-time direct reading organic  
27 vapor monitors with a PID, revealed that the organic vapor concentrations varied greatly  
28 over the course of the workday. Peaks occurred when 1-BP was added or when loads  
29 were removed from the dry cleaning equipment. Blando et al. [2010] stated that the real-  
30 time measurements, when correlated with video exposure monitoring, revealed that

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1 specific workplace activities, including adding 1-BP, loading/unloading clothes, and  
2 opening the equipment's door during a cycle, may result in relatively high exposures to  
3 1-BP. Overall, the results of this study indicated that workers employed in dry cleaning  
4 operations may be exposed to concentrations of 1-BP that lead to adverse health  
5 effects.  
6

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1 **TABLE 2-2 – SUMMARY OF DATA FROM HUMAN STUDIES AND EXPOSURE ASSESSMENTS**

Reference	Study purpose	Facility type	Total number (sex)	Airborne concentration* (range), ppm	Results
Ichihara et al. [2004a]	Evaluate health effects of 1-BP exposure; identify potential biomarkers of exposure for 1-BP	1-BP/ 2-BP manufacturer	37 (13 male, 24 female)	(ND-170)	Urinary 1-BP levels correlated with airborne 1-BP concentrations; neurological, reproductive, and hematological effects reported in workers†
Ichihara et al. [2004b]	Evaluate and compare neurological function of 1-BP exposed to nonexposed workers	1-BP manufacturer	27 cases, 23 controls (50 female)	2.92 GM (0.34–49.2)	Workers exposed to 1-BP had significantly increased neurological issues in comparison with controls†
Hanley et al. [2006]	Evaluate occupational exposures to 1-BP; assess the use of urinary Br <sup>-</sup> as a biomarker of exposure	Cushion factory	30 (5 male, 25 female)	92 GM (45–200)	Urinary Br <sup>-</sup> levels correlated with airborne 1-BP concentrations for both days of biological monitoring; urinary Br <sup>-</sup> identified as a potential biomarker of exposure
Hanley et al. [2009]	Evaluate occupational exposures to 1-BP; assess the use of urinary AcPrCys as a biomarker of exposure	Cushion factory	30 (5 male, 25 female)	92 GM (45–200)	Urinary AcPrCys levels associated with airborne 1-BP concentrations; urinary AcPrCys identified as an effective biomarker for workers exposed to high concentrations of 1-BP

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Reference	Study purpose	Facility type	Total number (sex)	Airborne concentration* (range), ppm	Results
Hanley et al. [2010]	Evaluate urinary Br- and AcPrCys concentrations as biomarkers of exposure in workers in low exposures to 1-BP	Vapor degreasing operations	22 near degreasers (20 male, 2 female)  9 non-degreasers (8 male, 1 female)	2.63 GM (GSD = 3.05)  0.31 GM (GSD = 2.98)	Study demonstrated that urinary Br- and AcPrCys are useful biomarkers for monitoring low-level exposures to 1-BP
		Adhesives manufacturing	3 who directly used 1-BP (3 male, 0 female)  8 who did not use 1-BP (7 male, 1 female)	3.79 GM (GSD = 5.04)  0.33 GM (GSD = 2.44)	
Li et al. [2010a]	Evaluate the health effects of worker exposure to 1-BP and its dose-dependency in 1-BP production facilities	1-BP production facilities	86 (26 male, 60 female)	(0.06–115) males (0.07–106) females	Evidence of a dose-dependent neurological and hematological changes in female workers attributed to occupational exposures to 1-BP <sup>†</sup>
Blando et al. [2010]	Evaluate airborne concentrations of 1-BP in dry cleaning operations that have converted from using PERC	4 independent dry cleaning facilities	3 operators (sex unspecified)  2 clerks (sex unspecified)  1 seamstress (sex unspecified)	(ND–54.5) (0.65–21.9) ND	Significant variation in 1-BP concentrations over course of workday; variations correlated with specific activities including loading of equipment, adding 1-BP to equipment, and opening equipment's door

1 \*All reported airborne concentrations represent 8-hour or 12-hour TWA PBZ samples; <sup>†</sup>Denotes the presence of 2-BP detected in the air samples and/or  
2 bulk 1-BP product. Abbreviations: 1-BP = 1-bromopropane; 2-BP = 2-bromopropane; AcPrCys = N-acetyl-S-(n-propyl)-L-cysteine; Br- = free bromide  
3 ion; CNS = central nervous system; GM = geometric mean; GSD = geometric standard deviation; n = number of subjects; ND = nondetectable; PERC =  
4 perchloroethylene; PNS = peripheral nervous system; ppm = parts per million; TWA = time-weighted averages.

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1 2.3 NIOSH HEALTH HAZARD EVALUATIONS

2 The Hazard Evaluations and Technical Assistance Branch (HETAB) of NIOSH conducts  
3 field investigations of possible health hazards in the workplace. These investigations,  
4 collectively referred to as HHEs, are conducted under the authority of Section 20(a)(6) of  
5 the Occupational Safety and Health (OSHA) Act of 1970, 29 U.S.C. 669(a)(6). The act  
6 authorizes the Secretary of Health and Human Services, following a written request from  
7 any employer or authorized representative of workers, to determine whether any  
8 substance normally found in the place of employment has potentially toxic effects in  
9 such concentrations as used or found. HETAB also provides, upon request, technical  
10 and consultative assistance to federal, state, and local agencies; labor; industry; and  
11 other groups or individuals to control occupational health hazards and to prevent related  
12 trauma and disease. Additional information on the NIOSH HHE program is available at  
13 <http://www.cdc.gov/niosh/hhe/>.

14  
15 This section provides an overview of the exposure and health data collected during  
16 several HHEs conducted from 1999 through 2008 to investigate the use of 1-BP in  
17 numerous workplace settings. The studies occurred in electronics manufacturing  
18 facilities, foam-cushion-fabricating facilities, and commercial dry cleaners. Table 2-3  
19 provides an overview of the industries investigated, along with symptoms reported by  
20 workers and a description of the activities conducted by NIOSH in each HHE. Table 2-4  
21 provides a summary of the exposure data collected from each HHE.

22  
23 NIOSH [2000] investigated a manufacturer of instrumentation and components for the  
24 radio frequency and microwave communications industry in April and November 2000.  
25 An employee was concerned about health effects possibly associated with the  
26 introduction of a new solvent, later identified as 1-BP, in the vapor degreaser. Workers in  
27 and near assembly areas reported experiencing headaches, nausea, vomiting,  
28 faintness, and mucous membrane irritation. The manufacturer, in response to employee  
29 symptoms, enclosed the degreaser and installed a local ventilation system to vent

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1 vapors in the room to the outside of the building. NIOSH collected 1-BP inhalation  
2 exposure data during a site visit. No individual employee interviews were conducted.

3  
4 The manufacturer identified 75 to 85 workers who might have used the degreaser two or  
5 three times per week. Workers who used the degreaser wore nitrile gloves and splash-  
6 proof goggles. Full-shift TWA 1-BP exposures ranged from 0.01 to 0.63 ppm. All the 2-  
7 BP exposure measurements were below the minimum detection concentration of 0.004  
8 ppm. Two 1-BP short-term measurements obtained while an employee used the  
9 degreaser were 2.3 ppm and 8.4 ppm. No 2-BP was detected in these samples. The 1-  
10 BP area air concentration in the degreaser room at the degreaser was 4.42 ppm. A 2-BP  
11 concentration of 0.02 ppm was found at the degreaser. Area air concentration of 1-BP  
12 taken 5 feet from the degreaser was 1.7 ppm.

13  
14 NIOSH investigated a cushion company from March 1998 to April 2001 in Mooresville,  
15 North Carolina, to assess potential 1-BP exposures during the manufacturing of foam  
16 seat cushions [NIOSH 2002a]. The company had four departments: Saw, Assembly,  
17 Sew, and Covers. Workers in Assembly and Covers worked directly with the adhesive;  
18 however, workers in all four departments were exposed. Symptoms included headache,  
19 abnormal fatigue, problems concentrating, feeling “drunk,” painful tingling in hands or  
20 feet, and tremors. Air sampling, ventilation assessment, and a medical survey  
21 (questionnaire and complete blood cell count) were used to assess the facility and  
22 participating workers. An adhesive spray in the Assembly department was 60% to 70%  
23 1-BP, and an adhesive spray in the Covers department was 60% to 80% 1-BP. The  
24 initial exposure assessment revealed that the 1-BP air concentration for workers ranged  
25 from 60.0 to 381.2 ppm (mean, 168.9 ppm). On average, the highest exposures were in  
26 the Covers department (mean, 197.0 ppm), the Assembly department (mean, 169.8  
27 ppm), and the Saw department (mean, 117.1 ppm). Area air sampling in the Sew  
28 department revealed a 1-BP concentration of 128.1 ppm. A follow-up exposure  
29 assessment was conducted after improvements to the ventilation system were made.  
30 The airborne 1-BP concentration for the workers was noticeably lower; PBZ air samples

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1 ranged from 1.2 to 58.0 ppm (mean, 19.0 ppm). Forty-six of the 70 workers participated  
2 in the medical survey. Blood cell counts were in normal ranges. When airborne 1-BP  
3 concentrations estimated from PBZ air samples were compared with symptoms reported  
4 in the questionnaire survey, no statistically significant differences were identified among  
5 workers with the highest exposures to 1-BP.

6  
7 NIOSH [2002b] investigated workplace exposures to 1-BP during the manufacturing of  
8 foam seat cushions in another cushion company in North Carolina from November 2000  
9 to August 2001. Most of the exposed workers were adhesive sprayers. Thirty-two of 84  
10 workers participated in the medical survey. Symptoms included abnormal nerve function,  
11 weakness and numbness of the lower extremities, dizziness, and headaches. Air  
12 sampling, ventilation assessment, and a medical survey (questionnaire, blood cell count,  
13 Br<sup>-</sup> urine analysis, neurobehavioral tests, and female reproductive test) were used to  
14 assess the facility and participating workers. Adhesive spray was found to contain 55%  
15 1-BP, 1% to 5% varnishing/painting naphtha, and 1% to 5% ethyl acetate. Before the  
16 enclosure of spray tables, the 1-BP air concentration for sprayers ranged from 41.3 to  
17 143 ppm [NIOSH 2002b]. The mean full-shift airborne 2-BP exposure for sprayers was  
18 0.66 ppm (range, 0.33–1.35 ppm). The short-term (15-minute) 1-BP concentration for  
19 sprayers ranged from 33.7 to 173.9 ppm, and the short-term 2-BP concentrations ranged  
20 from 0.30 to 1.56 ppm. The 1-BP ceiling (5-minute) concentrations for sprayers ranged  
21 from 39.5 to 151.9 ppm, and the 2-BP ceiling concentrations ranged from 0.37 to 1.13  
22 ppm. After enclosure of the spray tables, the 1-BP concentration for the sprayers was  
23 lower but the 2-BP concentration was not. Before the enclosure, the exhaust flow rates  
24 for each hood ranged from 230 to 1,545 cubic feet per minute (cfm). Approximately 38%  
25 of the workforce at the facility (n = 32) volunteered to participate in the medical survey.  
26 The analysis of the questionnaire revealed that 48% of volunteers reported headaches,  
27 28% had trouble falling asleep or staying asleep, 25% reported dizziness or feeling “off  
28 balance,” and 24% experienced blurred vision. Dizziness or feeling “off-balance” was  
29 significantly more common among the exposed groups than the comparison groups. All  
30 blood indices were in the normal value ranges. The start-of-week and end-of-week urine

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1 Br<sup>-</sup> concentrations for the exposed group were both significantly higher than the  
2 corresponding values for the comparison group. There was no significant elevation in  
3 urine Br<sup>-</sup> level in the end-of-week urine samples, compared with the start-of-week urine  
4 samples; urinary Br<sup>-</sup> concentrations were highly correlated to the airborne concentration  
5 of 1-BP. Thirty workers participated in the neurobehavioral testing. No differences in  
6 postural stability were noted and other findings were inconclusive. Data obtained via the  
7 medical survey were insufficient to assess the potential reproductive effects of 1-BP on  
8 exposed workers.

9

10 NIOSH investigated workplace exposures to 1-BP in another cushion company in North  
11 Carolina from April 1999 to May 2001, in response to reports of four workers suffering  
12 from neurologic problems [NIOSH 2003b]. The workers' symptoms included  
13 lightheadedness, dizziness, lower-extremity weakness, difficulty standing or walking,  
14 paresthesias, and visual hallucinations. Three of the workers had been with the  
15 company for at least 3 years as foam cushion fabricators. The fourth employee had been  
16 hired recently as a foam cushion fabricator. NIOSH conducted multiple site visits to  
17 assess the environmental conditions in the cushion company; as part of the site visits,  
18 personal and area air samples were collected. Additionally, workers were asked to  
19 participate in a medical survey that included a questionnaire, assessment of complete  
20 blood cell count, analysis of urine samples, nerve conduction testing, and evaluation of  
21 male reproduction system health.

22

23 NIOSH [2003b] conducted an initial site visit to measure 1-BP inhalation exposures. At  
24 follow-ups, inhalation exposures were measured again, potential sources of arsenic  
25 exposure were investigated, and a medical evaluation was performed [NIOSH 2003b].  
26 The medical evaluation included a questionnaire, complete blood cell count, urine  
27 collection to measure Br<sup>-</sup> and As<sup>+</sup> concentrations, and nerve conduction test; the male  
28 reproductive system also was evaluated. During the initial exposure assessment, the  
29 GM concentration for PBZ air samples was 81.2 ppm (18.1–253.9). For 2-BP, the GM  
30 concentration was 0.24 ppm (0.08–0.68). Airborne concentrations of 1-BP determined by

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1 PBZ air sampling in the follow-up assessment ranged from 7.2 to 280.5 ppm (GM, 45.7  
2 ppm), and those of 2-BP ranged from ND to 0.52 ppm. NIOSH determined during the  
3 initial site visit that 15 of the 16 monitored workers were exposed to airborne  
4 concentrations of 1-BP that exceeded 25 ppm; 7 of the 16 were exposed to airborne  
5 concentrations >100 ppm. A decrease in overall exposure to the brominated solvent was  
6 observed on the follow-up site visit.

7  
8 NIOSH [2003b] reported that approximately 72% of all workers employed at the cushion  
9 company (n = 43) participated in the questionnaire survey. Thirteen of these workers  
10 were identified as having direct 1-BP exposure; the other 30 were considered  
11 unexposed. The questionnaire showed that certain symptoms—*anxiety, feeling “drunk,”*  
12 *and headache*—were associated with 1-BP exposure. End-of-the-week and start-of-the-  
13 week serum and urine Br<sup>-</sup> concentrations and whole blood concentrations were  
14 determined for all participating workers. Analysis of the serum and urine Br<sup>-</sup>  
15 concentrations and whole blood concentrations revealed statistically significant  
16 differences between 1-BP-exposed workers and unexposed workers. Blood cell counts  
17 were found to be in normal ranges. No statistically significant correlations between  
18 exposure and male reproductive system problems were found. No statistically significant  
19 correlations between exposure and nerve conduction test results were found. The GM  
20 Br<sup>-</sup> concentration in end-of-the-week urine testing was 46.5 mg/dl (range, 15.4–595.4  
21 mg/dl). The cross-week urine Br<sup>-</sup> concentrations for exposed workers ranged from -20.1  
22 to 496.6 mg/dl (GM, 131.1 mg/dl), whereas those for unexposed workers ranged  
23 from -29.5 to 77.2 mg/dl (GM 3.6 mg/dl). Twelve of 41 workers who submitted urine  
24 samples had levels of inorganic arsenic above 25 µg/g creatinine. No arsenic was found  
25 in any of the air, bulk adhesive, or drinking water samples.

26  
27 In 2008, NIOSH received a request from the New Jersey Department of Health and  
28 Senior Services (NJDHSS) for technical assistance in evaluating the potential adverse  
29 health effects of exposure to 1-BP in dry cleaning facilities. This request was initiated by  
30 (1) the increased use of 1-BP in New Jersey dry cleaning establishments because of an

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1 anticipated ban on PERC by the NJDEP; and (2) a reported case of 1-BP poisoning in a  
2 dry cleaning owner/machine operator [CDC 2008]. Eight facilities in New Jersey were  
3 approved to use 1-BP as a substitute for PERC at the time of the request; four of these  
4 facilities participated in the study. Two site visits were conducted in 2008, which included  
5 (1) interviews of owners, operators, and an employee about the conversion process,  
6 work practices, and adverse health effects associated with 1-BP use and (2) PBZ and  
7 area air sampling, performed during normal operation of the 1-BP system.

8  
9 Out of the six interviews that were conducted with owners, operators, and workers, one  
10 person reported transient lightheadedness, which is consistent with general solvent  
11 exposure [NIOSH 2010a]. This person reported often feeling lightheaded and “buzzed”  
12 while handling 1-BP, particularly when “cooking” the solvent (boiling the solvent to  
13 remove impurities). These symptoms resolved minutes after he went outside. The dry  
14 cleaning owner/machine operator who previously had sought medical care for symptoms  
15 that occurred while handling 1-BP had no residual neurological deficits at the time of the  
16 NIOSH site visit. Review of this individual’s medical records did not reveal neurological  
17 abnormalities at an emergency department visit when symptoms first developed, and  
18 serum Br<sup>-</sup> levels determined during that visit were well under levels associated with  
19 adverse health effects [NIOSH 2010a]. NIOSH [2010a] reported that none of those  
20 interviewed reported persistent weakness, sensation deficits, or balance disturbances.

21  
22 Full-shift sampling for 1-BP conducted at one of the facilities revealed PBZ TWA  
23 concentrations of 40 ppm for the operator and 17 ppm for the cashier. For operators,  
24 PBZ concentrations ranging from 7.2 to 160 ppm were found in partial-shift samples; the  
25 sampling durations ranged from 163 to 241 minutes. Partial-shift PBZ concentrations  
26 ranged from 1.5 to 24 ppm for cashiers. Testing of the partial-shift samples revealed a  
27 wide variation in exposures in the individual facilities and a relatively high peak  
28 concentration (160 ppm) as compared with the TWA concentration of 40 ppm for  
29 operators. Ambient concentrations of 1-BP were measured at various locations in the dry  
30 cleaning facilities, including in front of and behind the equipment. Testing of these area

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1 air samples revealed high variable concentrations of 1-BP, depending on sampling  
2 location, duration of sampling, individual facilities, and type of dry cleaning equipment.  
3 For example, in one dry cleaning facility, the ambient concentrations of 1-BP varied  
4 during partial-shift sampling from 33 ppm in front of the equipment to 170 ppm behind  
5 the equipment. In comparison, partial-shift sampling in another facility revealed airborne  
6 levels of 1-BP ranging from 1.5 behind the equipment to 6.4 ppm in front of the  
7 equipment. NIOSH [2010a] concluded that the results of the HHE confirmed the release  
8 of 1-BP into the work environment at all four facilities, indicating a potential hazard to  
9 workers.

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1 **TABLE 2-3 – SUMMARY OF HEALTH HAZARD EVALUATIONS**

<b>Reference</b>	<b>Worksite</b>	<b>Solvent components (%)</b>	<b>Reported symptoms</b>	<b>Assessments conducted</b>
NIOSH [2000]	Radio frequency and microwave communications instrumentation manufacturer	N/A	Headache, nausea, vomiting, feeling faint, mucous membrane irritation	Personal and area exposure assessment; medical survey
NIOSH [2002a]	Foam cushion fabricating factory	Assembly dept. solvent: 1-BP (60–70); Covers dept. solvent: 1-BP (60–80)	Headache, abnormal fatigue, problem concentrating, feeling “drunk,” painful tingling in hands or feet, tremors, dizziness, blurred vision	Personal and area exposure assessment; ventilation assessment; medical survey
NIOSH [2002b]	Foam cushion fabricating factory	1-BP (55), VM&P naphtha (1–5), ethyl acetate (1–5)	Painful tingling, tremors, headaches, feeling “drunk,” abnormal fatigue, concentration problems	Personal and area exposure assessment; ventilation assessment; medical survey
NIOSH [2003a]	Foam cushion fabricating factory	N/A	Headache, anxiety, feeling “drunk,” lightheadedness, dizziness, lower extremity weakness, difficulty standing or walking, paresthesias, visual hallucinations	Personal and area exposure assessment; medical survey (questionnaire, assessment of complete blood count, analysis of urine samples, nerve conduction testing, and evaluation of male reproduction system)
NIOSH [2010a]	Four dry cleaning facilities	N/A	Transient lightheadedness, feeling lightheaded and “buzzed”	Personal and area exposure assessment; medical interviews and review of patient recorders

2 **Abbreviations: 1-BP = 1-bromopropane; 2-BP = 2-bromopropane; N/A = information not available**

3

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1 **TABLE 2-4 – SUMMARY OF EXPOSURE DATA COLLECTED DURING NIOSH HEALTH HAZARD EVALUATIONS**

Reference	Worksite	Exposure assessment date	Air samples		
			Number	Type	Airborne concentration (range), ppm
NIOSH [2000]	Radio frequency and microwave communications instrumentation manufacturer	November 2000	20	PBZ (full-shift TWA)	1-BP: (0.01–0.63) 2-BP: ND
			7	Area (full-shift TWA)	1-BP: (75.6–95.7) 2-BP: ND
NIOSH [2002a]	Foam cushion fabricating factory	November 1999 (first exposure assessment)	69	PBZ (full-shift TWA)	1-BP: 168.9 (60–381) 2-BP: ND
			11	Area (full-shift TWA)	1-BP: 128.1 (107–161) 2-BP: ND
NIOSH [2002a]	Foam cushion fabricating factory	November 2000 (follow-up exposure assessment)	30	PBZ (full-shift TWA)	1-BP: 19 (1.20–58.0) 2-BP: 0.14 (ND-0.55)
			12	STEL PBZ (15 min)	1-BP: (12.3–95.8) 2-BP: (0.10–0.40)
			5	Area (full-shift TWA)	1-BP: 1.38 (1.10–1.90) 2-BP: ND

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Reference	Worksite	Exposure assessment date	Air samples		Airborne concentration (range), ppm
			Number	Type	
NIOSH [2002b]	Foam cushion fabricating factory	November 2000	12	PBZ (full-shift TWA)	1-BP: 65.9 (41.3–143) 2-BP: 0.66 (0.33–1.35)
			9	STEL PBZ (15 min)	1-BP: (33.7–174) 2-BP: (0.30–1.56)
			11	Ceiling PBZ (5 min)	1-BP: (39.5–152) 2-BP: (0.37–1.13)
			3	Area (full-shift TWA)	1-BP: (1.70–7.70) 2-BP: (0.05–0.20)
NIOSH [2002b]	Foam cushion fabricating factory	July/August 2001 (follow-up exposure assessment)	34	PBZ (full-shift TWA)	1-BP: (8.80–32.7) 2-BP: (0.10–0.40)
			10	STEL PBZ (15 min)	1-BP: (0.20–56.0) 2-BP: (0.04–0.40)
			10	Ceiling PBZ (5 min)	1-BP: (ND–38.0) 2-BP: (ND–0.5.0)
NIOSH [2003a]	Foam cushion fabricating factory	November 1999 (first exposure assessment)	16	PBZ (full-shift TWA)	1-BP: 81.2 (GM) (181–254) 2-BP: 0.24 (GM) (0.08–0.68)
			3	Area (full-shift TWA)	1-BP: (0.06–8.70) 2-BP: ND

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Reference	Worksite	Exposure assessment date	Air samples		Airborne concentration (range), ppm
			Number	Type	
NIOSH [2003a]	Foam cushion fabricating factory	January 2001 (follow-up exposure assessment)	13	PBZ (full-shift TWA)	1-BP: 45.7 (GM) (7.20–281) 2-BP: 0.066 (GM) (ND–0.52)
NIOSH [2010a]	Four dry cleaning facilities	November 2008	2	PBZ (full-shift TWA)	1-BP: 40 (operator) 1-BP: 17 (cashier)
			5	PBZ (partial shift samples)	1-BP: (7.20 – 160) (operator)
			4	PBZ (partial shift samples)	1-BP: (1.50–24.0) (cashier)

1 **Abbreviations: 1-BP = 1-bromopropane; 2-BP = 2-bromopropane; GM = geometric mean; min = minute; ND = none detected; PBZ =**  
 2 **personal breathing zone; ppm = parts per million; STEL = short term exposure limit; TWA = time weighted average**

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1 2.4 SUMMARY

2 The data available from biomonitoring, human health assessment, and exposure  
3 assessments provide evidence of the use of 1-BP in multiple industrial and commercial  
4 processes in the United States, including metal stripping, foam cushion fabricating,  
5 electronics cleaning, and dry cleaning [Sclar 1999; NIOSH 2000, 2002a, 2002b, 2003b,  
6 2010a; Ichihara et al. 2002; Majersik et al. 2007; Raymond and Ford 2007; CDC 2008;  
7 Blando et al. 2010]. Other studies [Ichihara et al. 2004a, 2004b; Li et al. 2010a]  
8 described the production of 1-BP in China. Compounds identified in the reviewed studies  
9 contained ~55% to 99% 1-BP, and exposure to the compounds containing 1-BP  
10 occurred via the inhalation of vapors and direct contact with the skin.

11  
12 The primary health effects reported in these studies involved impairment of the CNS or  
13 PNS [Sclar 1999; NIOSH 2000, 2002a, 2002b, 2003b, 2010a; Ichihara et al. 2002;  
14 Majersik et al. 2007; Raymond and Ford 2007; CDC 2008; Li et al. 2010a]. Ichihara et al.  
15 [2004a] and Li et al. [2010a] respectively reported reproductive and hematological  
16 effects in exposed workers. The reviewed case studies provide evidence of 1-BP  
17 exposure, associated with adverse effects in the CNS and PNS. Common symptoms  
18 reported in these investigations include headaches, blurred vision, nausea, ataxic or  
19 unsteady gait, memory loss, mood changes, weakness in lower extremities, and  
20 paresthesia or dysesthesia [Sclar 1999; Ichihara et al. 2002; Majersik et al. 2007;  
21 Raymond and Ford 2007; CDC 2008]. Similar symptoms were reported by workers  
22 examined in the cross-sectional studies and the NIOSH HHEs [NIOSH 2002, 2002a,  
23 2002b, 2003b; Ichihara et al. 2004a, 2004b]. Potential clinical signs of 1-BP exposure  
24 and toxicity include changes in serum electrolyte levels, resulting in a negative anion gap  
25 and elevated urinary Br<sup>-</sup> levels. Li et al. [2010a] provide evidence of neurological and  
26 hematological effects in 1-BP-exposed female workers; these adverse effects occurred  
27 in a dose-response manner. In addition, Li et al. [2010a] reported a LOAEL of 1.28 ppm  
28 in female workers for the onset of neurological effects. No epidemiological studies were  
29 identified that investigated the delayed effects of 1-BP.

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The available exposure data indicate that the exposure patterns vary greatly among industries and in individual facilities on the basis of tasks or activities being performed. The ability to significantly reduce airborne concentrations of 1-BP was reported following the assessment of engineering controls in foam cushion fabricating [NIOSH 2002a, 2002b, 2003b]. In dry cleaning operations, the magnitude of exposures to 1-BP appears to be linked with specific activities [NIOSH 2010a; Blando et al. 2010]. For example, real-time monitoring revealed peak exposures that were an order of magnitude higher than full-shift TWA exposures; these peaks occurred during the loading/unloading of clothes, the opening of the equipment's door during a cycle, and the addition of 1-BP to the equipment [Blando et al. 2010]. Monitoring of ambient and personal airborne concentrations of 1-BP in production facilities in China revealed concentrations of 1-BP that varied by several orders of magnitude in the individual facilities on the basis of their placement. The findings of the reviewed studies demonstrate a close correlation between urinary metabolite levels and airborne 1-BP concentrations; urinary Br and AcPrCys may be viable biomarkers of exposure to 1-BP [NIOSH 2002b; Ichihara et al. 2004a, 2004b; Hanley et al. 2006, 2009, 2010].

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## 1 CHAPTER 3: DISPOSITION AND TOXICOKINETICS

2 There are few data in the literature concerning the absorption, metabolism, and  
3 disposition of 1-BP in animals and humans. Empirical evidence from rodent toxicity  
4 studies (see Chapter 4) and from occupational exposure studies (see Chapter 2)  
5 indicate that 1-BP is absorbed by both inhalation and dermal routes. Additional evidence  
6 of the systemic uptake of 1-BP via the oral route has been reported [Lee et al. 2005,  
7 2007]. Absorption by all routes is rapid, and a significant portion of the absorbed dose  
8 (39% to 48% in mice and 40% to 70% in rats) is eliminated in exhaled breath as  
9 unspecified volatile organic compounds (VOC) [Jones and Walsh 1979, Garner et al.  
10 2006]. Garner and Yu [2014] provided supplemental evidence on the toxicokinetics of 1-  
11 BP in rodents. Rodents exposed to 1-BP via either IV injection or inhalation exhibited  
12 rapid system clearance and elimination that decreased as the dose increased. Previous  
13 studies showed that the remaining absorbed dose is eliminated, unchanged, in urine in  
14 humans or as metabolites in the urine and exhaled breath of all species studied [Kawai  
15 et al. 2001; Garner et al. 2006]. Available toxicokinetic data indicate that glutathione  
16 (GSH) conjugation and oxidation via cytochrome P450 (CYP450) significantly contribute  
17 to the metabolism of 1-BP [Garner et al. 2006; Garner and Yu 2014]. Section 3.1  
18 provides a summary of the GSH-dependent metabolism of 1-BP, and Section 3.2  
19 describes the oxidative metabolism of 1-BP via CYP450.

### 20 3.1 GLUTATHIONE-DEPENDENT METABOLISM

21 GSH is a tripeptide molecule, consisting of cysteine, glycine, and glutamic acid, which  
22 can exist in two states—a reduced form (GSH) and an oxidized form (glutathione  
23 disulfide [GSSG]). In healthy tissues, the tripeptide molecule exists primarily as GSH at  
24 relatively high concentrations (5–10 mM). Both GSH and GSSG are involved in  
25 numerous cellular processes, and they are among the most important molecules in  
26 protecting the organism from damage by free radicals formed during normal metabolism  
27 and toxic insult. GSH also is conjugated with many exogenous chemicals or their  
28 metabolites, and it plays an important role in elimination. GSH may participate in  
29 conjugation reactions directly with free radicals and reactive oxygen compounds, and it

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1 forms conjugates with xenobiotics, facilitated by a family of enzymes called the  
2 glutathione-S-transferases (GSTs). These enzymes exist in many forms and are  
3 classified by cellular location and substrate preference [Parkinson and Ogilvie 2008].  
4

5 Early reports of metabolites in urine of rats exposed to 1-BP described the presence of  
6 S-(2-hydroxypropyl) mercapturic acid and its sulfoxide [Barnsley et al. 1964, 1966].  
7 Jones and Walsh [1979] characterized the mercapturic acids of the metabolites 2-  
8 hydroxybromopropane, 3-hydroxybromopropane, and bromopropionic acid in the urine  
9 of rats exposed to 1-BP and speculated that CYP450 may mediate 1-BP metabolism.  
10

11 Tachizawa et al. [1982] examined the in vitro metabolism of 1-propyl halides, including  
12 1-BP. Microsomes from phenobarbital-treated rats were incubated with <sup>14</sup>C-labeled-1-  
13 BP, and metabolites formed were detected in the incubation head space by gas  
14 chromatography (GC). Addition of GSH to the incubation mixture resulted in the  
15 formation of S-propyl glutathione (GSP) and S-(2-hydroxyl-1-propyl) GSH. In addition,  
16 the authors found that elimination of nicotinamide adenine dinucleotide phosphate  
17 (NADPH) from the incubation mixture, in order to eliminate contribution of CYP450  
18 pathways, resulted in increased levels of GSP, implying the direct conjugation with GSH.  
19

20 Wang et al. [2002] examined biochemical changes in the CNS of male Wistar rats  
21 exposed to 200, 400, or 800 ppm 1-BP for 8 hours/day for 7 days. The authors reported  
22 morphological and protein changes in neural tissues from exposed animals and dose-  
23 dependent decreases of GSH and other protein sulfhydryls. The authors proposed that  
24 GSH depletion or modification of other sulfur-containing proteins may underlie the toxic  
25 mechanism of 1-BP. In a follow-up study, Wang et al. [2003] exposed rats under similar  
26 conditions to 1-BP for 12 weeks. The authors reported results consistent with those for  
27 the 7-day study, which included biochemical changes in the CNS. A more in-depth  
28 description of these studies is in Section 4.1.2.

29 Lee et al. [2005] examined the hepatotoxicity and conjugation of 1-BP with GSH in male  
30 ICR (imprinting control region) mice. Mice were given a single dose of 1-BP (0, 200, 500,

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1 or 1000 milligrams per kilogram body weight [mg/kg]) in corn oil by gavage. Animals  
2 were sacrificed at 0, 6, 12, and 24 hours after dosing, and for each time point, liver  
3 weight and levels of serum enzymes, GSH, malonaldehyde (a marker of lipid  
4 peroxidation), and GSP in liver were determined. At 12 hours after dosing, there was a  
5 dose-dependent, significant reduction in GSH in 1-BP-exposed animals, in comparison  
6 with control animals. GSH levels returned to near control levels after 24 hours. GSP,  
7 which is the GSH-conjugate metabolite of 1-BP, was found to have increased in a dose-  
8 dependent manner at 12 hours but decreased toward control values at 24 hours. Serum  
9 alanine aminotransferase and aspartate aminotransferase levels were elevated at 12  
10 and 24 hours, indicative of liver damage. In addition, malonaldehyde was increased in  
11 liver homogenates in a dose-dependent manner. In experiments to determine the time-  
12 dependent depletion of GSH, the formation of GSP was inversely proportional. At 6  
13 hours post treatment, maximum levels of GSP were concurrent with minimal GSH, and  
14 proportions remained the same at 12 hours. At 24 hours, GSH levels were returning to  
15 control levels and GSP was decreased. The authors concluded that 1-BP toxicity  
16 resulted from depletion of GSH via conjugation reactions of 1-BP with GSH.

17  
18 Garner et al. [2006] studied the metabolism and disposition of 1-BP in F344 male rats  
19 and B6C3F1 male mice dosed by inhalation and intravenous routes. The findings  
20 demonstrated GSH-dependent metabolism of 1-BP. F344 male rats and B6C3F1 male  
21 mice were treated with radiolabelled 1-BP by inhalation (800 ppm) or 5, 20, and 100  
22 mg/kg via intravenous injection. Exhaled breath was collected, and VOCs and CO<sub>2</sub>  
23 concentrations were determined. Metabolites of 1-BP were measured in urine of treated  
24 animals. Identified GSH conjugates of oxidative metabolites of 1-BP included AcPrCys,  
25 N-acetyl-3-(propylsulfinyl)alanine, N-acetyl-S-(2-hydroxypropyl)cysteine, 1-bromo-2-  
26 hydroxypropane-O-glucuronide, N-acetyl-S-(2-oxopropyl)cysteine, and N-acetyl-3-[(2-  
27 oxopropyl)sulfinyl]alanine. Treatment of rats with 1-aminobenzotriazole (ABT), a potent  
28 inhibitor of CYP450, led to excretion of a lower proportion of the administered 1-BP in  
29 urine. These animals had decreased exhaled <sup>14</sup>CO<sub>2</sub> (↓80%) and increased radioactivity  
30 expired as VOC (↑52%). Urinary metabolites in ABT pretreated rats were reduced in

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1 number from 10 to 1; AcPrCys accounted for >90% of the total urinary radioactivity. This  
2 work demonstrates that formation of AcPrCys from conjugation of 1-BP with GSH can  
3 occur via conjugation by GST, independent of oxidative metabolism.

4  
5 Lee et al. [2007] examined the role of GSH conjugation on 1-BP-dependent hepatic  
6 toxicity and immunotoxicity in mice. Mice were treated by gavage with 200, 500, and  
7 1000 mg/kg 1-BP and sacrificed 12 hours post dosing. A second group of animals were  
8 dosed with 1000 mg/kg 1-BP and sacrificed at 6, 12, 24 and 48 hours post dosing.

9 Levels of GSH and the 1-BP metabolite, GSP, in liver and measures of liver toxicity and  
10 immunotoxicity were determined. The authors reported a dose-dependent decrease of  
11 GSH in the liver and spleen of animals treated with 1-BP. Decreases of GSH were  
12 maximal at 6 and 12 hours but returned to near-control levels by 24–48 hours.

13 Concurrent with the drop in GSH were dose- and time-dependent increases in GSP. Lee  
14 et al. [2007] concluded that 1-BP toxicity is the result of GSH depletion as a  
15 consequence of 1-BP conjugation metabolism.

16  
17 Valentine et al. [2007] developed methods to measure globin S-propyl cysteine (PrCYS)  
18 in blood and AcPrCys in urine from animals and humans exposed to 1-BP. These

19 biomarkers reflect binding of 1-BP to protein sulfhydryls of cellular proteins and ultimate  
20 GSH metabolites, respectively. In separate experiments, groups of male Wistar rats  
21 were exposed to 1-BP at 0, 50, 200, or 800 ppm by inhalation for 8 hours/day for 2  
22 weeks or at 50 ppm, 8 hours/day, 5 days/week, for 4 weeks. Animals were sacrificed  
23 immediately after the last exposure or allowed to recover for 8 days. Levels of PrCYS  
24 and AcPrCys showed a linear dose response relative to exposure level and were  
25 measurable 8 days after exposure ended. As a second experiment, Valentine et al.

26 [2007] measured PrCYS in blood and AcPrCys in urine of workers with occupational  
27 exposure to 1-BP. The authors found that hemoglobin PrCYS levels were higher in  
28 exposed workers than in unexposed workers and urinary levels of AcPrCys were  
29 positively correlated to workplace 1-BP exposure. Valentine et al. [2007] concluded that  
30 both PrCYS and AcPrCys were potential biomarkers for assessing worker exposure to 1-

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1 BP. Although its findings supported previous reports of 1-BP interaction with protein  
2 sulfhydryls, this study was not able to answer whether 1-BP conjugates with sulfhydryls  
3 or GSH directly, via GST or after oxidative metabolism.

4  
5 Hanley et al. [2009] measured AcPrCys in urine from workers with workplace 1-BP  
6 exposures. To assess workplace exposure to 1-BP, full-shift breathing zone air was  
7 sampled from workers with use of NIOSH method 1025 (see Appendix A). Worker urine  
8 samples were collected sequentially over 48 hours and divided among the following  
9 categories: first day pre-shift, during work day 1, a post-work sample before bed time,  
10 next morning before work, work shift day 2, before bed, and final pre-workday sample.  
11 Levels of AcPrCys were found to be significantly higher in exposed workers with active  
12 spraying jobs versus nonspraying jobs; levels in unexposed controls were very low or  
13 not detectable. Urinary AcPrCys and bromine were found to be highly correlated; a  
14 weaker but significant correlation of AcPrCys with 1-BP exposure in air was noted,  
15 perhaps reflecting patterns or route of exposure not measured by TWA sampling. This  
16 study strongly supports the significant role of GSH in 1-BP metabolism, but it was not  
17 able to determine the mechanism of formation of the measured metabolites. Additional  
18 information on this study is in Section 2.2.

### 19 3.2 OXIDATIVE METABOLISM VIA CYTOCHROME P450 (CYP450)

20 Tachizawa et al. [1982] examined the in vitro metabolism of 1-propyl halides, including  
21 1-BP. Microsomes from phenobarbital-treated rats were incubated with <sup>14</sup>C-labeled-1-  
22 BP, and metabolites formed were detected in the incubation head space by GC. The  
23 authors found that 1,2 propanediol is the predominant metabolite for 1-BP, followed by  
24 propionic acid and low but measurable quantities of propene. Elimination of NADPH in  
25 the incubation mixture resulted in almost a complete reduction of metabolites formed,  
26 documenting the importance of the CYP450 oxidative enzymes in metabolism. Addition  
27 of GSH to the incubation mixture resulted in the formation of GSP and S-(2-hydroxyl-1-  
28 propyl) GSH, and the authors found that elimination of NADPH from the incubation  
29 mixture resulted in increased levels of GSP, indicating the direct conjugation with GSH.

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1

2 Kaneko et al. [1997] examined the partition coefficients and hepatic metabolism of 1-BP  
3 and 2-BP in vitro. Results from the partition coefficient experiments quantified the  
4 empirical observation that 1- and 2-BP are readily absorbed in animals and humans.  
5 Metabolic studies were carried out by incubating microsomes from male Wistar rats with  
6 multiple concentrations of 1- or 2-BP and measuring n-propyl alcohol formed from 1-BP  
7 or isopropyl alcohol formed from 2-BP. Double reciprocal plots of metabolite formation  
8 against substrate concentration indicated that multiple metabolic constants ( $V_{max}$  and  $K_m$   
9 values) appear to exist for both substrates, and researchers observed that as uptake  
10 rates exceed production of the alcohol metabolites measured, other pathways may be  
11 observed.

12

13 Kim et al. [1999a] examined sex differences in enzyme activities and hepatic  
14 microsomes CYP450 content in groups of Sprague-Dawley (SD) rats exposed to 50,  
15 300, or 1,800 ppm by inhalation for 6 hours/day, 5 days/week, for 8 weeks. Toxicology  
16 parameters of this study are described in Section 4.2.1. The study authors described the  
17 effects of these exposures on total CYP450, CYP b5, NADPH-CYP450 reductase,  
18 NADH b5 reductase, and characteristic activities and protein content of CYP1A1/2,  
19 CYP2B1/2 and CYP2E1. No changes to total CYP450, CYP b5, NADPH-CYP450  
20 reductase, or NADH b5 reductase were observed between control and treated animals.  
21 No changes occurred to CYP450 form-specific metabolic marker activities and protein,  
22 such as ethoxyresorufin-O-deethylase (CYP1A1/2) or pentoxyresorufin-O-dealkylase  
23 (CYP2B1/2). However, exposure to 1-BP was found to cause a dose-dependent  
24 increase in *p*-nitrophenol hydroxylase activity and CYP2E1 protein content, but it was  
25 significantly increased only in the 1,800 ppm animals. Exposure to 1-BP was also found  
26 to increase GST activities, GSH peroxidase activities and lipid peroxides; the latter  
27 measures are indicative of increased formation of ROS. Kim et al. [1999a] concluded  
28 that (1) rats exhibit differences in the metabolism of 1-BP based on sex, (2) CYP2E1  
29 may possibly be the primary CYP450 responsible for the oxidative biotransformation of

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1 1-BP, (3) free radicals are produced during metabolism of 1-BP, and (4) GST plays a  
2 role in the detoxification and protection of tissues.

3  
4 Metabolism and disposition of 1-BP may be sex-, strain-, and species-specific. In a study  
5 by Ishidao et al. [2002], groups of male Wistar rats were exposed to 1,500 ppm 1-BP for  
6 6 hours/day, 5 days/week, for 3 or 4 weeks, or 700 ppm 1-BP for 6 hours/day for 5  
7 days/week for 1 day, 4 weeks, or 12 weeks. Unlike the study by Kim et al. [1999a], the  
8 reported results indicate that CYP450 was decreased immediately following a 700-ppm  
9 exposure, but levels in animals recovered after 1 week clearance. Animals treated for 4  
10 weeks had a significant decrease in total CYP450.

11  
12 Garner et al. [2006] reported that disposition and metabolism patterns in the F344 rat  
13 were dose dependent; this was not seen in the B6C3F1 mouse. They found that in rats,  
14 low doses of 1-BP are primarily metabolized by oxidative metabolism; as concentration  
15 increased, metabolism shifted from oxidative to other pathways, such as GSH  
16 conjugation. This was further confirmed by experiments in which animals were  
17 pretreated with inhibitors of CYP450 that resulted in reducing metabolites in urine, from  
18 10 metabolites to a single metabolite, AcPrCys. Overall, B6C3F1 mice were found to  
19 have a greater capacity for oxidative metabolism of 1-BP than rats.

20  
21 Garner et al. [2007] utilized CYP2E1-knockout mice to demonstrate the role of CYP2E1-  
22 catalyzed oxidation in 1-BP-dependent sperm toxicity in mice. Both wild-type (WT) and  
23 CYP2E1 knockout mice were exposed in inhalation chambers to an initial concentration  
24 of 800 ppm 1-BP and remained there for 6 hours; 1-BP concentration, relative humidity,  
25 and oxygen levels were monitored throughout the exposure, and urine was collected in  
26 the chamber. After the 6 hours of exposure to 1-BP, the mice were sacrificed and urine,  
27 sperm, and liver specimens were collected for analysis. CYP2E1- knockout mice were  
28 found to have lower uptake and clearance rates than WT mice, and to produce less N-  
29 acetyl-S-(2 hydroxypropyl) cysteine and greater levels of products resulting from the  
30 direct conjugation of 1-BP with GSH than did WT mice. WT mice were substantially

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1 more sensitive to 1-BP-induced sperm toxicity than CYP2E1-knockout mice. Finally, in  
2 vitro experiments using sperm from WT and CYP2E1-knockout mice demonstrated that  
3 whereas 1-BP and 1-bromo-2-hydroxypropane were toxic to WT sperm, only 1-bromo-2-  
4 hydroxypropane was toxic to sperm from CYP2E1-knockout mice. The authors  
5 concluded that CYP2E1-mediated oxidation of 1-BP to 1-bromo-2-hydroxypropane is  
6 required for 1-BP-mediated sperm toxicity in mice.

7

8 Liu et al. [2009] examined mouse strain differences in susceptibility to 1-BP. Male mice  
9 from C57BL/6J, DBA/2J, and BALB/cA were divided into groups and exposed to 0, 50,  
10 110, and 250 ppm 1-BP (8 hours/day for 28 days) by inhalation. At the end of the  
11 exposure period, the authors evaluated susceptibility of each strain to 1-BP-mediated  
12 hepatotoxicity and male reproductive toxicity. In addition, the authors examined strain-  
13 specific levels of biotransformation enzymes, GSH levels, and expression of the  
14 putatively protective Phase II enzyme NADPH quinone reductase and heme oxygenase  
15 levels. In order of susceptibility, BALB/cA mice were most susceptible to liver toxicity,  
16 followed by C57Bl/6J and DBA/2J mice. All mice demonstrated dose-dependent male  
17 reproductive toxicity to 1-BP above 50 ppm, as evidenced by decreased sperm count  
18 and motility and increased numbers of sperm with abnormal heads. BALB/cA mice were  
19 found to have the highest CYP2E1 content, but GSH content and GST activity were  
20 lower than in the other strains tested.

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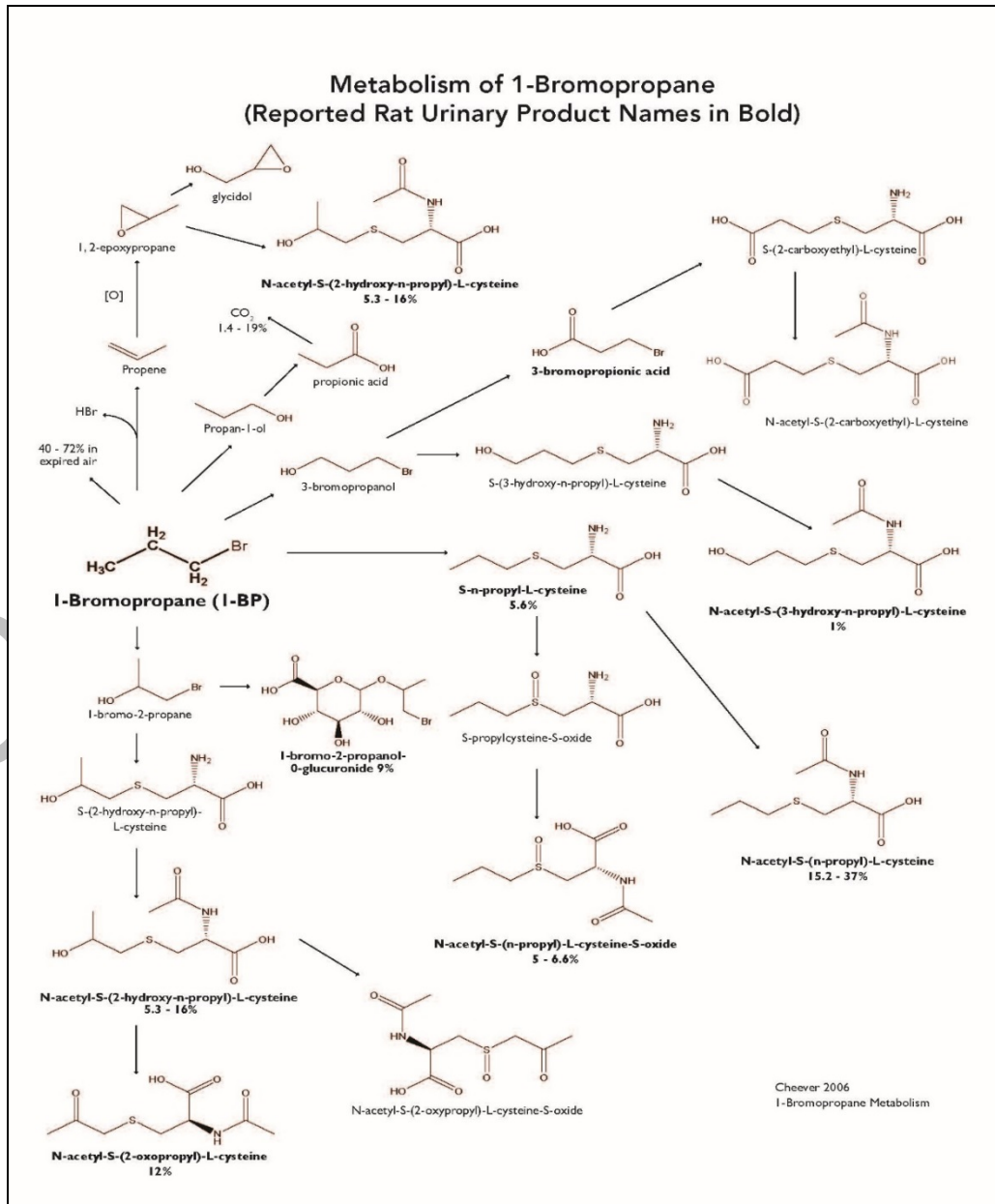
1 3.3 SUMMARY

2 Although no study was identified that defined the absorption, metabolism, and  
3 disposition of 1-BP in animals and humans, useful information is provided in the  
4 previously described reports. Figure 3-1 shows a proposed metabolic pathway in the rat.  
5 Exposure to 1-BP can occur by inhalation, oral, and dermal routes, with 1-BP being  
6 rapidly distributed through the body tissues. Depending on species and activity levels,  
7 30% to 70% of the absorbed dose is eliminated unchanged in exhaled breath. The  
8 retained 1-BP may be eliminated by conjugation with GSH directly or by GST enzymes,  
9 or it may undergo oxidative biotransformation by the CYP450 monooxygenases. Animal  
10 studies strongly suggest that toxicity of 1-BP is dependent on the metabolic pathway of  
11 the compound. GSH-dependent metabolic pathways are integral to toxic actions, but it is  
12 not likely that the GSH-1-BP conjugates are the source of toxicity. Instead, a stronger  
13 case can be made that toxicity of 1-BP is dependent on the generation of reactive  
14 oxidative metabolites of 1-BP by CYP450 monooxygenases that are conjugated with  
15 GSH for elimination. Toxicity of 1-BP likely results when GSH levels are depleted from  
16 neutralizing reactive metabolites; as free GSH is utilized, GSH-1-BP conjugates increase  
17 until GSH is consumed. At this point critical cellular components can be damaged, and  
18 toxicity results. The strongest support for a mechanism such as this is derived from  
19 experiments using sensitive species or strains, or more elegantly, genetically engineered  
20 animal models that are missing the key step in the toxic pathway [Liu et al. 2009; Garner  
21 et al. 2007]. This theory of 1-BP toxicity being mediated by the generation of free  
22 radicals associated with the biotransformation of 1-BP via CYP450 monooxygenases  
23 has been suggested by Ghanayem and Hoffler [2007]. Mice with higher levels of  
24 relevant CYP450 (CYP2E1 and others) were generally more susceptible to 1-BP than  
25 are rats; mouse strains with higher levels of CYP2E1 were more susceptible to 1-BP  
26 than strains with lower constitutive CYP2E1, and wild-type mice were more susceptible  
27 to 1-BP than CYP2E1-knockout mice.  
28

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1 **FIGURE 3-1 – PROPOSED METABOLIC PATHWAY FOR 1-BP IN THE RAT**



2

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1 **Figure 3-1 illustrates the potential metabolic pathways of 1-BP in rats. These pathways yield multiple**  
2 **potential metabolites. The names in bold text represents metabolites identified in rat urine [Cheever**  
3 **2006].**

4

5

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1 **CHAPTER 4: STUDIES OF NON-CANCER ENDPOINTS IN EXPERIMENTAL**  
2 **ANIMALS**

3  
4 This chapter describes the results of experimental toxicological investigations of 1-BP in  
5 animals and in vitro studies. Only those experimental studies most critical to  
6 understanding the toxicity of 1-BP in the workplace, including those considered in the  
7 derivation of the NIOSH REL, are presented. Inhalation and dermal exposures are the  
8 most relevant occupational exposure pathways for 1-BP, because these are the two  
9 routes by which workers are most likely to be exposed to the brominated solvent.  
10 Section 4.1 provides an overview of key experimental studies in which animals were  
11 exposed via the inhalation route, Section 4.2 reviews data relating to genotoxicity, while  
12 Section 4.3 provides a summary of the dermal data.

13 **4.1 INHALATION STUDIES**

14 This section summarizes inhalation toxicology studies only. The information has been  
15 divided into sections based on the primary health endpoint evaluated. Tables 4-1  
16 through 4-3 provide summaries of biologically and statistically significant findings and the  
17 corresponding treatment levels described in the reports of various experimental animal  
18 studies.

19  
20 **4.1.1 DEVELOPMENTAL AND REPRODUCTIVE EFFECTS**

21 The developmental and reproductive toxic effects of 1-BP have been evaluated on the  
22 basis of results of several experimental animal studies. This section provides summaries  
23 of key studies; Table 4-1 provides a summary of all animal studies reviewed in this  
24 section.

25  
26 ClinTrials BioResearch [1997a] examined the effects of subchronic inhalation exposure  
27 to 1-BP in a 13-week study. Male and female SD rats were exposed to airborne  
28 concentrations of 0, 398, 994, or 1,590 ppm for 6 hours/day, 5 days/week, for 28 days.  
29 Body weight and food consumption were monitored weekly; laboratory investigations

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1 were conducted at the end of the experiment to assess hematological indices, clinical  
2 biochemistry, and urinalysis. Microscopic lesions were reported in the reproductive  
3 systems in the surviving male rats of the highest treatment group (1,590 ppm). Atrophic  
4 changes were observed in testis of animals treated with 994 and 1,590 ppm 1-BP; these  
5 changes were correlated with exposure to 1-BP. No other effects on the reproductive  
6 systems of male or female rats were reported.

7

8 Huntingdon Life Sciences [1999] conducted a one-generation range-finding study to  
9 investigate the developmental toxicity of 1-BP. Pregnant SD rats received whole-body  
10 inhalation exposures of 0, 100, 199, 598, and 996 ppm for 6 hours/day on gestation days  
11 6–19; pups were exposed on lactation days 4–20. One pup from each litter was exposed  
12 to 1-BP during postnatal days (PND) 22–28 following the end of weaning. All animals  
13 were sacrificed on PND 29. Body and organ weight measurements, in addition to  
14 hematology and clinical chemistry analyses, were conducted on dams in the lactation  
15 period and on pups from PND 29. The growth and development of pups were monitored  
16 from birth through weaning.

17

18 Huntingdon Life Sciences [1999] reported significant increases in the relative weights of  
19 the liver and kidneys in dams exposed to 598 and 996 ppm. No toxicologically significant  
20 changes were observed in hematology or clinical chemistry parameters in dams at the  
21 end of the lactation period. No deaths or significant signs of toxicity beyond salivation  
22 and lacrimation were observed in rats in the highest treatment group. Body weight gains  
23 were decreased in the upper three treatment groups (199, 598, and 996 ppm) during  
24 gestation. Exposure to 1-BP did not affect gestation length, litter size, number of live  
25 births, or number of dead pups. No gross malformations were observed. Body weight  
26 gains in pups in the 596-ppm group were reduced 20% and body weight gains in the 994  
27 ppm treatment group were reduced 40%. No external abnormalities or reduced birth  
28 weight were reported. Body-weight gain during the post-weaning period was significantly  
29 decreased in male pups exposed to 598 and 996 ppm and in female pups in the 996

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1 ppm treatment group. Decreased brain weight was reported in the highest treatment group. Statistically significant hematological and biochemical effects in both male and female pups exposed to 996 ppm 1-BP were reported. The toxicological effects of inhalation exposures of pregnant SD rats on the development of offspring were investigated. Test animals received whole-body inhalation exposures to 103, 503, or 1,005 ppm 1-BP for 6 hours/day on gestation days 6 through 19. At day 20, pregnancy was terminated and the fetuses underwent soft-tissue evaluations or skeletal evaluations. No exposure-related effects on pregnancy rates were reported. Rats exposed to 503 and 1,005 ppm experienced significant decreased weight gain and food intake. Lacrimation and salivation occurred in animals exposed to 1,005 ppm 1-BP. Fetal body weight was significantly decreased in all treatment groups. A statistically significant increase in litter incidence of bent ribs was reported for the 1,005-ppm treatment group; a significant reduction in skull ossification was observed in the 503- and 1,005-ppm treatment groups.

Subsequently, Huntingdon Life Sciences [2001] conducted another inhalation study of the developmental toxicity of 1-BP. Pregnant SD rats (25/group) were whole-body exposed to 0, 103, 503, or 1,005 ppm (0, 520, 2,530, or 5,060 mg/m<sup>3</sup>) 1-BP for 6 hours/day on gestation days (GD) 6–19. Dams were sacrificed on GD 20 and fetuses were obtained by cesarean section. After being weighed, one-half of the fetuses were prepared for soft-tissue evaluation, and the other half for skeletal evaluation. One dam in the 1,005-ppm group had to be euthanized before study termination, but the finding in this animal was not considered to be treatment related. Mean maternal body weight, body weight gain, food consumption, and weights of gravid uteri were significantly reduced at 503 and 1,005 ppm, compared with controls. 1-BP exposure did not cause excess fetal mortality, but fetal body weights were significantly reduced in all exposed litters. However, the study director [Rodwell 2000] pointed out that part of the observed reduction in fetal body weights may have been a procedural artifact because of the practice of holding one or two control dams until the end of the daily cesarean section

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1 period, resulting in fetuses that weighed significantly more and displayed a more  
2 advanced degree of ossification. No evidence of external or visceral malformations was  
3 noted. There was an increased incidence of bent ribs, which was insignificant in fetuses  
4 of the 503-ppm group but significant in the 1,005-ppm group. The study authors [Rodwell  
5 2000; Huntingdon Life Sciences 2001] considered this a reversible developmental delay,  
6 but a review by the NTP [2003b] classified it as a fetal aberration (albeit not a frank  
7 malformation). Reduced skull ossification was seen at the 503- and 1,005-ppm  
8 concentrations but was considered the result of maternal toxicity and reduced fetal body  
9 weights [Huntingdon Life Sciences, 2001]. Huntingdon Life Sciences [2001] considered  
10 103 ppm to be a NOAEL for maternal or fetal toxicity and 1,005 ppm a NOAEL for  
11 teratogenicity. NTP [2003b] used EPA's benchmark dose software (BMD) (version 1.3)  
12 to calculate a benchmark concentration (BMC) and its lower 95% bound (BMCL) for  
13 reduced fetal body weights after excluding one litter from the 103-ppm group as an  
14 outlier. With benchmark response set at 5%, the polynomial model produced a BMC of  
15 561 ppm and a BMCL of 305 ppm.

16

17 Ichihara et al. [2000a] investigated the dose-response reproductive toxicity of 1-BP. Male  
18 Wistar rats were exposed to 1-BP at concentrations of 0, 200, 400, or 800 ppm for 8  
19 hours/day, 7 days/week, for 12 weeks. Epididymal sperm indices (i.e., epididymal sperm  
20 count and motility, abnormal sperm morphology), sexual organ and body weight,  
21 spermatogenic cells, and hormone levels were evaluated. Statistically significant  
22 decreases in total body weight were noted in rats exposed to 400 and 800 ppm 1-BP.  
23 Compared with weights in controls, absolute liver and spleen weights were significantly  
24 reduced in 800-ppm-exposed males, as were relative liver weights of animals exposed  
25 to 400 and 800 ppm. Similarly, the weights of epididymis were significantly reduced at  
26 the mid and high concentrations, prostate weights at 800 ppm, and seminal vesicle  
27 weights at all exposures. Because of the parallel body weight loss, only the relative  
28 weights of seminal vesicles were significantly reduced at all exposure levels, along with  
29 epididymis weights at 800 ppm. Testicular mass was nominally decreased, by 6%, in the

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1 800-ppm exposure group. A decrease in epididymal sperm counts (26% less than the  
2 control number at 400 ppm, and 70% less at 800 ppm) and a decrease in the percent  
3 motility (19% less than the control number at 400 ppm, and 70% less at 800 ppm) were  
4 noted, in addition to an increase in the number of sperm with morphological  
5 abnormalities, including tailless sperm and sperm with abnormal head shapes, at 800  
6 ppm. The observation that elongated spermatids were retained in the seminiferous  
7 tubules during post-spermiation stages IX to XI led the authors to speculate that 1-BP  
8 may act through an inhibition of spermiation. However, there was no indication that total  
9 sperm and their individual developmental stages in seminiferous tubules at stage VII  
10 were affected, although there was a significant increase in the numbers of degenerate  
11 sperm at this stage and there were abnormal spermatids at stages IX–XI. The findings  
12 of this study indicate that exposure to 1-BP may significantly reduce the epididymal  
13 sperm count and motility in a dose-response manner, in addition to increasing the  
14 number of sperm with abnormal morphology. Among the reproductive hormones, only  
15 testosterone levels in blood were reduced; the effect was minimal at 200 and 400 ppm  
16 but highly significant at 800 ppm (64% of controls). Ichihara et al. [2000a] concluded that  
17 1-BP caused failure of spermiation that might involve lowered testosterone levels, on the  
18 basis of the assumption that the weight of the seminal vesicle is highly sensitive to  
19 testosterone levels.

20  
21 WIL Research Laboratories [2001] conducted a two-generational toxicity study of 1-BP  
22 administered via whole-body inhalation. As part of this study, clinical observations, body  
23 weight, food consumption, and changes in the multiple organ systems were monitored;  
24 test animals were subjected to gross pathology. The F<sub>0</sub> generation treatment groups  
25 consisted of male and female Crl:CD (SD)IGS BR rats that were exposed to 0, 99, 252,  
26 505, or 750 ppm 1-BP; the F<sub>1</sub> generation treatment groups were exposed to 0, 100, 252,  
27 or 500 ppm 1-BP. The authors noted that because of the occurrence of complete  
28 infertility of the F<sub>0</sub> generation, treatment animals precluded exposure of F<sub>1</sub> or F<sub>2</sub>  
29 generation animals at 750 ppm. F<sub>0</sub> and F<sub>1</sub> generation treatment groups were exposed to

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1 1-BP for 70 days prior to mating, throughout mating, and until GD 20. After parturition,  
2 exposure to F<sub>0</sub> and F<sub>1</sub> females was reinitiated on lactation day 5 and continued until the  
3 test animals were sacrificed. Clinical observations, body weight, food consumption, and  
4 changes in the multiple organ systems were monitored; test animals were subjected to  
5 gross pathology.

6  
7 WIL Research Laboratories [2001] reported that no mortalities occurred in the F<sub>0</sub>  
8 generation, but one male F<sub>1</sub> rat in the 500-ppm treatment group was sacrificed during he  
9 second week of exposure. Food consumption was not affected in any treatment group in  
10 the F<sub>0</sub> or F<sub>1</sub> generation. Parent and offspring body weights were reduced in the 500-ppm  
11 group (F<sub>0</sub>, F<sub>1</sub>, and F<sub>2</sub> generations) and 750-ppm (F<sub>0</sub> generation) groups. Decreased  
12 organ weights were noted, in the pituitary gland in the 500 (F<sub>1</sub>) and 750 (F<sub>0</sub>) ppm  
13 treatment group males and in the spleen in the F<sub>2</sub> male and female pups. Increased  
14 thymus weights were observed in the 250 and 500 ppm (F<sub>1</sub>) treatment groups' males.  
15 Relative liver weights were increased in both male and female F<sub>0</sub> animals treated at 500  
16 and 750 ppm; similar results were reported for the 500 ppm (F<sub>0</sub> and F<sub>1</sub>) treatment  
17 groups. Microscopic centrilobular hepatocellular vacuolation and increased glycogen  
18 were observed in animals with increased liver weight. Mild pelvic mineralization occurred  
19 in the 250-ppm group F<sub>1</sub> females, the 500-ppm group (F<sub>0</sub> and F<sub>1</sub> males and females),  
20 and the 750-ppm group (F<sub>0</sub> males and females). All animals in the 750-ppm F<sub>0</sub>  
21 generation treatment group were identified as infertile. Fertility indices were significantly  
22 reduced in the 500-ppm F<sub>0</sub> generation treatment group; no significant changes in fertility  
23 indices were reported for animals treated at lower levels in the F<sub>0</sub> generation or any F<sub>1</sub>  
24 treatment group. The mean number of pups born and live litter size at time of birth were  
25 statistically decreased in the 500-ppm (F<sub>0</sub> and F<sub>1</sub>) treatment groups. Postnatal survival  
26 was not affected by parental exposure to 1-BP in any treatment group (F<sub>1</sub> and F<sub>2</sub>). Both  
27 decreased body weight and decreased body weight gains were noted in male and  
28 female pups born to animals treated at 500 ppm (F<sub>1</sub> and F<sub>2</sub>). Gross examination of the F<sub>0</sub>  
29 generation revealed small testis and epididymis in male rats in the 500 and 750 ppm

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1 treatment groups. Reduced sperm motility, morphologically normal sperm, and  
2 epididymal sperm number were observed in F<sub>0</sub> and F<sub>1</sub> generation male rats exposed to  
3 500 and 750 ppm 1-BP. The researchers noted reduced weight in multiple organs in the  
4 male reproductive system in F<sub>0</sub> and F<sub>1</sub> generations rats exposed to 250, 500, and 750  
5 ppm. Decreased ovary weights were reported in female rats in the highest treatment  
6 groups of the F<sub>0</sub> and F<sub>1</sub> generations; microscopic findings were observed in the ovaries  
7 in the 500-ppm (F<sub>0</sub> and F<sub>1</sub>) and 750-ppm (F<sub>0</sub>) group females.

8  
9 Sekiguchi et al. [2002] exposed female F344 rats to 1-BP and 2-BP to determine the  
10 comparative toxicity of the bromopropane isomers on the estrous cycles and  
11 spontaneous ovulation. Test animals were exposed to 1-BP at concentrations of 50, 200,  
12 and 1,000 ppm, or 2-BP at concentrations of 50, 100, and 200 ppm, for 8 hours/day, 7  
13 days/week, for 3 weeks. No significant differences in the mean number of estrous  
14 cycles, the number of days per estrous cycle, ovary and uterus weight, or number of  
15 ovulated ova were observed in rats exposed to 1-BP or 2-BP in comparison with  
16 controls.

17  
18 Yamada et al. [2003] examined the effects of 1-BP on the ovarian follicles of female  
19 Wistar rats. Test animals were exposed to 1-BP at concentrations of 0, 200, 400, or 800  
20 ppm for 8 hours/day, 7 days/week, for 7 or 12 weeks. Rats in the 800-ppm treatment  
21 group became seriously ill following 7 weeks of exposure. Monitoring of estrous cycle,  
22 histopathological examinations of multiple organs, counting of ovarian follicles, and  
23 hormonal assays were conducted. The thymus, adrenal gland, kidney, spleen, liver,  
24 brain, right ovary, uterus, and vagina were dissected, weighed, and prepared for  
25 histopathologic evaluation. The body weight of the 800-ppm treatment group was  
26 significantly decreased in comparison with controls. There were concentration-related  
27 changes in several absolute organ weights: adrenal (significantly increased at 400 ppm),  
28 kidney and liver (significantly increased at 200 and 400 ppm), and brain (significantly  
29 decreased at 400 ppm). When relative organ weights were considered, kidney and liver

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1 weights were significantly increased at 200 and 400 ppm, but adrenal and brain weights  
2 were in the control range. There was mild dilatation of the proximal tubules in kidneys in  
3 the 800-ppm group but not in the other exposed animals. In livers of the 800-ppm  
4 animals, scattered cytoplasmic degeneration was detected in the centrilobular area,  
5 accompanied by nuclear pyknosis, but no necrosis was observed. The livers of the other  
6 exposed animals were normal. On the basis of organ weight changes, 200 ppm was  
7 identified as a LOAEL.

8

9 Yamada et al. [2003] reported that vaginal smear examination revealed a significant  
10 number of irregular estrous cycles, with extended diestrus in the 400- and 800-ppm  
11 treatment groups. In the 800-ppm group, 4 of 10 animals had irregular estrous cycles  
12 during the first 3-week exposure interval; during the second interval, 5 animals had  
13 irregular and 5 had no estrous cycle (there was no third interval because the animals  
14 had to be euthanized). In the 400-ppm group, the animals displayed increasingly  
15 irregular or absent estrous cycles with exposure duration. No abnormalities were  
16 observed in the 200-ppm animals. The weights of reproductive organs were unaffected.  
17 Follicle maturation appeared to be inhibited because there were fewer growing and  
18 antral follicles in the 200- and 400-ppm groups, with a tendency toward increased  
19 numbers of primordial follicles. However, the blood concentrations of LH and FSH were  
20 not affected by the treatment.

21

22 The effects in the 800-ppm group appeared to be similar but more severe than in the  
23 400-ppm group; however, Yamada et al. [2003] did not provide statistical evaluations of  
24 the 800-ppm animals, probably because they did not live through the full 12-week  
25 exposure period. No significant changes in plasma luteinizing hormone and follicle-  
26 stimulating hormone concentrations were reported. Yamada et al. [2003] concluded that  
27 1-BP can induce a dose-dependent impairment of female rats' reproductive function,  
28 potentially caused by the disruption of the follicular growth process.

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1 Banu et al. [2007] examined the reversibility of reproductive effects of 1-BP in rats,  
2 including changes in epididymal sperm count and motility; morphological abnormalities;  
3 and histopathological changes in reproductive organs. Male Wistar rats (24/group) were  
4 exposed to either 400 or 1,000 ppm of 1-BP vapor for 8 hours/day, 7 days/week, for 6  
5 weeks. At the end of the treatment period, 8 rats/group were sacrificed, and the  
6 remaining 16 were allowed to recover for 4 and 14 weeks, respectively, and then  
7 sacrificed. Sperm were collected from the right cauda epididymis. The body, testis,  
8 prostate, seminal vesicle, and epididymis weights of rats exposed to 1,000 ppm 1-BP  
9 were significantly lower than those of controls. Testis weight was 70% less than in  
10 controls following the 6-week exposure period, and weight continued to decrease, to  
11 36% of controls', during a 14-week recovery period. No recovery of weight was reported  
12 in the epididymis. The researchers noted, in other reproductive organs, a partial  
13 recovery of weight following the recovery period. Serum testosterone was dose-  
14 dependently reduced at the end of exposures (to 30% of controls' at 1,000 ppm;  $p$   
15  $<0.05$ ) but had returned to normal 4 weeks later. Epididymal sperm count was  
16 significantly decreased in rats exposed to either 400 or 1,000 ppm 1-BP. After 4 weeks'  
17 recovery, the sperm count returned to normal level in the 400-ppm-exposed rats. No  
18 such observation was reported in the 1,000-ppm treatment group. Sperm motility was  
19 significantly decreased, whereas morphological abnormalities increased in the 1,000-  
20 ppm treatment group. The sperm motility and count of normal sperm heads continued to  
21 decrease during the 14-week recovery period. The histopathological examinations of the  
22 reproductive organs revealed severe atrophic changes in the seminiferous tubules,  
23 testicles, seminal vesicles, and prostate in rats exposed to 1,000 ppm 1-BP. Banu et al.  
24 [2007] concluded that, whereas a low dose of 1-BP (400 ppm) caused mild and  
25 reversible male reproductive toxicity, a high (1,000 ppm) dose caused severe and  
26 irreversible damage.

27

28 Liu et al. [2009] compared the susceptibility of three inbred mice strains to 1-BP-  
29 mediated male reproductive toxicity. Male C57BL/6J, DBA/2J, and BALB/cA mice were

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1 exposed to 1-BP at 0, 50, 110, or 250 ppm for 8 hours/day for 28 days. The exposure  
2 concentrations were chosen on the basis of preliminary studies that showed the  
3 concentrations remaining at or below the maximum tolerated level for any of the strains.  
4 Two C57BL/6J mice and one BALB/cA mouse of the highest concentration group died  
5 during the first week of exposure, but all DBA/2J mice survived. Histopathological  
6 examination of the reproductive system was conducted. There was no clear treatment  
7 effect on body weights, and although there were increased liver weights, the changes  
8 displayed no concentration dependence. There was a tendency toward reduced testis  
9 weights that showed no concentration dependence, but the weights of seminal vesicles  
10 decreased in all exposed animals with increasing exposure levels. Sperm collected from  
11 the left cauda epididymis were evaluated to determine sperm count and motility, in  
12 addition to morphological abnormalities of sperm head. The reported results include a  
13 significant decrease in absolute weight of the testis of DBA/2J exposed to 110 ppm, in  
14 comparison with controls. C57BL/6J mice in the 250-ppm treatment group experienced a  
15 significant decrease in absolute weights of the testis and seminal vesicles. The sperm of  
16 all three strains of mice were significantly altered at the lowest treatment level of 50 ppm,  
17 in comparison with controls. C57BL/6J mice had reduced sperm count and increased  
18 abnormalities of the sperm head at all three treatment levels; decreased sperm motility  
19 occurred at concentrations of 1-BP of 110 and 250 ppm. DBA/2J mice exposed to  
20 concentrations of 1-BP at 50 ppm and higher had reduced sperm count and motility. At  
21 treatment levels above 50 ppm, the authors noted a significant increase in sperm with  
22 abnormal heads. In BALB/cA mice, all three treatment levels resulted in significant  
23 alterations in the sperm count and motility, in addition to the number of sperm with  
24 abnormal morphology. Liu et al. [2009] concluded that 1-BP is capable of causing  
25 significant changes in the male reproductive system of mice at relatively low  
26 concentrations and that mice were more sensitive to 1-BP than were rats.  
27  
28 NTP [2011] conducted a series of sub-chronic (3-month) studies to evaluate the  
29 toxicological effects of 1-BP. In one study, male and female F344/N rats were exposed

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1 to 1-BP vapor at concentrations of 0, 250, 500, or 1,000 ppm, 6 hours plus T<sub>90</sub> (10  
2 minutes)/day, 5 days/week, for 3 months (14 weeks). Among the reported results of the  
3 study, a significant exposure-concentration-related decrease in sperm motility was  
4 observed in male rats exposed to 250 ppm 1-BP or greater. More specifically, sperm  
5 motility was reduced by 6.7% in rats in the 250-ppm treatment group, by 10.1% in the  
6 500-ppm group, and by 27.7% in the 1,000-ppm group. NTP [2011] reported a significant  
7 25.2% decrease in the number of sperm per gram cauda and a 36.8% decrease in the  
8 total sperm per gram cauda, as well as significant decreases in the absolute weights of  
9 the cauda (14%) and left epididymis (19%) in the 1,000-ppm male treatment group.  
10 Female rats in all treatment groups had significant alterations in their estrous cycles in  
11 comparison with controls. Specific changes included the relative amount of time spent in  
12 the various estrous cycle stages; NTP [2011] noted that each exposed group spent  
13 significantly more time in extended estrus and significantly less time in extended  
14 diestrus. Additional information on this study is in Section 4.1.4.

15  
16 In the second sub-chronic study, NTP [2011] exposed male and female B6C3F1 mice to  
17 1-BP vapor at concentrations of 0, 125, 250, or 500 ppm, 6 hours plus T<sub>90</sub> (10  
18 minutes)/day, 5 days/week, for 3 months (14 weeks). A significant reduction in cauda  
19 epididymis weight and decreased sperm motility were reported in the 250- and 500-ppm  
20 treatment groups. In the 500-ppm treatment group, a significant decrease in the sperm  
21 per gram cauda was also observed. In female mice in all treatment groups, there were  
22 significant alterations in the relative amount of time spent in the various stages of  
23 estrous. For example, animals in the 500-ppm treatment group spent significantly more  
24 time in extended diestrus than controls, whereas animals treated at 250-ppm spent  
25 significantly more time in extended estrus than controls.

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1 **TABLE 4-1 – REPRODUCTIVE AND DEVELOPMENTAL EFFECTS CAUSED BY INHALATION EXPOSURES TO 1-BP IN ANIMAL STUDIES**

<b>Reference</b>	<b>Species; strain</b>	<b>Number per treatment (sex)</b>	<b>Treatment level (ppm)</b>	<b>Treatment regimen</b>	<b>Results (treatment level)</b>
ClinTrials BioResearch [1997a]	Rat; SD	10 (male); 10 (female)	0, 398, 994, 1,590	6 hours/day, 5 days/week, 4 weeks	Microscopic lesions in the male reproductive systems (1,590)
Huntingdon Life Sciences [1999]	Rat; SD	N/A (female)	0, 100, 199, 598, 996	6 hours/day during gestation days 6–19; pups on lactation days 4–20	Decreased body weight gains during gestation (199, 598, 996); reduction in body weight gains in pups (598, 996); decreased brain weight (996); hematological changes in pups (996)
Ichihara et al. [2000a]	Rat; Wistar	9 (male)	0, 200, 400, 800	8 hours/day, 7 days/week, 12 weeks	Decreased total body weight (400, 800); decreased epididymal weights (800); decreased seminal vesicle weights (200, 400, 800); decreased epididymal sperm count and motility (400, 800); increased sperm abnormalities (800); changes in sex hormone levels (800)
Huntingdon Life Sciences [2001]	Rat; SD	N/A (female)	0, 103, 503, 1,005	6 hours/day during gestation days 6–19; pups on lactation days 4–20	Decreased weight gain and food intake (503, 1,005); abnormal behavior (1,005); decreased fetal weight (103, 503, 1,005); increased litter incidence of bent ribs in pup (1,005); reduced skull ossification in pups (503, 1005)

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<b>Reference</b>	<b>Species; strain</b>	<b>Number per treatment (sex)</b>	<b>Treatment level (ppm)</b>	<b>Treatment regimen</b>	<b>Results (treatment level)</b>
WIL Research Laboratories [2001]	Rat; Crl:CD (SD) IGS BR	(F <sub>0</sub> ) generation: 20 (male) 20 (female) (F <sub>1</sub> ) generation: 50 (male) 50 (female)	0, 99, 252, 505, 750  0, 100, 252, 504	6 hours/day, 70 days prior to mating and throughout the mating period until gestation day 20, exposure resumed on lactation day 5 until sacrificed	Reduced parental and offspring body weight (500 [F <sub>0</sub> , F <sub>1</sub> , F <sub>2</sub> ], 750 ppm [F <sub>0</sub> ]); decreased pituitary gland weight in male rats (500 [F <sub>1</sub> ], 750 [F <sub>0</sub> ]); reduced spleen weight in F <sub>2</sub> male and female pups; increased thymus weights in male rats (250, 500 [F <sub>1</sub> ]); increased relative liver weights both male and female (500, 750 [F <sub>0</sub> ], 500 [F <sub>0</sub> , F <sub>1</sub> ]); microscopic centrolobular hepatocellular vacuolation and increased glycogen were observed in animals with increased liver weight; mild pelvic mineralization (250 [F <sub>1</sub> females]; 500 [F <sub>0</sub> , F <sub>1</sub> males/females], 750 [F <sub>0</sub> males/females]); infertility, male and female (750 [F <sub>0</sub> ]); reduced fertility indices (500 [F <sub>0</sub> ]); decreased mean number of pups born and live litter size at time of birth (500 [F <sub>0</sub> and F <sub>1</sub> ]); decreased body weight and body weight gains in male and female pup (500 [F <sub>1</sub> and F <sub>2</sub> ]); gross examination revealed small testis and epididymis, male rats (500, 750 [F <sub>0</sub> ]); reduced sperm motility, morphologically normal sperm, and epididymal sperm number (500, 750 [F <sub>0</sub> and F <sub>1</sub> ]); reduced weight in male reproductive organs (250, 500, 750 [F <sub>0</sub> and F <sub>1</sub> ]); decreased ovary weights (500, 750 [F <sub>0</sub> and F <sub>1</sub> ]); microscopic findings in the ovaries (500 [F <sub>0</sub> and F <sub>1</sub> ], 750 [F <sub>0</sub> ])

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<b>Reference</b>	<b>Species; strain</b>	<b>Number per treatment (sex)</b>	<b>Treatme nt level (ppm)</b>	<b>Treatment regimen</b>	<b>Results (treatment level)</b>
Sekiguchi et al. [2002]	Rat; F344	7-8 (female)	0, 50, 200, 1,000	8 hours/day, 7 days/week, 3 weeks	No changes in total body weight (50, 200, 1,000); no significant changes in number of days per estrous cycle (50, 200, 1,000); no significant changes in ovary and uterus weight (50, 200, 1,000)
Yamada et al. [2003]	Rat; Wistar	10 (female)	0, 200, 400, 800	8 hours/day, 7 days/week, 7 or 12 weeks	Decreased in body weight (800); increased absolute liver and kidney weight (200, 400); histological abnormalities in the ovaries, liver, and kidney (400); reduced number of antral and normal growing follicles (400)
Banu et al. [2007]	Rat; Wistar	24 (male)	0, 400, 1,000	8 hours/day, 7 days/week, 6 weeks	Decreased weight of testis, prostate, seminal vesicle, and epididymis (1,000); decreased body weight (1,000); decreased testosterone levels (1,000); decreased epididymal sperm count (400, 1,000); decreased sperm motility (1,000); increased sperm morphology abnormalities (1,000); histopathological abnormalities in the reproductive organs (1,000)

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<b>Reference</b>	<b>Species; strain</b>	<b>Number per treatment (sex)</b>	<b>Treatment level (ppm)</b>	<b>Treatment regimen</b>	<b>Results (treatment level)</b>
Liu et al. [2009]	Mice; C57BL/6J, DBA/2J, BALB/cA	6 (male)	0,50, 110, 250	8 hours/day, 7 days/week, 4 weeks	Decreased absolute weights of the testis and seminal vesicles of C57BL/6J mice (250); decreased absolute weight of the testis of DBA/2J mice (110); reduced sperm count and increased abnormalities of the sperm head in C57BL/6J mice (50); decreased sperm motility in C57BL/6J mice (110); reduced sperm count and motility in DBA/2J mice (50); increased sperm abnormalities in DBA/2J mice (110); decreased sperm count and motility in BALB/cA mice (50); increased number of sperm with abnormal morphology (50)
NTP [2011]	Rat; F344/N	10 (male); 10 (female)	0, 62.5, 125, 250, 500, 1,000	6 hours plus T <sub>90</sub> (10 minutes)/day, 5 days/week, 14 weeks	Exposure concentration-related decrease in sperm motility (250, 500, 1,000); decrease in the number of sperm per gram cauda and the total sperm per cauda (1,000); reduced absolute weights of the cauda and left epididymis (1,000); alterations in estrous cycles (250, 500, 1,000)
NTP [2011]	Mice; B6C3F1	10 (male); 10 (female)	0, 62.5, 125, 250, 500, 1,000	6 hours plus T <sub>90</sub> (10 minutes)/day, 5 days/week, 14 weeks	Reduced epididymis weight (250, 500); decreased sperm motility (250 and 500); decreased sperm per gram cauda (500); alterations in their estrous cycles (125, 250, 500)

1 **Abbreviations: N/A = information not available or provided; ppm = part per million; SD = Sprague-Dawley rats.**

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1 4.1.2 NEUROTOXIC EFFECTS

2 This section provides summaries of key studies investigating neurological effects  
3 associated with exposure to 1-BP in both the CNS and PNS. Table 4-2 summarizes the  
4 studies reviewed in this section.

5  
6 ClinTrials BioResearch [1997a] evaluated the neurotoxic effects of 28 days of inhalation  
7 exposure to 1-BP at 0, 98, 994, or 1,590 ppm in SD rats. An overall summary of this  
8 study is in Section 4.1.1. Functional observational battery and motor activity  
9 assessments were conducted prior to exposure and at 4 weeks. Gross pathological  
10 examinations were performed. Clinical observations made on week 4 of the 28-day 1-BP  
11 inhalation study revealed several functional neurological deficits. Among them, the most  
12 prominent were ataxia and changes in gait, nominally more severe in females but  
13 observed in both sexes at the highest concentrations of 1-BP (1,590 ppm). It is not  
14 established to what extent these findings reflect muscle loss in emaciated animals or  
15 direct injury to the nervous system. Increased mortality of male animals at the highest  
16 concentration (80% in group 4 males versus 30% among females) was reported.  
17 Reduced arousal relative to the control animals was observed in both sexes at all  
18 concentrations. Urine wetting is consistent with the observed ataxia and decreased  
19 arousal. Locomotor activity levels were harder to interpret, but they did not appear to be  
20 significantly altered in response to 1-BP exposure. Microscopic lesions in the form of  
21 vacuolization in the white and grey matter and axonal swelling or fiber degeneration in  
22 the cervical spinal cords were observed via gross pathological examination. Grey matter  
23 vacuolization was described as consisting of discrete, punctuated, variable-sized, clear  
24 vacuoles in the neuropil of the grey matter. White matter vacuoles were described as  
25 being prominent, irregular, and variable in size.

26  
27 ClinTrials BioResearch [1997b] investigated the potential toxicity of subchronic inhalation  
28 of 1-BP, using SD rats. Test animals were exposed to airborne concentrations of 1-BP at  
29 0, 99, 199, 398, or 596 ppm for 6 hours/day, 5 days/week, for 13 weeks. Functional  
30 observational battery and motor activity assessments were conducted prior to exposure

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1 and at weeks 4, 8, and 13. In addition, gross pathological examinations were conducted  
2 on the CNS and PNS. The functional observation battery, which included assessment of  
3 limb strength and hind limb splay, did not reveal any consistent changes suggestive of 1-  
4 BP-induced neurotoxicity in either male or female animals exposed to 1-BP  
5 concentrations of 99, 199, 398, or 596 ppm. The findings of the motor activity  
6 assessments did not demonstrate a dose-response relationship or differences from  
7 controls. Neither changes in brain weight nor histological lesions were observed in either  
8 male or female animals. Furthermore, in the 13-week study, researchers found no  
9 evidence of 1-BP-induced degeneration of cervical spine, optic, or sciatic nerves.  
10 ClinTrials BioResearch [1997b] indicated that findings of the functional observational  
11 battery and motor activity assessments demonstrated no dose-response relationship or  
12 differences in comparison with controls.

13  
14 Yu et al. [1998] exposed male Wistar rats to 0 or 1,000 ppm of 1-BP vapor for 8  
15 hours/day, 7 days/week, for either 5 or 7 weeks. Body weights were reduced by  
16 approximately 20% in treated animals at week 4. Reported observations included rats in  
17 the 1-BP treatment group walking with a paddle-like gait and dragging their hind limbs,  
18 with the plantar surface of the hind limb turned upward by week 5 of the experiment. The  
19 exposure to 1-BP was terminated because of hind limb paralysis and severe emaciation  
20 after 5 or 7 weeks. Rats exposed to 1,000 ppm of 1-BP had electrophysiological  
21 changes, in the form of slowed motor nerve conduction velocity (MCV) and increases in  
22 the DL of the peripheral nerves, and hind limb paralysis. Degeneration of the peripheral  
23 nerves was observed, as was axonal swelling in the gracilis; pyknotic shrinkage of the  
24 cerebellar Purkinje cells in the 1-BP-exposed rats was reported. Histopathological  
25 changes in the Purkinje cells suggest 1-BP may be toxic to the CNS.

26  
27 As a follow-up, Yu et al. [2001] conducted a subchronic study to compare the relative  
28 neurotoxicity of 1-BP and 2-BP. Male Wistar rats were exposed to one of the following  
29 conditions: (1) 1-BP at 1,000 ppm, (2) 2-BP at 100 ppm, or (3) 2-BP at 1,000 ppm for 8

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1 hours/day, 7 days/week, for 12 weeks. Exposure to 1-BP was terminated after 5 to 7  
2 weeks because the subjects developed a paddle-like gait that led to hind limb paralysis  
3 and severe emaciation. All rats in this treatment group appeared alert and moved  
4 vigorously, using their forelimbs. The body weight in 1-BP-exposed paralyzed rats  
5 decreased dramatically; the test animals became emaciated. Yu et al. [2001] reported a  
6 significant change in MCV and DL in this treatment group in comparison with controls.  
7 Degeneration of the peripheral nerve, characterized by ovoid- and bubble-like debris of  
8 various sizes, was reported; additionally, degeneration in the spinal cord in the form of  
9 axonal swelling in the gracilis occurred in rats exposed to 1,000 ppm 1-BP. Decreased  
10 body weight in the 1-BP treatment group was reported. In rats exposed to 2-BP at 1,000  
11 ppm, substantial changes were observed in MCV and DL in the tail nerve, in addition to  
12 abnormalities in the myelin sheath of teased common peritoneal nerves. These findings  
13 were not reported in rats exposed to 2-BP at 100 ppm. Yu et al. [2001] suggested that,  
14 based on the findings reported in this study, 1-BP may potentially be a more potent  
15 neurotoxicant than 2-BP. Additionally, the authors concluded that 2-BP is neurotoxic to  
16 peripheral nerves.

17  
18 Ohnishi et al. [1999] investigated the neurotoxicity of 1-BP in male Wistar rats via  
19 histopathological examinations. Test animals were exposed to 1-BP vapors at 0 or 1,500  
20 ppm for 6 hours/day, 5 days/week, for 4 weeks. Rats in the treatment group were judged  
21 to be less active than those control group animals exposed only to air. By the third week,  
22 5 of 8 rats in the treatment group exhibited a slight-to-moderate ataxic gait, which  
23 progressed to include all the animals by the fourth week. No deaths were reported. The  
24 authors noted that in the brain of 6 of 8 of the exposed rats, cytoplasmic shrinkage of the  
25 Purkinje cells was reported to be significant. Arborized (branching) projections were also  
26 observed. No differences were noted in the fifth funiculus of the spinal cord. However, in  
27 the third cervical posterior funiculus, 3 of 8 rats showed marrow globules, which were not  
28 observed in the control group animals. In the nucleus gracilis of the medulla oblongata,  
29 definite axonal swelling was noted in 2 of 8 rats exposed to 1-BP, which was not

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1 observed in the control group animals. An examination of the sural and fibula nerves did  
2 not reveal any differences in the extent of axonal degeneration, nor in the frequency of  
3 marrow globules between the two groups. The results of this study indicate limited  
4 degeneration of Purkinje cells in the cerebellum of 1-BP-exposed rats.

5  
6 Fueta et al. [2000, 2002a, 2002b, 2004, 2007] conducted a series of studies assessing  
7 induction of feedback inhibition in the hippocampus of male Wistar rats exposed via  
8 inhalation to 1-BP. Fueta et al. [2000] studied effects of 1-BP on neuronal excitability in  
9 the dentate gyrus (DG) via histopathological and electrophysiological examinations. Rats  
10 were exposed to 0 to 1,500 ppm of 1-BP for 6 hours/day, 5 days/week, for 1, 3, or 4  
11 weeks. Test animals were then sacrificed and transverse hippocampal brain slices were  
12 prepared. The slices were incubated in artificial cerebrospinal fluid, and neurons were  
13 stimulated electrically to measure specific nerve cell responses in the granular cell layer  
14 of the DG. The authors observed ataxic gait and convulsion behavior in some rats at the  
15 end of the experiment. Control rats exhibited strong inhibition of the second paired-pulse  
16 response, whereas the 1-BP exposed rats exhibited almost complete disinhibition of the  
17 second response, even after the first week of exposure. This effect remained after the 1-  
18 week clearance following the 4-week exposure. Fueta et al. [2000] concluded exposure  
19 to 1,500 ppm of 1-BP for 4 weeks resulted in neuronal dysfunction in the DG and  
20 represented a predisposing neural mechanism of 1-BP-induced neurotoxicity preceding  
21 abnormal behavior.

22  
23 Fueta et al. [2002a] assessed the subchronic effects of inhalation exposures to 1-BP  
24 vapors on the CNS by measuring hippocampal excitability. Male Wistar rats were  
25 exposed to 0 or 1,500 ppm 1-BP for 6 hours/day, 5 days/week, for 1, 3, or 4 weeks.  
26 Fueta et al. [2002a] reported the occurrence of paired-pulse disinhibition in both the DG  
27 and CA1 pyramidal neuron, without modification of the field excitatory postsynaptic  
28 potential (fEPSP), of 1-BP-treated rats. Furthermore, 1-BP modified involvement of  
29 neurotransmitter receptors in excitability and inhibition of synaptic transmittance.

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1 Reported behavioral abnormalities included ataxic gait and convulsion. Fueta et al.  
2 [2002a] concluded that subchronic exposure to 1-BP induces hyperexcitability in the  
3 CA1 and DG, associated with an overactivation of N-methyl-D-aspartate receptors.

4  
5 Fueta et al. [2002b] continued investigation of the relationship between the  
6 hyperexcitability in the CA1 region of the hippocampus and the DG caused by inhalation  
7 exposures to 1-BP and intercellular signaling changes in multiple proteins associated  
8 with learning and memory, including CA2+/calmodulin-dependent kinases (II), mitogen-  
9 activated protein kinase, and protein kinase C. Male Wistar rats were exposed to 0 or  
10 700 ppm 1-BP vapors for 6 hours/day, 5 days/week, for 8 weeks. Paired-pulse  
11 disinhibition was observed in both the DG and cornu ammonis area 1 (CA1) pyramidal  
12 neuron. The authors indicated that these findings may be caused by a decrease in  
13 gamma aminobutyric acid (GABA)-mediated inhibition. No behavioral abnormalities were  
14 observed. Intracellular signaling activities were also modified, as indicated by changes in  
15 total amounts or activity of CA2+/calmodulin-dependent kinases (II), mitogen-activated  
16 protein kinase, and protein kinase C. Significant increases were observed in active  
17 mitogen-activated protein kinase and total CA2+/calmodulin-dependent kinases (II)  $\alpha$   
18 and  $\beta$ , whereas protein kinase C activity was not changed. Elevated mitogen-activated  
19 protein kinase and protein kinase C activity may be associated with overactivation of N-  
20 methyl-D-aspartate receptors.

21  
22 Fueta et al. [2004] focused on evaluation of behavioral abnormalities in the form of  
23 disinhibitory effects in the hippocampal CA1 and the DG induced by chronic repetitive  
24 inhalation exposures to 1-BP vapor in rats, in addition to reversal of the disinhibitory  
25 effects in rats exposed for 12 weeks. Test animals were exposed to 1-BP vapor at a  
26 concentration of 0 or 700 ppm for 6 hours/day, 5 days/week, for 4, 8, or 12 weeks. Rats  
27 exposed for 12 weeks were subjected to an additional 4-week clearance period. No  
28 behavioral abnormalities were observed. Paired-pulse disinhibition was observed in both  
29 the DG and CA1 pyramidal neuron. The authors reported that the disinhibition in the DG

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1 was associated with activation of N-methyl-D-aspartate receptors caused by a reduced  
2 GABA inhibition, but not in the CA1. This provides a preliminary indication of the target  
3 area and involved neurotransmission systems. Notably, this effect was reversed 4 weeks  
4 after cessation of exposure. Immunohistochemical evaluation revealed no apparent  
5 morphological defects in either excitatory or inhibitory neuronal components of the  
6 hippocampus and granule cells in the DG.

7

8 Fueta et al. [2007] investigated the relationship between the total exposure level (dose)  
9 of 1-BP and the occurrence of disinhibition in the CA region and DG of the hippocampal  
10 or the time to death. Male Wistar rats were exposed for 6 hours/day, 5 days/week, for 8  
11 or 12 weeks to 0, 200, or 400 ppm 1-BP. Paired-pulse disinhibition was observed in the  
12 DG from rats exposed to 400 ppm but not in test animals exposed to 200 ppm 1-BP  
13 vapor. Significant paired-pulse disinhibition was not observed in CA1 pyramidal neurons  
14 from rats exposed to 200 or 400 ppm 1-BP. The electrophysiological study suggests that  
15 differential and reversible disinhibitory effects in the DG and the CA1 are induced by 1-  
16 BP. Immunohistochemical methods indicated no apparent morphological defects in  
17 either excitatory or inhibitory neuronal components, supporting the reversibility of  
18 physiological changes. At 4 weeks, Br<sup>-</sup> concentrations were significantly higher in rats  
19 exposed to 400 ppm. No additional increases were observed during the exposure  
20 period. The authors concluded that disinhibition and time of death associated with the  
21 inhalation of 1-BP vapors are dose dependent on both Br<sup>-</sup> concentrations and the total 1-  
22 BP dose.

23

24 Ichihara et al. [2000b] investigated the dose-dependent effects of 1-BP on the nervous  
25 system of male Wistar rats. Test animals were exposed to airborne concentrations of 1-  
26 BP corresponding to 0, 200, 400, or 800 ppm for 8 hours/day, 7 days/week, for 12  
27 weeks. The researchers assessed multiple neurological endpoints, including (1) walking  
28 status, (2) forelimb and hind limb grip strength, and (3) electrophysiological examinations  
29 of the tail nerve in the form of maximum MCV and DL. Additional tests were conducted

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1 to evaluate (1) brain weights, (2) blood biochemical indices, and (3) morphological  
2 changes of the nervous system and muscle. Serum clinical chemistry gave no indication  
3 of liver toxicity. The weights of brain (excluding cerebellum) and gastrocnemius muscle  
4 were concentration-dependently reduced, reaching statistical significance at 800 ppm.  
5 Ichihara et al. [2000b] observed weakened limb strength, a decline in MCV and DL of the  
6 rat tail, and morphological changes in the peripheral nerve and preterminal axon in the  
7 gracile nucleus, in addition to swelling in the posterior pretibial nerve in a concentration-  
8 dependent and exposure period-dependent relationship starting at 200 ppm. Forelimb  
9 grip strength was reduced from 4 weeks of exposure at 400 and 800 ppm, and the  
10 reduction became statistically significant from week 8 onward. Hind-limb grip strength  
11 was significantly reduced at all concentrations in week 4, at 800 ppm in week 8, and at  
12 400 and 800 ppm in week 12. Tail NCV was concentration-dependently reduced at 8  
13 and 12 weeks but reached statistical significance only at 800 ppm. Distal latency was  
14 significantly increased at 800 ppm after 4, 8, and 12 weeks of exposure. For both  
15 parameters the effect got stronger with exposure duration. Animals exposed to 800 ppm  
16 showed motor deficits (weak kicking, inability to stand still on a slope, abnormal up-and-  
17 down landing, poor control of extremities). The overall findings of this study indicate the  
18 ability of 1-BP to induce neurological changes in rats and the potentially potent  
19 neurotoxicity of 1-BP.

20  
21 Sohn et al. [2002] examined the morphological changes in the nervous systems of SD  
22 rats exposed to 1-BP following repeated inhalation exposures to airborne 1-BP  
23 concentrations of 0, 200, 500, or 1,250 ppm for 6 hours/day, 5 days/week, for 13 weeks.  
24 No histopathological changes were observed in the gray and white matter of the brain  
25 and spinal cords of rats exposed to 1,250 ppm 1-BP, in comparison with controls.  
26 Neither microscopic examinations of the sacral and peroneal nerves nor nerve fiber  
27 teasing yielded evidence of neurotoxic effects in any test animals. No pathological  
28 features were observed in the brain and spinal cord. Sohn et al. [2002] hypothesized that  
29 the rat nervous system is resistant to repeated inhalation exposures to 1-BP up to 1,250

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1 ppm and reported that no substantial morphological changes were observed during this  
2 study.

3

4 Wang et al. [2002] assessed biochemical changes in the CNS of male Wistar rats  
5 exposed to 1-BP. Test animals were exposed to 200, 400, or 800 ppm 1-BP for 8  
6 hours/day for 7 days. The assessments involved morphological and biochemical  
7 analysis, including measurements of neuron-specific gamma-enolase, GSH, protein and  
8 non-protein sulfhydryl content,  $\beta$ -S100 protein, and creatine kinase subunits B and M.  
9 Body weights were decreased in rats exposed to 800 ppm. No significant decreases in  
10 whole brain, cerebrum, or cerebellum weights were reported. Histopathological changes  
11 observed in this study included the swelling of preterminal axons in the gracile nucleus  
12 and the inclusion of a dark-staining material in the nerve myelin sheath in the 800-ppm  
13 treatment group. The posterior tibial nerve also showed swelling or a dense mass of  
14 myelin sheath, especially in the vicinity of the nodes of Ranvier. Schwann cell  
15 hypertrophy was noted in the 800-ppm treatment group. In the cerebrum and  
16 cerebellum, decreases in neuron-specific gamma-enolase were observed for both the  
17 400- and 800-ppm-exposed animals. A decline in this enzyme reflects a decreased  
18 number of neurons, suggesting adverse effects on neurons. CK activity decreased dose-  
19 dependently in the cerebrum, cerebellum, brain stem, and spinal cord, whereas changes  
20 in measurements of lactate dehydrogenase and glutamine oxaloacetic transaminase did  
21 not achieve statistical significance. Similarly, levels of total GSH and non-protein  
22 sulfhydryl content were decreased in the cerebellum, cerebrum, and spinal cord. The  
23 authors speculate that the observed changes in biochemical neuron-specific markers  
24 may relate to a loss of neurons and that modification of sulfhydryl-sensitive proteins or  
25 GSH depletion may be germane to the mechanism of 1-BP toxicity.

26

27 Wang et al. [2003] examined the subchronic effects of exposure to 1-BP on biochemical  
28 components in the CNS of male Wistar rats. Changes in the concentrations of neuron-  
29 specific gamma-enolase, glia-specific  $\beta$ -S100 protein, heat shock protein (Hsp27), and

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1 CK subunits B and M were monitored, in addition to enzymatic activity of other enzymes  
2 in the cerebrum, cerebellum, brainstem, and spinal cord. Test animals were exposed to  
3 0, 200, 400, or 800 ppm 1-BP for 8 hours/day, 7 days/week, for 12 weeks. In rats  
4 exposed to 800 ppm 1-BP, significant changes were observed in nearly all biochemical  
5 markers throughout the brain and spinal cord. The authors reported a decrease in  
6 neuron-specific gamma-enolase in the cerebrum, associated with long-term exposure of  
7 rats to 1-BP, and indicated biochemical changes in neurons with decreased wet weight  
8 of the cerebrum in rats exposed to 400 and 800 ppm 1-BP. No significant changes were  
9 observed in  $\beta$ -S100 protein levels in any region of the CNS. Hsp 27 levels were  
10 significantly higher in the cerebellum, brainstem, and spinal cords of rats exposed to 800  
11 ppm 1-BP. CK activity decreased in a dose-dependent relationship and to an observable  
12 level in the CNS. Total GSH concentrations were significantly lower in CNS of rats in the  
13 highest-exposure group. Limited changes in several markers were observed at 400 ppm,  
14 and isolated changes were observed at 200 ppm. The authors suggest that their findings  
15 are consistent with two possible mechanisms by which 1-BP could affect CNS function.  
16 The first is that 1-BP could reduce the amount and/or activity of CK and thereby reduce  
17 the replenishment of ATP that is required for neural function. The second is that  
18 depletion of GSH indicates that a reactive metabolite of 1-BP may lead to oxidative injury  
19 in neuronal or glial cells.

20  
21 Honma et al. [2003] investigated the effects of 1-BP on animal behavior as an  
22 assessment of the extent of CNS toxicity. Male F344 rats were exposed to 1-BP  
23 concentrations of 0, 10, 50, 200, or 1,000 ppm for 8 hours/day, 7 days/week, for 3  
24 weeks. Neurotoxicity was examined via numerous behavioral tests to assess locomotor  
25 activity, passive avoidance, open-field activities (e.g., freezing, rearing, defecation), and  
26 performance in a water maze. Body weights were dramatically reduced by exposure to  
27 1,000 ppm of 1-BP, indicating the overt toxicity of this exposure. Rats exposed to 50 and  
28 200 ppm 1-BP exhibited significant increases in spontaneous locomotor activity (SLA) at  
29 the end of the 3-week exposure, and the increase in SLA returned to control levels 3–4

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1 days post exposure. Passive avoidance and maze swimming were not affected by 1-BP  
2 exposure, but traction performance was decreased in a dose-dependent fashion and did  
3 not recover 7 days post exposure. The results indicate that at the concentrations of 1-BP  
4 tested, rats exhibited increased CNS excitatory response and reduced muscle strength,  
5 but motor coordination and memory were not affected.

6  
7 Banu et al. [2007] evaluated the recovery of the CNS at 4 and 14 weeks after subchronic  
8 inhalation exposure to 1-BP. Male Wistar rats were exposed to 0, 400, or 1,000 ppm of  
9 1-BP vapor for 8 hours/day, 7 days/week, for 6 weeks. The effects of 1-BP on the CNS  
10 were evaluated via measurement of hind limb muscle strength and monitoring of neuron-  
11 specific gamma-enolase levels. Additionally, tail blood pressure and skin temperature  
12 were monitored to assess the effects on the autonomic CNS disturbances. The authors  
13 reported that rats in the 1,000 ppm treatment group tended to sit with legs stretched and  
14 were unable to stand up steadily on their hind limbs to feed. Other observations included  
15 the tendency for rats to drag their hind limbs instead of walking. Hind limb muscle  
16 strength diminished significantly and did not recover after 14 weeks following cessation  
17 of 1-BP exposure. Hind-limb muscle strength was at one third of control levels at the end  
18 of exposure to 1,000 ppm and showed recovery that paralleled but never reached the  
19 level of the 400-ppm-exposed or control animals. The neuron-specific gamma-enolase  
20 levels remained unchanged during the experiment. Rats exposed to 1,000 ppm 1-BP  
21 experienced decreased tail skin temperature and elevated blood pressure.

22  
23 Ueno et al. [2007] assessed the effects of subchronic inhalation exposures to 1-BP on  
24 CNS function, with a focus on the inhibitory neurotransmitter system mediated by GABA.  
25 Male Wistar rats were exposed for 6 hours/day, 5 days/week, for 12 weeks to 1-BP at a  
26 concentration of 0 or 400 ppm. Function of the brain regional GABA type A (GABA<sub>A</sub>)  
27 receptors, hippocampal excitability, and the expression of GABA<sub>A</sub> receptor unit mRNAs  
28 in the hippocampus were assessed. The reported results included significantly  
29 decreased paired-pulse inhibition of the population spike amplitudes in the DG,

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1 indicating neuronal disinhibition. Decreased levels of GABA<sub>A</sub> in the mRNA of the  
2 hippocampus were also noted in 1-BP-exposed rats. Ueno et al. [2007] concluded that  
3 subchronic inhalation exposures to 1-BP at 400 ppm caused hyperexcitability in the DG,  
4 associated with expression and decreased levels of GABA<sub>A</sub> in the mRNA, further  
5 suggesting that this system may be involved in neurological effects of 1-BP.

6  
7 Suda et al. [2008] investigated the effects of 1-BP on changes in brain levels of  
8 neurotransmitters and amino acids to assess the toxic effects of 1-BP on the CNS. Male  
9 F344 rats were exposed to 1-BP at concentrations of 50, 200, and 1,000 ppm for 8  
10 hours/day, 7 days/week, for 3 weeks. Test animals were sacrificed either at 2 hours  
11 (Case 1) or 19 hours (Case 2) after the cessation of exposure. Levels of selected  
12 neurotransmitters, amino acids, and their metabolites, in eight distinct regions of the  
13 brain were monitored. No effects were noted in acetylcholine levels in any region of the  
14 brain in rats in Case 1 or Case 2. Other reported findings included numerous changes in  
15 monoamines, their metabolites, and amino acid levels in various regions of the brain. In  
16 Case 1, dopamine concentrations were decreased in the striatum at 50 ppm, 3,4-  
17 dihydroxyphenylacetic acid levels were significantly less in the hippocampus at 1,000  
18 ppm, and 5-hydroxyindoleacetic acid content in the striatum was significantly decreased  
19 in a dose-response manner. Monitoring of the amino acids in the brains of rats sacrificed  
20 2 hours after cessation of exposure revealed significantly higher levels of aspartate and  
21 glutamine at 1,000 ppm and decreased GABA concentrations in the 1,000-ppm  
22 treatment group. In Case 2, homovanillic acid in the striatum and norepinephrine in the  
23 hypothalamus declined in a dose-dependent manner, with significant decreases in the  
24 neurotransmitter concentrations in the 1,000-ppm treatment group in comparison with  
25 controls. In rats exposed to 1,000 ppm 1-BP, serotonin levels in the occipital cortex and  
26 5-hydroxyindoleacetic in the medulla oblongata were significantly elevated, whereas the  
27 3-methoxy-4-hydroxyphenylglycol content in the occipital cortex decreased. Aspartate  
28 levels were significantly increased in multiple regions of the brain. Levels of glutamine  
29 were higher in all regions of the brain except the medulla oblongata. GABA

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1 concentrations were significantly lower in rats exposed to 1,000 ppm than in controls.  
2 Suda et al. [2008] concluded that subchronic inhalation exposures to 1-BP, especially at  
3 1,000 ppm, significantly changed amino acid and neurotransmitter concentrations in the  
4 brain.

5  
6 Mohideen et al. [2009] investigated the effects of 1-BP on the expression levels of  
7 neurotransmitter receptor genes in the rat brain. Male F344 rats were exposed to 1-BP  
8 at concentrations of 0, 400, 800, and 1,000 ppm for 8 hours/day, 7 days/week, for 4  
9 weeks. Following the cessation of exposure, the brains of the test animals were  
10 dissected and prepared for analysis. Real-time polymerase chain reaction (PCR)  
11 analysis was conducted to quantify mRNA levels of specific serotonin, dopamine, and  
12 GABA receptors. Protein levels in the cortex and hippocampus were determined via  
13 Western blot analysis. RT-PCR analysis revealed a significant decrease in a dose-  
14 response manner of specific serotonin, dopamine, and GABA mRNA receptor levels in  
15 the hippocampus. Significant changes in the mRNA levels of serotonin, dopamine, and  
16 GABA were observed in multiple areas of the rat, associated with 1-BP exposure at 800  
17 and 1,000 ppm. The regional and sometimes concentration-dependent changes in  
18 expression of the mRNAs of specific 5-hydroxytryptamine receptors, dopamine  
19 receptors, and GABA receptors in some cases began at the lowest concentration (400  
20 ppm). The findings of the real-time PCR indicate that specific serotonin and dopamine  
21 mRNA expressions in the hippocampus and pons-medulla region were the most  
22 sensitive indicators of 1-BP neurotoxicity. The results of the Western blot analysis  
23 revealed no significant changes in the cortex or hippocampus of the rat brain. Mohideen  
24 et al. [2009] concluded that inhalation exposures of 1-BP may elicit critical changes in  
25 the expression of neurotransmitter receptor genes in the rat brain and suggested that  
26 expression of neurotransmitter mRNAs was a useful potential biomarker for the CNS  
27 toxicity of 1-BP.

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1 In a second study, Mohideen et al. [2011] investigated the effects of repeated exposures  
2 of 1-BP on monoamine neurons, more specifically noradrenaline and serotonin axons, in  
3 the neo-cortex region of the rat brain. Male F344 rats were exposed to 1-BP at  
4 concentrations of 0, 400, 800, and 1,000 ppm for 8 hours/day, 7 days/week, for 4 weeks.  
5 Test animals were sacrificed and the brains were harvested one day after the final  
6 exposure. Mohideen et al. [2011] reported a significant decrease in the density of  
7 noradrenergic axons in rats treated at 800 and 1000 ppm 1-BP. These effects were  
8 diffuse but more pronounced in the medial prefrontal cortex and amygdalae. No such  
9 changes in the density of serotonergic axons were observed at any treatment level. The  
10 authors theorized that the 1-BP-induced degeneration of noradrenergic axons may be  
11 associated with the altered mood states, such as depression, cognitive impairment, and  
12 sleep disturbances associated with workplace exposures to 1-BP [Mohideen et al. 2011].  
13 In conclusion, the study demonstrated the onset of morphological changes in a dose-  
14 response manner in the brains of 1-BP-exposed rats.  
15 Mohideen et al. [2013] continued the investigation into the neurotoxic effects of 1-BP on  
16 the CNS of male F344 rats. Test animals were exposed to 1-BP at concentrations of 0,  
17 400, 800, and 1,000 ppm for 8 hours/day, 7 days/week, for 4 weeks. Following  
18 treatment, biochemical and histopathological examinations were conducted to ascertain  
19 the effects of 1-BP in the cerebellum and hippocampus. The analyses revealed pyknotic  
20 shrinkage of granular cells, degeneration of Purkinje cells in the cerebellum, and  
21 shrinkage of nuclei of the granular cells of test animals in the highest treatment group.  
22 Morphological changes in the form of elongation of processes in the astrocytes of rats  
23 exposed to 800 and 1,000 ppm 1-BP were also observed. The number of astrocytes per  
24 tissue volume was elevated in rats exposed to 400 ppm 1-BP. Despite the lack of  
25 evidence of demyelination, Mohideen et al. [2013] reported decreased levels of myelin  
26 basic protein and oligodendrocytes, in addition to down-regulation of mRNA and proteins  
27 associated with myelin-related genes in rats exposed to 1000 ppm. The authors  
28 theorized that these findings indicate that inhalation of 1-BP may contribute to  
29 demyelination.

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2 Huang et al. [2011] attempted to identify the molecular mechanisms of 1-BP-induced  
3 neurotoxicity. Male F344 rats were exposed to 1-BP at concentrations of 0, 400, and  
4 1,000 ppm for 8 hours/day, 7 days/week, for 1 or 4 weeks. Protein expression in the  
5 hippocampus of 1-BP-exposed rats was analyzed. The reported results demonstrated  
6 significant changes of the hippocampal proteome and differential modification of the  
7 expression of 19 hippocampal proteins. Eight hippocampal proteins experienced  
8 significant upregulation after 1 or 4 weeks of exposure to 1-BP; upregulation occurred in  
9 a dose-response manner for 3 proteins in rats exposed to 1-BP for 4 weeks. Significant  
10 downregulation occurred in 11 hippocampal proteins, with 6 of the modifications in  
11 regulation occurring in a dose-dependent manner. Huang et al. [2011] stated that the  
12 identified modified proteins may mediate the effects of 1-BP in the hippocampus,  
13 including oxidative stress, loss of ATP production, and GABA dysfunction, and contribute  
14 to neurotoxicity.

15  
16 Huang et al. [2012] evaluated the protein expression of 1-BP-exposed rats to identify the  
17 molecular mechanism of 1-BP-induced neurotoxicity in the hippocampus. Male F344 rats  
18 were exposed to 1-BP at concentrations of 0, 400, and 1,000 ppm for 8 hours/day, 7  
19 days/week, for 1 or 4 weeks. Differential protein expressions were analyzed. ROS were  
20 measured to reflect the level of oxidative stress associated with 1-BP exposure, and  
21 protein carbonyl content was measured to evaluate ROS-associated damage at the  
22 protein level. Huang et al. [2012] reported dose-dependent increases in levels of ROS  
23 and total protein carbonyl content in the hippocampus. Ten unique protein species  
24 involved with numerous biological processes, including glycolysis, ATP production, and  
25 neuronal metabolism, were identified with increased carbonyl modifications. These  
26 findings provide supplemental evidence of 1-BP-induced oxidative stress and protein  
27 damage in the CNS of exposed rats.

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2 Subramanian et al. [2012] examined microglial changes and oxidative stress in the CNS  
3 of 1-BP-exposed rats. Wistar-ST rats were exposed to 1-BP at concentrations of 0, 400,  
4 800, or 1000 ppm for 8 hours/day for 28 consecutive days. The authors reported a  
5 significant reduction in body and whole brain weights in animals treated at 1000 ppm.  
6 Numerous changes were noted in the markers of oxidative stress. For example, rats  
7 experienced increases in TBARSs, protein carbonyl and ROS concentrations in a dose-  
8 response manner. The authors observed morphological changes in the microglia,  
9 primarily described as enlarged cell bodies, in animals treated at 1000 ppm 1-BP. The  
10 authors theorized that the described morphological changes are associated with  
11 oxidative stress via ROS formation in the CNS and may be a key neurotoxic mechanism  
12 of 1-BP.

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1 **TABLE 4-2 – NEUROTOXIC EFFECTS CAUSED BY INHALATION EXPOSURES TO 1-BP IN ANIMALS STUDIES**

<b>Reference</b>	<b>Species; strain</b>	<b>Number per treatment group (sex)</b>	<b>Treatment levels (ppm)</b>	<b>Treatment regimen</b>	<b>Results (treatment)</b>
ClinTrials BioResearch [1997a]	Rat; SD	10 (male); 10 (female)	0, 398, 994, 1,590	6 hours/day, 5 days/week, 4 weeks	Movement disorders (ataxia and changes in gait) (1,590); behavioral abnormalities (994, 1,590); increased incidence of mortality (1590); altered locomotor activity levels (994, 1,590); histopathological abnormalities in CNS (398, 994, 1,590)
ClinTrials BioResearch [1997b]	Rat; SD	15 (male); 15 (female)	0, 99, 199, 398, 596	6 hours/day, 5 days/week, 13 weeks	No changes in body weight (99, 199, 398, 596); no changes in functional observational battery (99, 199, 398, 596); no changes in motor activity (99, 199, 398, 596); no histopathological changes in CNS or PNS (99, 199, 398, 596)
Yu et al. [1998]	Rat; Wistar	9 (male)	0, 1,000	8 hours/day, 7 days/week, 5 or 7 weeks	Reduced body weight; degeneration of peripheral nerves; histopathological changes in Purkinic cells; movement disorders; electrophysiological changes in PNS
Ohnishi et al. [1999]	Rat; Wistar	8 (male)	0, 1,500	6 hours/day, 5 days/week, 4 weeks	Decreased activity in 1-BP exposed animals; histopathological changes in Purkinic cells; behavioral abnormalities; movement disorders (ataxic gait)
Fueta et al. [2000]	Rat; Wistar	16 (exposed male); 14 (control male)	0, 1,500	6 hours/day, 5 days/week, 4 weeks	Paired pulse disinhibition; neuronal dysfunction in DG; convulsive behaviors

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<b>Reference</b>	<b>Species; strain</b>	<b>Number per treatment group (sex)</b>	<b>Treatment levels (ppm)</b>	<b>Treatment regimen</b>	<b>Results (treatment)</b>
Ichihara et al. [2000b]	Rat; Wistar	8-9 (male)	0, 200, 400, 800	8 hours/day, 7 days/week, 12 weeks	Decreased forelimb strength (800); decreased hind limb strength (400, 800); electrophysiological changes in the MCV and DL of tail nerve (800); morphological changes in PNS and preterminal axons in a dose-response manner (200, 400, 800)
Yu et al. [2001]	Rat; Wistar	9 (male)	0, 1,000	8 hours/day, 7 days/week, 5 or 7 weeks	Decreased body weight; movement disorder; electrophysiological changes in the MCV and DL of tail nerve; histopathological changes in CNS and PNS
Fueta et al. [2002a]	Rat; Wistar	3-7 (male)	0, 1,500	6 hours/day, 5 days/week, 1,3, or 4 weeks	Paired pulse disinhibition in the DG and CA1 pyramidal neuron; electrophysiological changes; behavioral abnormalities
Fueta et al. [2002b]	Rat; Wistar	12 (male)	0, 700	6 hours/day, 5 days/week, 8 weeks	Paired pulse disinhibition in the DG and CA1 pyramidal neuron; decreased GABA-mediated inhibition; increased enzymatic activities
Sohn et al. [2002]	Rat; SD	10 (male) 10 (female)	0, 200, 500, 1,250	6 hours/day, 5 days/week, 13 weeks	No histopathological changes in the CNS (200, 500, 1,250); no morphological evidence of neurotoxicity in sacral and peroneal nerves (200, 500, 1,250)

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<b>Reference</b>	<b>Species; strain</b>	<b>Number per treatment group (sex)</b>	<b>Treatment levels (ppm)</b>	<b>Treatment regimen</b>	<b>Results (treatment)</b>
Wang et al. [2002]	Rat; Wistar	9 (male)	0, 200, 400, 800	8 hours/day, 7 days	Decreased body weight (800); decreased whole brain, cerebrum, or cerebellum weight (200, 400, 800); histopathological changes in gracile nucleus and nerve myelin sheath (800); changes in neuron specific markers (400, 800)
Honma et al. [2003]	Rat; F344	5 (male)	0, 10, 50, 200, 1,000	8 hours/day, 7 days/week, 3 weeks	Decreased body weight (1,000); increased electrophysiological changes in SLA (50, 200); no changes in passive avoidance and maze swimming (10, 50, 200, 1,000); decreased traction performance in a dose-response manner
Wang et al. [2003]	Rat; Wistar	9 (male)	0, 200, 400, 800	8 hours/day, 7 days/week, 12 weeks	Changes in neuron specific biochemical markers throughout the CNS (800); decreased wet weight of cerebrum (400, 800); limited changes in neuron specific biochemical markers (400)
Fueta et al. [2004]	Rat; Wistar	29 (exposed males); 29 (controls)	0, 700	6 hours/day, 5 days/week, 4, 8, or 12 weeks	Paired pulse disinhibition in DG and CA1 pyramidal neuron; effects in DG reversed 4 weeks after cessation of exposure
Banu et al. [2007]	Rat; Wistar	24 (male)	0, 400, 1000	8 hours/day, 7 days/week, 6 weeks	Abnormal posture (outstretched legs when sitting) (1,000); movement disorder (inability to stand on hind legs) (1,000); decreased tail skin temperature (1,000); elevated blood pressure (1,000); decreased hind limb strength (1,000)

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<b>Reference</b>	<b>Species; strain</b>	<b>Number per treatment group (sex)</b>	<b>Treatment levels (ppm)</b>	<b>Treatment regimen</b>	<b>Results (treatment)</b>
Fueta et al. [2007]	Rat; Wistar	6 (male)	0, 200, 400	6 hours/day, 5 days/week, 8 or 12 weeks	Pair pulse disinhibition in the DG and CA1 pyramidal neuron (400); Increased Br <sup>-</sup> levels in the brain at week 4 (400)
Ueno et al. [2007]	Rat; Wistar	N/A (male)	0, 400	6 hours/day, 5 days/week, 12 weeks	Decreased paired pulse inhibition in the DG; hyperexcitability in the DG associated with expression and function of specific neurotransmitter receptors including the GABA <sub>A</sub>
Suda et al. [2008]	Rats; F344	N/A (male)	0, 50, 200, 1000	8 hours/day, 7 days/week, 3 weeks	Case 1 (animals sacrificed 2 hours after cessation of exposure): Changes in neurotransmitters and amino acids levels in multiple regions of the brain (1,000); decreased 5-hydroxyindoleacetic content in the striatum in a dose-response manner; decreased dopamine concentrations in the striatum (50)  Case 2 (19 hours after cessation of exposure): Changes in neurotransmitters and amino levels in multiple regions of the brain (1,000); decreased homovanillic acid in the striatum and norepinephrine in the hypothalamus dose-dependent manner
Mohideen et al. [2009]	Rats; F344	12 (male)	0, 400, 800, 1,000	8 hours/day, 7 days/week, 4 weeks	Significant changes in the mRNA levels of serotonin, dopamine, and GABA (800, 1,000)

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<b>Reference</b>	<b>Species; strain</b>	<b>Number per treatment group (sex)</b>	<b>Treatment levels (ppm)</b>	<b>Treatment regimen</b>	<b>Results (treatment)</b>
Mohideen et al. [2011]	Rats; F344	6 (male)	0, 400, 800, 1,000	8 hours/day, 7 days/week, 4 weeks	Decrease in the density of noradrenergic axons in multiple sections of the brain, but more pronounced in the medial prefrontal cortex and amygdale (800, 1,000)
Mohideen et al. [2013]	Rats; F344	12 (male)	0, 400, 800, 1,000	8 hours/day, 7 days/week, 4 weeks	Pyknotic shrinkage of granular cells, degeneration of Purkinje cells in the cerebellum and shrinkage of nuclei of the granular cells (1,000); Elongation of processes of astrocytes (800, 1,000); Increased number of astrocytes per tissue volume (400); Decreased levels of MBP and oligodendrocytes (1000), Down-regulation of mRNA and proteins associated with myelin-related genes (1000)
Huang et al. [2011]	Rats; F344	9 (male)	0, 400, 800, 1,000	8 hours/day, 7 days/week, 1 or 4 weeks	Up-regulation of 9 hippocampal proteins; Up-regulation of HSP60, TPI and Ran occurred in a dose-dependent manner (4 weeks exposure); Down-regulation of 11 hippocampal proteins; Down-regulation of Mi-CK, B-CK, HNRNPH1, ECH1, PSMA1, TPI, and DJ-1 (4 weeks exposure)
Huang et al. [2012]	Rats; F344	9 (male)	0, 400, 800, 1000	8 hours/day, 7 days/week, 1 or 4 weeks	Increased hippocampal ROS levels (1,000 for 1 week; 400, 1,000 for 4 weeks); Increased total hippocampal protein carbonyl content (1,000 for 4 weeks) ; Increased total plasma protein carbonyl content;(1,000 for 1 week; 400, 1,000 for 4 weeks)

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<b>Reference</b>	<b>Species; strain</b>	<b>Number per treatment group (sex)</b>	<b>Treatment levels (ppm)</b>	<b>Treatment regimen</b>	<b>Results (treatment)</b>
Subramanian et al. [2012]	Rats; Wistar-ST	12 (male)	0, 400, 800,1000	8 hours/day, 7 days/week, 4 weeks (28 consecutive days)	Reduction in body weight and whole brain weight (1,000); Changes in the levels of TBARS (400, 800, 1,000), protein carbonyl (800, 1000), and ROS (800, 1,000); Morphological changes manifesting as larger cell bodies and longer ramified processes of microglial cells in the cerebrum

1 **Abbreviations: 1-BP = 1-bromopropane; B-CK = creatine kinase B-type; Br<sup>-</sup> = bromide ion; CNS = central nervous system; DG = dentate**  
2 **gyrus; DJ-1 DL = distal latency; ECH1 = delta (3,5)-delta (2,4)-dienoyl-CoA isomerase, mitochondrial; ; fEPSP = field excitatory**  
3 **postsynaptic potential; GABA<sub>A</sub> = GABA type a; GABAergic = gamma aminobutyric acid; HNRNPH1 = heterogeneous nuclear**  
4 **ribonucleoprotein H; HSP60 = 60kDa heat shock protein, mitochondrial; MBP = myelin basic protein; MCV = motor nerve conduction**  
5 **velocity; Mi-CK = creatine kinase U-type, mitochondrial; ML = motor latency; N/A = information not available or provided; PNS =**  
6 **peripheral nervous system; PSMA1 = proteasome subunit alpha type-1; Ran = GTP-binding nuclear protein Ran; ROS = reactive oxygen**  
7 **species; SLA = spontaneous locomotor activity; SD = Sprague-Dawley rats; TBARS = thiobarbituric acid-reactive substances; TPI =**  
8 **triosephosphate isomerase**  
9

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1 4.1.3 OTHER NON-CANCER TOXICOLOGICAL EFFECTS

2 This subsection summarizes adverse health outcomes beyond developmental and  
3 reproductive toxicity and neurotoxicity. Toxic effects reported in this subsection include  
4 hepatotoxicity, hematotoxicity, immunotoxicity, and gross pathological changes (such as  
5 decreased organ weight). Table 4-3 provides a summary of the reviewed studies.

6  
7 ClinTrials BioResearch [1997a] conducted a range-finding study to assess the potential  
8 toxicity of 1-BP. SD rats were exposed to airborne concentrations of 0, 398, 994, or  
9 1,590 ppm for 6 hours/day, 5 days/week for a total of 28 days. Among the reported  
10 results, 8 males and 3 females in the 1,590-ppm treatment group died between days 13  
11 and 23. All groups experienced fur staining. Clinical signs of 1-BP toxicity occurred  
12 primarily in the highest treatment group (1,590 ppm); these signs included wet and  
13 stained coats, abnormal behavior, hypersensitivity, salivation, tremors, decreased  
14 activity, and ataxia. Statistically significant decreases in weight gain and food  
15 consumption were reported in animals exposed to 1,590 ppm 1-BP. Laboratory  
16 investigations revealed low erythrocyte parameters in rats exposed to 994 and 1,590  
17 ppm 1-BP. Blood chemistry analysis showed significant changes in blood urea nitrogen,  
18 total bilirubin, phosphorus, chloride, and total protein levels in rats in the 994- and 1,590-  
19 ppm treatment groups. No significant findings were reported from the urinalysis.  
20 Histopathological lesions were observed in the CNS, urinary system, nasal cavities,  
21 sternal bone marrow, lymphoid tissues, and male reproductive system. These  
22 pathological changes were observed in both male and female rats in the 1,590-ppm  
23 treatment group. Additional information on the effects on the reproductive and  
24 neurological systems is provided in subsections 4.1.1 and 4.1.2.

25  
26 ClinTrials BioResearch [1997b] investigated the potential toxicity of subchronic exposure  
27 to 1-BP via a whole-body inhalation study of male and female SD rats. Test animals  
28 were exposed to airborne concentrations of 1-BP at 0, 99, 199, 398, or 596 ppm for 6  
29 hours/day, 5 days/week, for 13 weeks.. No clinical signs of treatment were observed  
30 during the 13-week exposure period. When compared to controls, body weight and food

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1 consumption were not affected in any treatment group. At week 6, a significant decrease  
2 in WBC count and absolute lymphocytes was observed in female rats exposed to the  
3 highest treatment dose (596 ppm). No biologically significant changes were noted in  
4 hematology, biochemistry, and urinalysis following 13 weeks of exposure to 1-BP. A  
5 significant increase in the relative liver weights and absolute adrenal weights of male  
6 rats in the highest treatment group (596 ppm) was reported. Histopathological  
7 examination revealed no significant differences in absolute or relative organ weights in  
8 treated animals. Histopathological lesions on the liver in male rats in the highest  
9 treatment group (596 ppm) and in multiple animals in the 398-ppm treatment group were  
10 identified as vacuolations of centrolobular hepatocytes. ClinTrials BioResearch [1997b]  
11 reported a no observed effect level (NOEL) of 199 ppm. Supplemental information on  
12 the effects of 1-BP reported in this study on the reproductive and neurological systems is  
13 described in Sections 4.1.1 and 4.1.2.

14  
15 Elf Atochem [1997] exposed groups of Wistar rats (via the nose only) to 0, 6,003, 6,878,  
16 6,978, 7,355, or 8,449 ppm of 1-BP for 4 hours. The authors calculated a 4-hour LC<sub>50</sub>  
17 value of 7000 ppm.. Severe respiratory distress due to acute inflammatory response  
18 and alveolar edema occurred before the rats died. Increased lung weights were  
19 reported. The cause of death was attributed to acute inflammatory response and  
20 alveolar edema.

21  
22 Kim et al. [1999b] conducted two independent experiments to investigate the effects of  
23 acute and repeated inhalation exposures to 1-BP. In the acute study (Experiment 1),  
24 male and female SD rats received whole-body exposure for 4 hours to 0, 11,000,  
25 13,000, 15,000, or 17,000 ppm 1-BP. Test animals were monitored for 14 days following  
26 exposure to assess health status. The authors observed piloerection, decreased activity,  
27 ataxia, and lacrimation in all treatment groups 1 hour after acute exposure to 1-BP. Two  
28 male rats died within 6 hours of exposure to 15,000 ppm. One female rat died 12 hours  
29 after exposure to 13,000 ppm, and 4 female rats died within 24 hours after exposure to

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1 15,000 ppm. All survivors were considered clinically normal from 24 hours after  
2 exposure. Limited histopathological changes were observed, in the form of cytoplasmic  
3 vacuolation in the hepatocytes around the central veins. No gross pathological  
4 observations were reported. Kim et al. [1999b] derived a LC<sub>50</sub> value (i.e., the lethal  
5 concentration causing the death of 50% of a group of test animals) of 14,374 ppm for a  
6 4-hour inhalation exposure to 1-BP.

7

8 In the repeated inhalation experiment (Experiment 2), male and female SD rats were  
9 exposed to 0, 50, 300, or 1,800 ppm 1-BP for 6 hours/day, 5 days/week, for 8 weeks  
10 [Kim et al. 1999b]. No deaths were caused by exposure to 1-BP at these concentrations.  
11 Test animals exposed to 1,800 ppm experienced mild ataxia; decreased activity;  
12 increased testis, ovary, liver, and kidney weight; and significant changes in blood  
13 chemistry. WBCs, RBCs, hematocrit, and mean corpuscular volume were significantly  
14 decreased. Mean corpuscular hemoglobin and hemoglobin concentrations were  
15 significantly increased. Urinalysis revealed decreased urobilinogen in male rats and  
16 increased bilirubin levels in female rats exposed to 1,800 ppm 1-BP. Kim et al. [1999b]  
17 reported no additional significant changes associated with feed consumption, urinalysis,  
18 hematology, or serum biochemistry.

19

20 Liu et al. [2009] investigated the susceptibility of three inbred mice strains to 1-BP-  
21 mediated hepatotoxicity. Male C57BL/6J, DBA/2J, and BALB/cA mice were exposed to  
22 1-BP at 0, 50, 110, or 250 ppm for 8 hours/day for 28 days. Two of 6 BALB/cA mice  
23 exposed to 250 ppm 1-BP died in 4 days, whereas 1 of 6 C57BL/6J mice treated with  
24 250 ppm 1-BP died in 7 days. Liver toxicity was evaluated on the basis of hepatic  
25 enzyme levels and activities, in addition to histopathological findings. BALB/cA mice  
26 exposed to 250 ppm had significant increases in body weight; similar results were not  
27 reported for the other strains or treatment levels. Liver damage, in the form of  
28 hepatocellular degeneration and focal necrosis, occurred in all three strains of mice in a  
29 dose-response manner. Liu et al. [2009] indicated that the area of necrosis was

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1 significantly larger at all treatment levels in BALB/cA and C57BL/6J mice than in  
2 controls. Hepatic CYP2E1 levels were higher in BALB/cA and DBA/2J mice treated at 50  
3 and 110 ppm in comparison with baselines; C57BL/6J mice had increased CYP2E1  
4 levels in the liver only at 50 ppm. Only BALB/cA mice demonstrated significantly reduced  
5 CYP2E1 levels, at 250 ppm after 28 days. GST activity in the liver was significantly lower  
6 in BALB/cA mice than in other mice strains. Total GSH content was decreased in  
7 BALB/cA and DBA/2J mice treated at 50 and 110 ppm 1-BP. At 250 ppm, all three  
8 strains were similar. When compared to the baseline, total GSH content in C57BL/6J  
9 and BALB/cA mice exposed at 250 ppm was significantly increased. In addition, GSSG  
10 content was increased in all treatment levels of BALB/cA mice, relative to baseline. The  
11 results of the study indicate that 1-BP is capable of inducing hepatotoxicity in all three  
12 strains. Liu et al. [2009] concluded that BALB/cA is the strain most susceptible to liver  
13 toxicity, followed by C57BL/6J and DBA/2J.

14  
15 Anderson et al. [2010] investigated the immunotoxicity of 1-BP in B6C3F1 mice and  
16 F344/N rats following whole-body inhalation exposure. Test animals were exposed by  
17 whole-body inhalation to 1-BP at concentrations of 0, 125 (mice only), 250, 500, or 1,000  
18 ppm (rats only) for 6 hours plus T<sub>90</sub> (10 min)/day, 5 days/week, for approximately 4 or 10  
19 weeks. Three mice in the 500-ppm treatment group died during the first week of  
20 exposure. Significant decreases in body weight were reported for mice exposed for 4  
21 weeks to 1-BP; no such changes were observed in mice exposed to 1-BP for 10 weeks.  
22 Mice treated at 250 ppm 1-BP for 4 weeks and 250 to 500 ppm 1-BP for 10 weeks  
23 experienced significant decreases in spleen weight. In addition, the spleen  
24 immunoglobulin M (IgM) response to sheep red blood cells (SRBCs) was significantly  
25 decreased in animals treated at 125, 250, and 500 ppm 1-BP for 10 weeks. After 4  
26 weeks, total spleen cells and T cells were significantly decreased in the 125–500 ppm  
27 treatment groups. In rats, Anderson et al. [2010] reported no deaths during the study  
28 period or changes in body or spleen weight following exposure to 1-BP for 4 or 10  
29 weeks. In mice, there was a concentration-dependent decrease in plaque-forming cells

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1 per spleen and per  $10^6$  cells that showed maximum effect by 10 weeks. A similar trend  
2 was observed in rats exposed to 1,000 ppm. In mice, but not in rats, a concentration-  
3 related decrease in spleen cellularity was noted. Splenic CD3+ T cells were significantly  
4 reduced at all exposure concentrations in mice at 4 weeks but not at 10 weeks; in rats,  
5 this effect was observed only at 1,000 ppm at the 4-week and 10-week time points. In  
6 both species there was a concentration-related increase in the number of splenic NK  
7 cells, but the function of these cells was not modulated by the treatment. Splenic  
8 CD45/B220+ and CD4+CD8+ cells were increased in rats after 10 weeks of treatment.  
9 Serum IgM levels were not affected in either species. Anderson et al. [2010] suggested  
10 that the observed changes of spleen cellularity, cell phenotype patterns, and humoral  
11 immune function raised concern about the potential for immunological impairment in  
12 humans from exposure to 1-BP.

13  
14 NTP [2011] conducted a series of studies to evaluate the acute, subchronic, and chronic  
15 toxic effects of 1-BP exposures in F344 rats and B6C3F1 mice. These studies included  
16 2-week (acute), 3-month (subchronic), and 2-year (chronic) bioassays designed to  
17 evaluate the toxicity of 1-BP under different exposure scenarios.

18  
19 In the first NTP study, male and female F344/N rats were exposed to airborne  
20 concentrations of 1-BP of 0, 125, 250, 500, 1,000, or 2,000 ppm for 6 hours plus T90 (12  
21 minutes)/day, 5 days/week, for 16 days. NTP [2011] reported that all animals survived  
22 the experiment except one male rat treated at 500 ppm. In comparison with controls, rats  
23 treated at 2,000 ppm had a significant reduction in body weight. Similar results were not  
24 observed in the other treatment groups. Pathological examination revealed significant  
25 increased relative kidney weights in all exposed groups of males, in addition to  
26 increased absolute and relative kidney weights among the three highest-exposure  
27 groups of females. Male rats had significantly increased absolute and relative liver  
28 weights (1,000-ppm treatment group), absolute kidney weight (1,000-ppm treatment  
29 group), and relative liver weights (500- and 2,000-ppm treatment groups). In female rats,

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1 increased absolute and relative liver weights were observed (500-, 1,000-, and 2,000-  
2 ppm treatment groups). Nasal lesions and suppurative inflammation in males exposed to  
3 500 ppm or greater, respiratory epithelial necrosis in 1,000- and 2,000-ppm-exposed  
4 males, and respiratory epithelial regeneration in 1,000- and 2,000-ppm-exposed females  
5 were reported [NTP 2011]. Histopathological examination revealed microscopic lesions  
6 in the nose indicating minimal to mild suppurative inflammation, mild epithelial necrosis,  
7 and minimal epithelial regeneration.

8

9 In the second study, NTP [2011] exposed male and female B6C3F1 mice to 1-BP vapor  
10 at concentrations of 0, 125, 250, 500, 1,000, or 2,000 ppm for 6 hours plus T90 (12  
11 minutes)/day, 5 days/week, for 17 days. Survival rates were reduced in animals treated  
12 at 500 ppm or greater. All male mice treated at 2,000 ppm died [NTP 2011]. In addition,  
13 two 2,000 ppm females, four 500 ppm males, one 1,000 ppm male, and one 1,000 ppm  
14 female died within the first 3 to 5 days of treatment. Body weights in males were  
15 reduced, at  $\geq 250$  ppm, but body weights of females did not differ from those of controls.  
16 Absolute and relative heart weights were reduced at an exposure of 1,000 ppm in males.  
17 Absolute and relative liver weights were increased at 500 and 1,000 ppm in both sexes  
18 and at 2,000 ppm in females (no male survivors in this group). In females, absolute  
19 kidney weights were increased, at  $\geq 250$  ppm, and relative kidney weights were also  
20 increased, at  $\geq 1,000$  ppm. Absolute and relative thymus weights in females were  
21 decreased with exposure, becoming statistically significant at  $\geq 1,000$  ppm.  
22 Histopathologic lesions were noted in the lung, liver, and nose of both sexes at  $\geq 500$   
23 ppm. Bronchiole necrosis was observed in the lungs of all exposed animals; the severity  
24 of this lesion was higher in the 2,000-ppm groups than in the other exposed groups. The  
25 lungs of some exposed mice displayed signs of regeneration, cytoplasmic vacuolization,  
26 and acute inflammation of the bronchiolar epithelium. Centrilobular necrosis occurred in  
27 the livers of most animals at  $\geq 500$  ppm, with centrilobular chronic inflammation and  
28 cytoplasmic vacuolization at  $\geq 1,000$  ppm. There were also sporadic nasal lesions  
29 occurring in exposed mice, with a NOAEL of 250 ppm in males and 500 ppm in females.

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1 Abnormal breathing, lethargy, and eye discharge were reported, primarily during week 1,  
2 in treatment groups exposed to 500 ppm or greater [NTP 2011].

3  
4 In the third study, NTP [2011] exposed male and female F344/N rats to 1-BP vapor at  
5 concentrations of 0, 62.5, 125, 250, 500, or 1,000 ppm for 6 hours plus T<sub>90</sub> (10  
6 minutes)/day, 5 days/week, for 14 weeks. Mean body weight was reduced in the 1,000-  
7 ppm male treatment group; similar effects were not observed in other treatment groups.  
8 At 1,000 ppm, absolute and relative liver weights were increased in both sexes, but  
9 absolute or relative spleen and kidney weights were increased only in females.  
10 Hematology endpoints were not affected by the treatment. Clinical chemistry revealed  
11 early, transient decreases in serum albumin, total protein, and alanine aminotransferase  
12 (ALT) activity, which the study authors considered secondary to hepatic enzyme  
13 induction. Pathological examination revealed evidence of mild hepatotoxicity in male rats  
14 (500 and 1,000 ppm) and female rats (1,000 ppm). Sorbitol dehydrogenase activity in  
15 blood was increased at 500 and 1,000 ppm and was considered reflective of mild liver  
16 damage. Increased incidence of cytoplasmic vacuolation of the liver in male rats  
17 (exposed to 250 ppm or greater) and in female rats (exposed to 500 ppm or greater) was  
18 reported. Hepatocyte degeneration was observed in 1,000-ppm-exposed females. Male  
19 rats (exposed to 250 ppm or greater) and female rats (exposed to 125 ppm) had  
20 significantly increased liver weight. Other gross pathological changes included increased  
21 spleen and kidney weights of female rats exposed to 1,000 ppm. Significant changes in  
22 the sperm motility and estrous cycles in exposed animals were noted; supplementary  
23 information on these effects can be located in Section 4.1.1.

24  
25 In the fourth study, NTP [2011] exposed male and female B6C3F1 mice to 1-BP vapor at  
26 concentrations of 0, 62.5, 125, 250, or 500 ppm, 6 hours plus T<sub>90</sub> (10 minutes)/day, 5  
27 days/week, for 14 weeks. A significant reduction in the survival rates of male and female  
28 mice treated with 500 ppm was reported. Survival rates and mean body weights of male  
29 and female animals in all treatment groups were similar to those observed in controls

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1 [NTP 2011]. Several organ weights were affected in a concentration-dependent manner:  
2 in males, decreased kidney weights (absolute, significant at  $\geq 250$  ppm; relative, at 500  
3 ppm) and increased liver weights (relative, significant at  $\geq 250$  ppm). In females, all  
4 affected organ weights were increased: kidney (absolute and relative, significant at 500  
5 ppm), liver (absolute, at 500 ppm; relative, at  $\geq 250$  ppm), and lung (absolute and  
6 relative, at 500 ppm). In the 500-ppm treatment groups, lethargy and abnormal breathing  
7 were observed. Pathological examination revealed increased weight of multiple organs  
8 (kidney, liver, lungs) in 500-ppm-exposed females. In the 500-ppm-exposed males,  
9 kidney weight was decreased. Nonneoplastic lesions in the nose, larynx, trachea, lung,  
10 and liver of 500-ppm-exposed males and females, in addition to lesions in the adrenal  
11 cortex of 500-ppm-exposed females were reported. Specific nonneoplastic lesions  
12 included the following:

- 13 1. Significantly increased incidence of cytoplasmic vacuolation of the respiratory  
14 epithelium in the nose of all exposed groups of males and in 125- and 250-ppm-  
15 exposed females.
- 16 2. Significantly greater incidence of respiratory epithelial hyperplasia in all exposed  
17 female groups and in 62.5- and 250-ppm-exposed males.
- 18 3. Significantly increased incidences of respiratory metaplasia of olfactory  
19 epithelium in male mice treated at 62.5 and 125 ppm and female mice treated at  
20 125 and 250 ppm.

21  
22 Other effects noted in the subchronic study in mice included treatment-related nasal  
23 lesions in mice that died before study termination [NTP 2011]. Cytoplasmic vacuolization  
24 of the respiratory epithelium was significantly more common in 500-ppm-exposed males  
25 and females than in controls. Necrosis of the respiratory epithelium was significantly  
26 increased, only in 500-ppm-exposed females. Lesions of the respiratory epithelium were  
27 typically noted in the lateral walls and turbinates (nasal conchae) of level I (immediately  
28 posterior to the upper incisor teeth), and olfactory necrosis occurred in the dorsal meatus  
29 of level II (incisive papilla anterior to the first palatal ridge) and in the dorsal meatus,

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1 septum, and turbinates of level III (area associated with the middle of the second molar  
2 teeth) . Necrotic cells were characterized by increased cytoplasmic eosinophilia with loss  
3 of cellular detail and pyknotic or fragmented nuclei. Cytoplasmic vacuolization and  
4 necrosis were also observed in the respiratory epithelium of larynx and trachea in  
5 animals of both sexes that died early. Vacuolization of the bronchiolar epithelium  
6 occurred in 500 ppm males and females and in the 250 ppm male that died early.  
7 Necrosis of the bronchiolar epithelium was seen in surviving 500 ppm females and in  
8 males that died early. Incidences of bronchiolar epithelial regeneration were observed in  
9 females at all concentrations and in males at  $\geq 250$  ppm. In liver, the incidences of  
10 necrosis, hepatocyte degeneration, chronic inflammation, and mineralization were  
11 significantly elevated in both sexes at 500 ppm. In females at 500 ppm, a significant  
12 incidence of adrenal cortex necrosis was noted. On the basis of bronchiolar epithelial  
13 regeneration, 62.5 ppm is identified as the LOAEL in female mice and 125 ppm as the  
14 NOAEL and 250 ppm as the LOAEL in males.

15  
16 In the fifth study, NTP [2011] reported the nonneoplastic effects of chronic (2-year)  
17 exposure to 1-BP. The dosing regimen for this study is described in Section 5.1. Survival  
18 rates and body weights of 1-BP-exposed mice (both sexes) were not significantly  
19 different from those of controls. Cytoplasmic vacuolization of bronchiolar epithelium  
20 occurred in all treatment groups. In male mice, the incidences of these effects along with  
21 regeneration of the bronchiolar epithelium were significantly increased in all treatment  
22 groups. An increased incidence of cytoplasmic vacuolization of respiratory epithelium in  
23 the nose was observed in males (all treatment groups) and females (125, 250 ppm). In  
24 addition, NTP [2011] reported that in all exposed female groups and in male mice  
25 treated at 62.5 and 250 ppm, there were increased incidences of respiratory epithelial  
26 hyperplasia in the dorsal meatus of the nose. There were treatment-related increased  
27 incidences of respiratory metaplasia of olfactory epithelium in male mice and exposure  
28 concentration-related increases in female mice; incidences of this lesion were  
29 significantly increased in 62.5- and 125-ppm-exposed males and in 125- and 250-ppm-

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1 exposed females. A significant increase was reported in the incidences of cytoplasmic  
2 vacuolization of respiratory epithelium in the larynx and trachea of all exposed male  
3 groups and in the trachea of 62.5- and 125-ppm-exposed females. The histological  
4 report characterized the cytoplasmic vacuolization as, “large, solitary, clear vacuoles,  
5 expanding the cytoplasm of bronchiolar epithelial cells” [NTP 2011]; the lesions were  
6 similar to those observed in the subchronic (13-week) study.

7  
8 In the final study, NTP [2011] examined the nonneoplastic endpoints in rats in a 2-year  
9 bioassay. There was a significant reduction in survival rates of rats in the 500-ppm  
10 treatment group. Only 13 of 50 male rats exposed to 500 ppm 1-BP survived for the  
11 entire duration of the study. The majority of these deaths among the 500-ppm-exposed  
12 males were attributed to various types of neoplasia, none of which were treatment  
13 related. However, 25% of the deaths were attributed to inflammation in various organs,  
14 which were microscopically shown to be suppurative inflammation, including Splendore-  
15 Hoeppli materials, which may represent the deposition of immunoglobulins, major basic  
16 proteins and debris from the host inflammatory cells and is seen amid wide areas of  
17 degeneration and necrosis [Hussein 2008]. Lesions with Splendore-Hoeppli material  
18 were not observed in control rats. It was thought that immunosuppression in 1-BP-  
19 exposed rats contributed to the development of Splendore-Hoeppli material. The  
20 presence of such material is associated with suppurative inflammation, primarily in the  
21 nose and skin, of exposed male and female rats. Splendore-Hoeppli material is often  
22 seen in association with infections caused by bacteria. NTP [2011] raised cultures from  
23 four of the five rats with Splendore-Hoeppli material and found them to be positive for  
24 *Pseudomonas aeruginosa* (*P. aeruginosa*).

25  
26 There were no significant effects on mean body weights in exposed groups compared to  
27 controls [NTP 2011]. There was an exposure-related increased incidence of soft, pale-  
28 yellow to green, variably sized nodules predominantly located in the nose and skin; the  
29 incidences of these lesions were greater in males than in females. In addition, the

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1 number of animals with multiple masses was increased in the 500-ppm-exposure  
2 groups. Numerous nonneoplastic lesions in the nose, trachea, larynx, and lungs were  
3 identified in exposed male and female rats. Female rats in every treatment group had  
4 increased incidences of suppurative chronic inflammation, chronic active inflammation,  
5 glandular hyperplasia, respiratory epithelial hyperplasia, and respiratory metaplasia of  
6 the olfactory epithelium. In the trachea, there were increased incidences of chronic  
7 active inflammation in all exposed groups of females and male rats (500 ppm); the  
8 incidence of epithelial hyperplasia was increased in female rats (500 ppm) [NTP 2011].  
9 Chronic active inflammation and squamous metaplasia were increased in the larynx in  
10 most treatment groups of female rats. In female rats treated at 500 ppm, a significant  
11 increase in the incidence of suppurative chronic inflammation in the larynx was also  
12 reported. Chronic inflammation of the lung was observed in the 500-ppm-exposed  
13 females.

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1 **TABLE 4-3 – OTHER TOXIC EFFECTS CAUSED BY INHALATION EXPOSURES TO 1-BP IN ANIMALS**

Reference	Species; strain	Number per treatment group (sex)	Treatment levels (ppm)	Treatment regimen	Results (treatment)
ClinTrials BioResearch [1997a]	Rat; SD	10 (male); 10 (female)	0, 398, 994, 1,590	6 hours/day, 5 days/week, 4 weeks (28 days)	Clinical signs of 1-BP toxicity (1,590); decreased weight gain and food consumption (1,590); decreased erythrocyte parameters (994, 1,590); changes in blood urea nitrogen, total bilirubin, phosphorus, chloride, and total protein levels (994, 1,590); histopathological changes in the CNS, urinary system, nasal cavities, sternal bone marrow, lymphoid tissues, and male reproductive system (1,590)
ClinTrials BioResearch [1997b]	Rat; SD	15 (male); 15 (female)	0, 99, 199, 398, 596	6 hours/day, 5 days/week, 13 weeks	Decreased WBC count and absolute lymphocytes in female rats (596); increased relative liver weights and absolute adrenal weights of male rats (596); no changes in absolute or relative organ weights (99, 199, 398, 596); histopathological changes in the livers of male rats (398, 596); NOEL of 199 ppm reported
Elf Atochem [1997]	Rat; Wistar	5 (male); 5 (female)	0, 6,003, 6,878, 6,978, 7,355, 8,449	4 hours	Elf Atochem [1997] exposed groups of Wistar rats via the nose only to 0, 6,003, 6,878, 6,978, 7,355, or 8,449 ppm of 1-BP for 4 hours. The authors calculated a 4-hour LC <sub>50</sub> value of 7000 ppm with a 95% confidence limit of 6,00-7,200 ppm. Prior to death, severe respiratory distress due to acute inflammatory response and alveolar edema was reported. Lung weights were increased. The cause of death was attributed to acute inflammatory response and alveolar edema.

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<b>Reference</b>	<b>Species; strain</b>	<b>Number per treatment group (sex)</b>	<b>Treatment levels (ppm)</b>	<b>Treatment regimen</b>	<b>Results (treatment)</b>
Kim et al. [1999b]	Rat; SD	5 (male); 5 (female)	0, 11,000, 13,000, 15,000, 17,000	4 hours	Increased abnormal behavior (piloerection, decreased activity, ataxia, and lacrimation) (11,000, 13,000, 15,000, 17,000); deaths of two male rats in 6 hours of treatment (15,000); death of one female 12 hours after treatment (13,000); death of four female rats 24 hours after treatment (15,000)
Kim et al. [1999b]	Rat; SD	10 (male); 10 (female)	0, 50, 300, 1,800	6 hours/day, 5 days/week, 8 weeks	No reports of death; mild ataxia, decreased activity, increased testis, ovary, liver and kidney weight, and significant changes in blood chemistry (1,800); decreased in WBC, RBC, hematocrit, and mean corpuscular volume (1800); increased mean corpuscular hemoglobin and hemoglobin concentrations (1,800); decreased urobilinogen in male rats (1,800); increased bilirubin levels in female rats (1,800)
Liu et al. [2009]	Mice; C57BL/6J, DBA/2J, BALB/cA	6 (male)	0, 50, 110, 250	8 hours/day, 7 days/week, 4 weeks	Two out of 6 BALB/cA mice treated at 250 ppm died in four days; one out of 6 C57Bl/6J mice treated at 250 ppm died in seven days; liver damage occurred in all three strains of mice in a dose-response manner; BALB/cA mice demonstrated significantly reduced CYP2E1 levels (250); total GSH decreased in BALB/cA and DBA/2J mice (50); total GSH levels decreased in all strains (250); BALB/cA identified as being the most susceptible strain of mice for liver toxicity

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<b>Reference</b>	<b>Species; strain</b>	<b>Number per treatment group (sex)</b>	<b>Treatment levels (ppm)</b>	<b>Treatment regimen</b>	<b>Results (treatment)</b>
Anderson et al. [2010]	Mice; B6C3F1 mice and F344/N rats	9 (female)	0, 125, 250, 500	6 hours plus T <sub>90</sub> (10 min)/day, day, 5 days/week, 4 or 10 weeks	Decreased body weight (125, 250, 500); decreased spleen weight in animals treated for 4 weeks (250); decreased spleen in animals treated for 10 weeks (250, 500); decreased spleen Ig M response to SRBC in animals treated for 10 weeks (125, 250, 500); significant decrease in total spleen cells and T cells in animals treated for 4 weeks (125, 250, 500)
Anderson et al. [2010]	Rats; F344/N rats	9 (female)	0, 250, 500, 1,000	6 hour plus T <sub>90</sub> (10 min)/day, day, 5 days/week, 4 or 10 weeks	Decreased spleen IgM response to SRBC in animals treated for 10 weeks (1,000 ppm); reduced total spleen cells and T cells in animals treated for 4 weeks (1,000 ppm)
NTP [2011]	Rats; F344/N	5 (male); 5 (female)	0, 125, 250, 500, 1,000, 2,000	6 hours plus T <sub>90</sub> (12 minutes)/day, 5 days/week, for 16 days	Male: Reduction in body weight (2,000); increased relative kidney weights (all treatment groups); increased absolute and relative liver weight (1,000); absolute kidney weight (1,000); relative liver weights (500, 2,000); increased absolute and relative liver weights (500, 1,000, 2,000); nasal lesions included suppurative inflammation (500, 1,000, 2,000); respiratory epithelial necrosis (1,000, 2,000); Female: Reduction in body weight (2,000); increased absolute and relative kidney weights (all treatment groups); respiratory epithelial regeneration (1,000, 2,000)

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<b>Reference</b>	<b>Species; strain</b>	<b>Number per treatment group (sex)</b>	<b>Treatment levels (ppm)</b>	<b>Treatment regimen</b>	<b>Results (treatment)</b>
NTP [2011]	Mice; B6C3F1	5 (male); 5 (female)	0, 125, 250, 500, 1,000, 2,000	6 hours plus T <sub>90</sub> (12 minutes)/day, 5 days/week, for 17 days	Male: Decreased survival rates (all treatment groups); deaths of all treated animals (2,000); reduced mean body weight gain (1,000); abnormal breathing, lethargy, and eye discharge (all treatment groups); increased liver weight (1,000); microscopic lesions in lungs, liver, and nose (500, 1,000, 2,000); Female: Decreased survival rates (all treatment groups); abnormal breathing, lethargy, and eye discharge (all treatment groups); increased kidney weights (1,000, 2,000); Lesions in lungs, liver, and nose (500, 1,000, 2,000)
NTP [2011]	Rats; F344/N	10 (male); 10 (female)	0, 62.5, 125, 250, 500, 1,000	6 hours plus T <sub>90</sub> (10 minutes)/day, 5 days/week, for 14 weeks	Male: Decreased mean body weight (1,000); mild hepatotoxicity (500, 1,000); increased incidence of cytoplasmic vacuolation of the liver (250, 500, 1,000); increased liver weight (250, 500, 1,000); Female: Mild hepatotoxicity (1,000); increased incidence of cytoplasmic vacuolization of the liver (500, 1,000); hepatocyte degeneration (1,000); increased spleen and kidney weights (1,000)
NTP [2011]	Mice; B6C3F1	10 (male); 10 (female)	0, 62.5, 125, 250, 500	6 hours plus T <sub>90</sub> (10 minutes)/day, 5 days/week, for 14 weeks	Male: Reduced survival rate (500); lethargy and abnormal breathing (500); decreased kidney weight (500); nonneoplastic lesions in the nose, larynx, trachea, lung, and liver (500); Female: Reduced survival rate (500); lethargy and abnormal breathing (500); Increased kidney, liver, and lungs weight (500); Nonneoplastic lesions in the nose, larynx, trachea, lung, liver, and adrenal cortex (500)

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<b>Reference</b>	<b>Species; strain</b>	<b>Number per treatment group (sex)</b>	<b>Treatment levels (ppm)</b>	<b>Treatment regimen</b>	<b>Results (treatment)</b>
NTP [2011]	Rat; F344/N	10 (male); 10 (female)	0, 125, 250, 500	6 hours plus T <sub>90</sub> (10 minutes)/day, 5 days/week, 105 weeks	Both sexes: Significant reduction in survival rates (500); Increased incidences of chronic active inflammation in the trachea (500) Male: Suppurative inflammation with Splendore-Hoeppli materials in numerous organs (500); Female: Chronic active inflammation and squamous metaplasia were increased in the larynx (all treatment levels); Increased in the incidences of suppurative chronic inflammation in the larynx and lung (500)
NTP [2011]	Mice; B6C3F1	10 (male); 10 (female)	0, 62.5, 125, 250	6 hours plus T <sub>90</sub> (10 minutes)/day, 5 days/week, 105 weeks	Both sexes: Cytoplasmic vacuolization of bronchiolar epithelium (all treatment levels) Male: Increased incidences of cytoplasmic vacuolization and regeneration of the bronchiolar epithelium (all treatment levels); Increased incidence of cytoplasmic vacuolization of respiratory epithelium in the nose (all treatment levels); Increased incidences of respiratory epithelial hyperplasia in the dorsal meatus of the nose (62.5, 250); Increased incidences of cytoplasmic vacuolization of respiratory epithelium in the larynx and trachea (all treatment levels); Female: Increased incidence of cytoplasmic vacuolization of respiratory epithelium in the nose (125, 250); Increased incidences of respiratory epithelial hyperplasia in the dorsal meatus of the nose (all treatment levels); Increased incidences of cytoplasmic vacuolization of respiratory epithelium in the larynx and trachea (62.5, 125)

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1  
2 **Abbreviations: 1-BP = 1-bromopropane; AFC = antigen-forming cells; CNS = central nervous system; CYP2E1 = cytochrome P-450 2E1; GSH =**  
3 **glutathione; IgM = immunoglobulin M; mg/kg = milligrams per kilogram body weight; N/A = information not available or provided; NK = natural killer**  
4 **cells; NOEL = no observed effect level; ppm = part per million; RBC = red blood cell; SD = Sprague-Dawley rats; SRBC = sheep red blood cells; WBC =**  
5 **white blood cell.**

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## 4.2 DERMAL STUDIES

This section summarizes the studies in which application of 1-BP to the skin is the primary exposure pathway. The reviewed investigations were conducted to assess the potential for systemic toxicity following dermal contact with 1-BP, in addition to determining the potential for 1-BP to act as a skin irritant, corrosive agent, and allergen.

Jacobs et al. [1987] exposed male and female New Zealand White rabbits to 1-BP for 4 hours to assess its potential to cause skin erythema and edema. Solutions of 1-BP in concentrations ranging from 5% to 50% were applied to the shaved dorsolumbar region of test animals. Evaluations of the effects of 1-BP were conducted at 1, 24, 48, and 72 hours following exposure. Skin irritation was scored with the Draize scale. A limit concentration for skin irritation, defined as the highest tested concentration for which the mean erythema (reddening of the skin) score remains below the moderate erythema classification, was reported at 50% (w/w) for 1-BP in rabbits. On the basis of the findings of this study, 1-BP is identified as a potential dermal irritant.

Elf Atochem [1995b] conducted an acute dermal toxicity test for 1-BP in SD rats. A dose of 2,000 mg/kg was administered to the shaved dorsal skin (48 cm<sup>2</sup>) and covered with a semi-occlusive patch for 24 hours. Following the exposure period, the semi-occlusive patch was removed and the clinical signs of toxicity, mortality, and body weight were monitored for 14 days. No adverse dermal reactions, abnormal behaviors, or deaths were reported. No significant changes in body weight or pathology were observed. The dermal LD<sub>50</sub> value was approximately 2,000 mg/kg.

Elf Atochem [1995c] investigated the ability of 1-BP to induce delayed hypersensitivity in Dunkin-Hartley guinea pigs following intradermal injection and dermal exposure. On day 1, test animals received 0.1 ml 1-BP at a concentration of 25% (w/w) via the intradermal route. On day 8, 0.5 ml of 1-BP was applied to the skin for 48 hours via an occlusive dressing. A dermal challenge was conducted on day 20 through the application of 0.5 ml of vehicle and 0.5 ml of 1-BP via occlusive dressing for 24 hours. Results of challenge were assessed at 24 and 48 hours. No deaths occurred. One treated animal had well-

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1 defined erythema. Histological examinations of samples that displayed skin reactions  
2 revealed lesions associated with skin irritation. No dermal reactions attributed to the  
3 sensitization potential of 1-BP were reported in this study.

4  
5 Pálovics [2004] investigated the potential for 1-BP to cause dermal irritation and edema.  
6 In accordance with guidelines of the Organization for Economic Co-operation and  
7 Development (OECD), 0.5 ml 1-BP was applied for 4 hours via a gauze patch to a 6-cm<sup>2</sup>  
8 area of shaved dorsum of male New Zealand rabbits. Residues were removed and  
9 dermal reactions were evaluated at 1, 24, 48, and 72 hours. No deaths occurred during  
10 this experiment. The authors classified the dermal reaction observed at 1 hour as a  
11 category 1 erythema (i.e., very slight or barely perceptible). In comparison, the response  
12 was classified as a category 3 erythema (i.e., moderate or severe irritation) and category  
13 1 edema (i.e., very slight or barely perceptible). Eight days after exposure to 1-BP, the  
14 skin had regenerated. No clinical symptoms of toxicity occurred during this study.

#### 15 16 4.3 SUMMARY

17 Multiple experimental studies provide evidence that 1-BP induces severe adverse health  
18 effects in animals following acute, subchronic, and chronic exposures. These effects  
19 target numerous organs, including the CNS, PNS, reproductive system, liver, skin, and  
20 blood. Developmental effects in the offspring of animals treated with 1-BP were  
21 reported.

22  
23 Adverse changes in the male reproductive system of rats have been reported [Clinical  
24 Trials BioResearch 1997a; Ichihara et al. 2001a; WIL Research Laboratories 2001;  
25 Furuhashi et al. 2006; Banu et al. 2007; Liu et al. 2009; NTP 2011]. Male rodents had  
26 significant changes in sperm morphology, count, and motility following repeated  
27 exposures to 1-BP [Ichihara et al. 2000a; WIL Research Laboratories 2001; Banu et al.  
28 2007; Liu et al. 2009; NTP 2011]. Complete or decreased fertility was noted in all male  
29 rats following repeated exposures to 750 ppm [WIL Research Laboratories 2001]. Liu et  
30 al. [2009] reported significant changes to the male reproductive system of mice following  
31 repeated exposures to 1-BP as low as 50 ppm. Female rodents had significant changes

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1 in their reproductive system, including alterations of their estrous cycle, attributed to 1-  
2 BP [NTP 2011]; other reported changes were decreased organ weight [WIL Research  
3 Laboratories 2001; NTP 2011] and infertility of all animals treated at 750 ppm 1-BP in  
4 one study [WIL Research Laboratories 2001]. Other adverse outcomes of 1-BP  
5 exposure noted in animal studies included decreased numbers of offspring, reduced  
6 offspring survival rates, and increased incidence of malformations in offspring  
7 [Huntingdon Life Sciences 2001; WIL Research Laboratories 2001; Furuhashi et al.  
8 2006].

9

10 Inhalation exposure to 1-BP has been reported to result in CNS and PNS effects.  
11 Adverse effects included movement disorders; biochemical, electrophysiological, and  
12 histopathological changes; and altered behavior [ClinTrials BioResearch 1997a; Yu et al.  
13 1998, 2001; Ohnishi et al. 1999; Fueta et al. 2000; Banu et al. 2007]. Histopathological  
14 examination of 1-BP-exposed animals revealed degeneration of nerves in the CNS and  
15 PNS; microscopic lesions in the white and grey matter; and fiber degeneration in the  
16 cervical spinal cords [ClinTrials BioResearch 1997a]. Also reported were cytoplasmic  
17 shrinkage of the Purkinje cells, branching projections, and axonal swelling in the brains  
18 of rats exposed to 1,500 ppm for 4 weeks [Ohnishi et al. 1999; Yu et al. 1998]. Similar  
19 changes were noted in the peripheral nerves in the form of ovoid- and bubble-like debris  
20 [Yu et al. 2001]. Wang et al. [2003] theorized that neurotoxicity in the CNS may be  
21 caused either by inhibition of the metabolic processes, which reduces the production of  
22 ATP needed for neural function, or by the oxidation of neurological cells associated with  
23 the reduction of GSH and presence of a reactive 1-BP metabolite. Other biochemical  
24 changes in the CNS of 1-BP-exposed rats included a reduction of GABA concentrations  
25 [Ueno et al. 2007; Suda et al. 2008].

26

27 Hepatotoxicity associated with inhalation exposure to 1-BP has been reported in multiple  
28 studies. ClinTrials BioResearch [1997b] reported increased relative liver weight and  
29 lesions in the form of vacuolation of centrolobular hepatocytes in male rats. Kim et al.  
30 [1999b] identified histopathological changes in the form of cytoplasmic vacuolation in the  
31 hepatocytes around the central veins of 1-BP-exposed animals. WIL Research

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1 Laboratories [2001] reported microscopic centrilobular hepatocellular vacuolation and  
2 increased glycogen in animals with increased liver weight. NTP [2011] reported  
3 increased liver weight and hepatotoxicity in rodents exposed to 1-BP under various  
4 conditions. Reported effects included increased incidence of cytoplasmic vacuolization  
5 of the liver in male and female rats, hepatocyte degeneration in female rats, and  
6 nonneoplastic lesions in the liver of male and female mice. In another study, Liu et al.  
7 [2009] investigated the susceptibility of three inbred strains of mice to 1-BP-mediated  
8 hepatotoxicity. Hepatocellular degeneration and focal necrosis were observed in all mice  
9 strains. In addition, significant changes in the concentration and activity of hepatic  
10 enzymes were noted. The results indicate that 1-BP is capable of inducing hepatotoxicity  
11 in all three strains of mice used in the study.

12  
13 Hematotoxicity attributed to 1-BP exposure has also been reported [ClinTrials  
14 BioResearch 1997a, 1997b; Kim et al. 1999b; Huntingdon Life Sciences 1999]. Specific  
15 effects noted in these studies included reduced erythrocyte parameters, decreased WBC  
16 counts, and changes in blood urea nitrogen, total bilirubin, phosphorus, chloride,  
17 hemoglobin, and total protein levels. Data on the immunotoxicity of 1-BP are limited. A  
18 single study provides evidence of the ability of 1-BP to induce significant immunological  
19 effects in both mice and rats following short-term whole-body inhalation exposure at  
20 occupationally relevant concentrations of 1-BP [Anderson et al. 2010].

21  
22 No in vivo data were identified for assessing the potential for 1-BP to be dermally  
23 absorbed. The literature indicates that 1-BP is not acutely toxic (LD<sub>50</sub>, >2,000 mg/kg) via  
24 the dermal route and is not a sensitizing agent [Elf Atochem 1995b, 1995c]. 1-BP was  
25 determined to cause erythema, irritation, and edema when applied to the skin of test  
26 animals and was recognized as a potential dermal irritant [Jacobs et al. 1987; Pálovics  
27 2004].

28

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1 **CHAPTER 5: STUDIES OF CANCER IN EXPERIMENTAL ANIMALS AND IN**  
2 **VITRO ASSAYS**

3 **5.1 CANCER STUDIES IN EXPERIMENTAL ANIMALS**

4 NTP [2011] conducted a 2-year (105-week) bioassay to assess the potential of 1-BP to  
5 induce cancer. Male and female F344/N rats and B6C3F1 mice were exposed to 1-BP  
6 vapors for 6 hours plus T<sub>90</sub> (10 minutes)/day, 5 days/week, for up to 105 weeks. Rats (n  
7 = 50/treatment group) were exposed to airborne concentrations of 0, 125, 250, or 500  
8 ppm; mice (n = 50/treatment group) were treated at 0, 62.5, 125, or 250 ppm. All  
9 exposures were whole body and lasted 6 hours/day, 5 days/week, for 105 weeks.  
10 Animals were observed twice daily and were weighed weekly for the first 13 weeks,  
11 every 4 weeks through week 93, every 2 weeks thereafter, and at study termination.  
12 Clinical observations were recorded every 4 weeks through week 93, every 2 weeks  
13 thereafter, and at study termination. The health effects observed during the 2-year NTP  
14 bioassay that relate to non-cancer endpoints are discussed in Chapter 4.

15  
16 Increased incidence of neoplastic lesions was reported in both rats and mice. Neoplastic  
17 lesions attributed to exposure to 1-BP were observed in both male and female rats in all  
18 treatment levels. Increased incidence of adenoma of the large intestine, more  
19 specifically in the colon or rectum, occurred in female rats treated at 500 ppm. In males  
20 exposed to 250 ppm 1-BP, increased incidence of adenomas in the large intestine were  
21 observed in comparison with historical control ranges for inhalation studies and all routes  
22 [NTP 2011]. Increased incidences of numerous types of skin cancer, such as  
23 keratoacanthoma, basal cell adenoma, basal cell carcinoma, and squamous cell  
24 carcinoma, were observed in male (250 and 500 ppm) and female (500 ppm) rats in  
25 comparison with historical controls. Other forms of neoplastic lesions noted in male rats  
26 included mesothelioma (500 ppm), pancreatic islet adenoma (all treatment groups), and  
27 pancreatic islet adenoma and carcinoma (125 and 250 ppm). Table 5-1 provides a  
28 detailed summary of data pertaining to neoplastic lesions in rats.

29  
30

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1 **TABLE 5-1 – NEOPLASIA IN F344 RATS EXPOSED TO 1-BP BY INHALATION FOR 2 YEARS**

Malignancy	Exposure concentration (ppm) <sup>a</sup>			
	0 (control)	125	250	500
<i>Males</i>				
Keratoacanthoma or squamous cell carcinoma <sup>b</sup>	1/50 (2.4%)	4/50 (9.8%)	6/50 (15.4%) <sup>c</sup>	8/50 (21.4%) <sup>c</sup>
Keratoacanthoma, basal cell adenoma or carcinoma, or squamous cell carcinoma <sup>b</sup>	1/50 (2.4%)	7/50 (17.0%) <sup>c</sup>	9/50 (22.6%) <sup>c</sup>	10/50 (26.7%) <sup>c</sup>
Malignant mesothelioma	0/50 (0.0%)	2/50 (4.9%)	2/50 (5.2%)	4/50 (10.8%) <sup>c</sup>
Large intestine adenoma	0/50 (0.0%)	0/50 (0.0%)	2/50 (5.3%)	1/50 (2.8%)
Pancreatic islet adenoma and carcinoma <sup>d</sup>	3/50 (7.2%)	10/50 (24.2%) <sup>c</sup>	9/50 (23.1%) <sup>c</sup>	8/50 (22.2%) <sup>c</sup>
<i>Females</i>				
Large intestine adenoma <sup>b</sup>	0/50 (0.0%)	1/50 (2.3%)	2/50 (4.7%)	5/50 (13.3%) <sup>c</sup>
Keratoacanthoma, basal cell adenoma or carcinoma, squamous cell papilloma <sup>b</sup>	1/50 (2.2%)	1/50 (2.3%)	1/50 (2.4%)	4/50 (10.6%)

2 <sup>a</sup>Incidence (in parentheses: rate adjusted for intercurrent mortality).

3 <sup>b</sup>Statistically significant positive trend,  $p < 0.05$  (poly-3 test).

4 <sup>c</sup>Significantly different from control,  $p < 0.05$ .

5 <sup>d</sup>Statistically significant negative trend,  $p < 0.05$  (poly-3 test).

6 Source: NTP [2011].

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1 Neoplastic lesions attributed to exposure to 1-BP were observed in female mice at all  
2 treatment levels. Increased incidences of alveolar/bronchiolar adenoma and  
3 alveolar/bronchiolar carcinoma were reported. In the 250-ppm treatment group, a  
4 significant difference in the incidence of alveolar/bronchiolar adenoma was observed. A  
5 significant increase in the incidence of alveolar/bronchiolar carcinoma occurred in the  
6 lowest treatment group (62.5 ppm). The incidence of alveolar/bronchiolar adenoma and  
7 carcinoma (combined) was significantly increased in all treatment groups. No neoplastic  
8 lesions were observed in male mice treated at any concentration. Table 5-2 provides a  
9 detailed summary of data pertaining to neoplastic lesions in mice.

10  
11 Exposure to 1-BP induced tumors in both rats and mice, but differences were noted  
12 between the sexes [NTP 2011]. Tumors of the large intestine occurred in both male and  
13 female rats, although the incidence of intestinal tumors was higher in females. In  
14 contrast, skin tumors were only observed in male rats. Multiple forms of malignant  
15 tumors of the lungs were reported for female mice but not for male mice. The available  
16 data are insufficient for determining a plausible theory about the role of sex in the  
17 carcinogenic potential of 1-BP.

18  
19 NTP [2011] stated that the results of the 2-year bioassay provide evidence of the  
20 carcinogenic activity of 1-BP in F344/N rats and B6C3F1 mice. The specific conclusions  
21 provided by NTP [2011] included the following.

- 22 • *There is some evidence of the carcinogenic activity of BP in male F344/N rats,*  
23 *on the basis of the occurrence of rare adenomas of the large intestine and*  
24 *increased incidences of neoplasms of the skin. Increased incidence of malignant*  
25 *mesothelioma and pancreatic islet adenoma may also have been related to 1-BP*  
26 *exposure.*
- 27 • *There is clear evidence of carcinogenic activity of 1-BP in female F344/N rats, on*  
28 *the basis of increased incidence of adenoma in the large intestine. Increased*  
29 *incidence of neoplasms of the skin may also have been related to 1-BP*  
30 *exposure.*

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- 1       • *There is no evidence of carcinogenic activity* of 1-BP in male B6C3F1 mice  
2       exposed to concentrations of 62.5, 125, or 250 ppm 1-BP.
- 3       • *There is clear evidence of the carcinogenic activity* of 1-BP in female B6C3F1  
4       mice, on the basis of increased incidences of alveolar/bronchiolar neoplasms.

5 In 2014, NTP published a report entitled *Monograph on 1-Bromopropane*, as part of the  
6 *Report on Carcinogens*. The monograph classified 1-BP as *reasonably anticipated to be*  
7 *a human carcinogen*. NTP [2014] based this classification on "...sufficient evidence of  
8 carcinogenicity from studies in experimental animals." These studies showed that  
9 exposure to 1-BP caused tumors at several tissue sites in rats and mice. 1-BP, either  
10 directly or via reactive metabolites, causes molecular alterations that typically are  
11 associated with carcinogenesis, including genotoxicity, oxidative stress, and glutathione  
12 depletion. These alterations, observed mainly *in vitro* and in toxicity studies in rodents,  
13 are relevant to possible mechanisms of human carcinogenicity and support the  
14 relevance of the cancer studies in experimental animals to cancer in humans.

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1 **TABLE 5-2 – INCIDENCES OF PULMONARY NEOPLASIA IN FEMALE B6C3F1 MICE EXPOSED TO 1-BP BY INHALATION FOR 2 YEARS**

Malignancy	Exposure concentration (ppm) <sup>a</sup>			
	0 (control)	62.5	125	250
Alveolar/bronchiolar adenoma <sup>b</sup>	1/50 (2.2%)	6/50 (12.8%)	4/50 (8.9%)	10/50 (20.8%) <sup>c</sup>
Alveolar/bronchiolar carcinoma	0/50 (0.0%)	7/50 (14.9%) <sup>c</sup>	5/50 (11.1%) <sup>c</sup>	4/50 (8.5%)
Alveolar/bronchiolar adenoma or carcinoma <sup>b</sup>	1/50 (2.2%)	9/50 (19.2%) <sup>c</sup>	8/50 (17.8%) <sup>c</sup>	14/50 (29.2%) <sup>c</sup>

2 <sup>a</sup>Incidence (in parentheses: rate adjusted for intercurrent mortality).

3 <sup>b</sup>Statistically significant positive trend,  $p < 0.05$  (poly-3 test).

4 <sup>c</sup>Significantly different from control,  $p < 0.05$ .

5 Source: NTP [2009].

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## 5.2 GENOTOXICITY STUDIES

The mutagenic potential of 1-BP has been evaluated in bacterial and mammalian cells in vitro and in rodents in vivo. Its clastogenic activity has been studied in animals in vivo, in occupationally exposed humans in vivo, and in human blood cells in vitro. The following section summarizes data related to the mutagenic potential of 1-BP.

The genotoxic potential of 1-BP has been evaluated in several short-term assays. The database of genotoxicity studies includes mutation studies in bacteria and mammalian cells (Section 5.2.1.1a and Section 5.2.1.1b); DNA damage studies using leukocytes and 1-BP-exposed workers (Section 5.2.1.2); micronuclei induction studies in rodents (Section 5.2.1.3); dominant lethal mutation studies in rodents (Section 5.2.1.4); *In vitro*, *in vivo* and epidemiology genotoxicity studies are also available on some metabolites of 1-BP (Section 5.2.1.5). The following section summarizes each study. An overall summary of the genotoxicity of 1-bromopropane is presented in section 5.3. and in Table 5-1.

### 5.2.1.1 Mutation

#### 5.2.1.1a Reverse mutation in prokaryotic organisms (bacteria)

Barber et al. [1981] evaluated the mutagenic potential of 1-BP (99.85% purity) using *Salmonella typhimurium* (*S. typhimurium*) strains TA98, TA100, TA1535, TA1537, and TA1538, with and without supernatant fraction 9 (S9) metabolic activation in a closed chamber specifically designed for testing volatile substances. Five concentrations of 1-BP, ranging from 1.09 to 20.3 micromoles ( $\mu\text{mol}$ )/plate (equivalent to 135–2497  $\mu\text{g}$ /plate), were tested in five replicates. In the *S. typhimurium* strains TA100 and TA1535, 1-BP induced increased mutation frequency with and without S9 metabolic activation; the lowest effective concentration was 4.9  $\mu\text{mol}$ . No increased mutation frequency was observed in the other strains of *S. typhimurium*. Barber et al. [1981] concluded that 1-BP is a direct-acting mutagen in *S. typhimurium*. NTP [2003b] pointed out that positive responses observed in TA100 and TA1535 have intrinsic GST activity,

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1 suggesting that a GSH metabolite of 1-BP might be responsible for the mutagenic  
2 activity.

3  
4 In another study using *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and  
5 TA1538, the mutagenicity of 1-BP (>99% purity) was assessed with and without S9  
6 metabolic activation in a closed stainless steel chambers [Elf Atochem 1994].  
7 Concentrations of 1-BP ranging from 0.813 to 8.13  $\mu\text{mol}$  /plate (equivalent to 100–  
8 10,000  $\mu\text{g}$ /plate) were tested in three replicates. Cytotoxicity was reported at the highest  
9 concentration (8.13  $\mu\text{mol}$  /plate). The findings of this study provided no evidence of  
10 mutagenicity in any strain of *S. typhimurium*, either with or without S9.

11  
12 Kim et al. [1998] used *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and  
13 *Escherichia coli* (*E. coli*) strain WP2uvrA with and without S9 metabolic activation to  
14 investigate the mutagenic potential of 1-BP (mentioned as a 1<sup>st</sup> class reagent grade and  
15 no actual purity was mentioned). They tested five concentrations, ranging from 2.54 to  
16 40.7  $\mu\text{mol}$  /plate (equivalent to 313–5,000  $\mu\text{g}$ /plate) in duplicates. Kim et al. [1998]  
17 observed no increases in the frequency of mutations at any concentration in 1-BP  
18 exposed strains of *S. typhimurium* or *E. coli*. No cytotoxicity information was provided by  
19 the study authors. In addition, no information was provided about the test system (open  
20 vs closed) used. Therefore, this study has insufficient information to evaluate the  
21 mutagenicity.

22  
23 NTP [2011] reviewed the bacterial mutagenicity assays from two independent contract  
24 labs that used *S. typhimurium* strains TA97, TA98, TA100, and TA1535, and *E.coli* strain  
25 WP2 uvrA/pKM101 with and without S9 metabolic activation to assess the mutagenic  
26 potential of 1-BP. Five concentrations of 1-BP (~99% purity), ranging from 0.268 to 8.13  
27  $\mu\text{mol}$  /plate (33–10,000  $\mu\text{g}$ /plate), were tested. NTP [2011] reported negative results with  
28 and without metabolic activation in both *S. typhimurium* and *E.coli* strains. These two  
29 studies were conducted in an open system, so the actual concentration of 1-BP that the  
30 bacteria exposed to could be lower because of the volatile nature of 1-BP.

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1 5.2.1.1b Forward mutation in eukaryotic organisms (mammalian cells)

2 Elf Atochem [1996] evaluated the potential for mutagenicity of 1-BP in L5178Y mouse  
3 lymphoma cells with and without S9 metabolic activation. The cells were treated with  
4 concentrations of 1-BP (99.3% purity) ranging from 125 to 1,500 µg/L in the absence of  
5 metabolic activation (S9) or concentrations of 1-BP ranging from 125 to 2,500 µg /L with  
6 metabolic activation (S9). The 2,500 µg /L concentration produced 100% cytolethality, in  
7 comparison with the 40% to 90% cytolethality produced by the 2,000- µg /L  
8 concentration. The authors reported a reproducible increase in mutation frequency in  
9 cells treated with 1,000–1,500 µg /L without S9 activation. Conflicting results were  
10 reported with regard to S9-activated cells: no increase in mutation was observed in the  
11 first experiment, whereas a second experiment resulted in increased mutation frequency  
12 at 1,500–2,000 µg /L.

13  
14 5.2.1.2 DNA damage

15 Toraason et al. [2006] evaluated deoxyribonucleic acid (DNA) damage in human  
16 leukocytes. In the first experiment, leukocytes collected from human volunteers were  
17 treated with 1-BP in solution at concentrations of 0, 0.01, 0.1 or 1mM. 1-BP induced  
18 significant DNA damage was detected with the comet assay, although only at the  
19 highest concentration used (1 mM). Significant degrees of apoptosis at ≥0.01 mM in the  
20 leukocytes exposed to 1-BP was also reported. In the second experiment, Toraason et  
21 al. [2006] investigated DNA damaged in 64 1-BP exposed workers employed at two  
22 different foam cushion manufacturing facilities. Additional information on these facilities  
23 can be located in NIOSH [2002b, 2003b]. The surveyed populations were categorized  
24 for gender, age, smoking habit, and the glutathione-S-transferases M1 and T1 (GSTM1)  
25 or glutathione-S-transferase T1 (GSTT1) genotype. 1-BP exposure was assessed with  
26 personal breathing zone air monitors. Blood and urine samples were collected at the  
27 beginning and end of each workweek and were assayed for bromide content. DNA  
28 damage in peripheral leukocytes was estimated with the comet assay. Apoptosis was  
29 tested with a specific gel staining procedure. GSTM1 and GSTT1 genotypes were  
30 evaluated in whole-blood DNA by PCR. Although the workplace concentrations of 1-BP  
31 were elevated and urinary Br<sup>-</sup> levels reflected exposure to the chemical, no indication of

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1 DNA damage was observed in peripheral leukocytes. However, by the end of a  
2 workweek, the tail moments in the comet assay were consistently (but not significantly)  
3 higher in GSTM1-positive workers than in GSTM1-null genotypes. Toraason et al.[2006]  
4 speculated that 1-BP-induced GSH depletion in GSTM1-positive workers made them  
5 more susceptible to DNA damage from oxidative stressors other than 1-BP.

#### 6 7 5.2.1.3 Micronuclei Induction

8  
9 Elf Atochem [1995a] investigated the clastogenic potential of 1-BP via a micronucleus  
10 study in bone marrow of mice. Eight male and female Swiss OF1 mice received two  
11 interpretational injections of 1-BP (99.3% purity) in corn oil. The authors reported that  
12 numerous dose levels were attempted, ranging from 100 to 800 mg/kg 1-BP. Analysis  
13 was conducted only on males exposed to 600 mg/kg and females exposed to 800 mg/kg  
14 because the polychromatic/normochromatic erythrocyte ratio in controls from other  
15 doses (100, 400, mg/kg) were outside of the historical control range and the test was  
16 considered invalid. The higher-level treatment (800 mg/kg) resulted in reduced survival  
17 rates in male mice. [Elf Atochem 1995a; NTP 2003b] reported no increase in bone  
18 marrow micronucleated polychromatic erythrocytes.

19  
20 Kim et al (1998) exposed the whole body of Sprague-Dawley rats (10/sex/group) to 1-BP  
21 vapor (mentioned as a 1<sup>st</sup> class reagent grade and no actual purity was mentioned) at  
22 concentrations of 0, 50, 300, 1,800 ppm 6 hr/day for 5 days/week for 8 weeks. The authors  
23 reported no increase in bone marrow micronucleated polychromatic erythrocytes.

#### 24 25 5.2.1.4 Dominant Lethal Mutation

26  
27 Two studies were identified that investigated the potential of 1-BP to induce dominant  
28 lethality in rodents. In the first study, Saito-Suzuki et al. [1982] gavaged male SD rats  
29 with a solution of 1-BP (> 98% purity) in olive oil equal to 400 mg/kg-day for 5 days.  
30 Following treatment, 15 exposed male rats were mated with nonexposed female rats [(1  
31 female/ week/male) for 8 weeks]] and examined vital status of fetuses 13-14 days after  
32 mating. The authors reported that 1-BP treatment had no effect on male fertility and had

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1 no effect on the dominant lethal mutation index (live embryos per test female/live  
2 embryos per control females).. NTP [2003b] stated that this study "... eliminates 1-BP as  
3 a germ cell mutagen and thereby rules out a mechanism of action exhibited by related  
4 halogenated propanes."

5  
6 In the second study, Yu et al. [2008] treated male ICR mice orally with doses of 1-BP  
7 (99% purity) in corn oil at 300 or 600 mg/kg-day for 10 days. Following treatment, males  
8 were mated with untreated females [20 males/exposure group mated with 40 unexposed  
9 females (2 females/week/ male) for 6 weeks] and vital status of fetuses were examined  
10 at 15 to 17 days gestation. The authors observed no treatment-related changes in  
11 clinical signs, gross findings, mating index, or male fertility. Yu et al. [2008] concluded  
12 that 1-BP did not induce dominant lethality in mice.

#### 13 14 5.2.1.5 Genotoxic effects of 1-bromopropane metabolites

15  
16 The genotoxic effects of several known or postulated metabolites of 1-BP have been  
17 evaluated in numerous *in vitro* and *in vivo* studies. Two reviews by the International  
18 Agency for Research on Cancer (IARC) provided most of the information for glycidol  
19 [IARC 2000] and propylene oxide [IARC, 1994] and primary studies were used to update  
20 or supplement this information (see IARC, 1994; Appendix D, Table D-5). Both glycidol  
21 (known metabolite in rats) and propylene oxide (postulated metabolite) are mutagenic in  
22 bacteria, yeast, *Drosophila*, and mammalian cells; they are direct-acting mutagens, as  
23 the addition of metabolic activation did not change the response. Both metabolites have  
24 been shown to form DNA adducts, and both induce DNA damage and chromosomal  
25 damage *in vitro*, *in vivo* and human cells. Available *in vivo* test results for glycidol  
26 indicate that it induces micronucleus formation but not chromosomal aberrations (CA) in  
27 the mouse. Studies of propylene oxide for chromosomal damage reported positive  
28 responses in mouse bone marrow for micronucleus induction and CA tests, as well as  
29 DNA damage in the sister chromatid exchange (SCE) assay, but results with monkey  
30 lymphocytes for both CA and SCE were negative. In occupationally exposed propylene  
31 oxide workers, DNA damage was induced in the SCE assay, and both DNA and  
32 hemoglobin (protein) adducts were formed. Propylene oxide has also been shown to

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1 bind to DNA in rodents and to hemoglobin in rodents, dogs, and monkeys. Other 1-BP  
2 metabolites have been shown to be direct-acting mutagens and to induce DNA damage  
3 in bacteria. Bromohydrin and 3-bromo-1-propanol were mutagenic in the *S. typhimurium*  
4 reversion assay, and 3-bromo-1-propanol and 1-bromo-2-propanol induced DNA  
5 damage in *E. coli*.

### 6 5.3 SUMMARY

7 Available data indicates that 1-BP exposure is associated with mutagenicity and DNA  
8 damage in *in vitro* studies [Barber et al. 1981; Toraason et al. 2006], and DNA damage  
9 in exposed workers [Toraason et al. 2006]. 1-BP did not induce micronuclei induction  
10 and dominant lethal mutations in *in vivo* studies [Kim et al.1998; Elf Atochem 1995a;  
11 Saito-Suzuki et al., 1982; Yu et al. 2008]. Several metabolites of 1-BP have been shown  
12 to increase DNA adducts, mutations, DNA damage, and chromosomal damage in *in*  
13 *vitro*, *in vivo*, and epidemiology studies [IARC 1994, 2000]. NTP [2013] critically  
14 reviewed all available 1-BP genotoxic data and summarized that the available data  
15 provided some support that 1-BP is genotoxic. Although the genotoxicity results are  
16 mixed, based on the overall weight of evidence, 1-BP is considered to be a potential  
17 genotoxicant. Table 5-1 provides a summary of available genotoxicity data for 1-BP and  
18 its metabolites.

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1 **TABLE 5-1 SUMMARY OF 1-BROMOPROPANE AND ITS METABOLITE GENOTOXICITY**  
 2 **INFORMATION**

3

Endpoint	<i>In vitro</i>	<i>In vivo</i> (mammals)	Humans (epidemiology studies)
1-bromopropane			
Mutation in prokaryotic organisms (bacteria)	±	NT	NT
Mutation in eukaryotic organisms (mammalian cells)	+	NT	NT
DNA damage	+	-	+
Micronuclei Induction	NT	-	NT
Dominant lethal mutation	NT	-	NT
1-bromopropane metabolites			
Mutation in prokaryotic organisms (bacteria)	+	NT	NT
Mutation in eukaryotic organisms (mammalian cells)	+	NT	NT
DNA damage	+	NT	+
DNA adducts	+	+	+
Chromosomal damage	+	+	NT

4 + = positive, ± = both positive and negative, - = negative.  
 5 NT = not tested.

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## 1 CHAPTER 6: MODE OF ACTION

### 2 6.1 INTRODUCTION

3 The specific mechanistic process of 1-BP-induced toxicity is unknown. The limited  
4 availability of mechanistic data on 1-BP inhibits characterization of the primary biological  
5 events and mechanisms associated with the onset of 1-BP-induced adverse health  
6 outcomes, including cancers and non-cancer endpoints. The absence of such data  
7 prevents determining the mechanism of action or molecular details of key events in the  
8 induction of cancer or other health endpoints [EPA 2003b]. However, an understanding  
9 of the mechanistic nature of 1-BP is possible through the characterization of the mode of  
10 action (MOA) for specified health endpoints. The MOA is defined as the key events and  
11 processes, starting with the interaction of an agent with the cell through functional and  
12 anatomical changes, resulting in cancer or other health endpoints [EPA 2003b].

13 Understanding the MOA for a chemical requires less detail than mechanism of action for  
14 the induction of cancer or other health endpoints.

15  
16 The following sections provide a basic conceptual description of potential MOAs for the  
17 following health endpoints: neurotoxicity, hepatotoxicity, immunotoxicity, reproductive  
18 toxicity, and cancers. 1-BP has been documented to cause these effects in exposed  
19 humans, animals, or both.

### 21 6.2 NEUROTOXICITY

22 The cellular mechanisms associated with 1-BP-induced neurotoxicity remain unknown,  
23 despite evidence of severe effects in the CNS and PNS [Ichiyama et al. 2012]. Wang et  
24 al. [2002, 2003] examined the role of GSH depletion in 1-BP-induced CNS toxicity in the  
25 rat. Reduced levels of creatinine kinase and neuron-specific gamma-enolase and  
26 increased oxidative stress are associated with GSH depletion. Wang et al. [2002, 2003]  
27 suggested that GSH depletion and changes in sulfhydryl-containing proteins might be  
28 the underlying mechanism of 1-BP neurotoxicity, but no studies to directly link  
29 neurotoxicity to GSH depletion have been performed. Depletion of GSH is associated

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1 with oxidative stress, which has been documented in the nervous system of animals  
2 treated with 1-BP [Huang et al. 2011, 2012; Subramanian et al. 2012]. Although the  
3 data are limited, it appears that depletion of GSH and oxidative stress represent one  
4 potential MOA for the neurotoxic effects of 1-BP.

5  
6 Another potential MOA for the neurological effects associated with 1-BP involves GABA  
7 inhibition. GABA is a major neurotransmitter in mammals that is multifunctional in the  
8 CNS, PNS, and nonneuronal tissues [Watanabe et al. 2002]. Among these functions,  
9 GABA regulates neuronal excitability and inhibition. Numerous studies in rodents provide  
10 evidence that 1-BP exposures influence GABA levels and activities [Fueta et al. 2002b,  
11 2004; Ueno et al. 2007; Suda et al. 2008; Mohideen et al. 2009; Huang et al. 2011], but  
12 the available data are insufficient to conclusively determine the role of GABA dysfunction  
13 in the onset of 1-BP-induced neurotoxicity.

### 14 15 6.3 HEPATOTOXICITY

16 Lee et al. [2007] examined the role of GSH depletion in 1-BP-induced hepatotoxicity in  
17 the mouse. The authors suggested that 1-BP hepatotoxicity could be due to the  
18 formation of GSH conjugates; however, no direct test of this hypothesis was performed.  
19 Lee et al. [2010] noted that 1-BP hepatotoxicity could be prevented by SKF-525A  
20 pretreatment, which suggests that cytochrome P-450-mediated metabolism may play a  
21 role in the development of hepatotoxicity. Lee et al. [2007] suggested that both the  
22 formation of reactive metabolites by P-450 enzymes and depletion of GSH may  
23 contribute to 1-BP-induced hepatotoxicity.

### 24 25 6.4 IMMUNOTOXICITY

26 In addition to hepatotoxicity, Lee et al. [2007] examined the role of GSH depletion in 1-  
27 BP-induced immunotoxicity in the mouse. The authors noted that oral exposure to 1-BP  
28 significantly suppressed the antibody response to a T-dependent antigen and reduced  
29 the production of splenic intracellular IL-2 in response to Con-A. The authors suggested  
30 that decreased GSH may play a role in 1-BP-induced immunotoxicity.

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## 6.5 REPRODUCTIVE TOXICITY

Garner et al. [2007] reported that CYP2E1-knockout mice are resistant to the spermatotoxicity of 1-BP. A comparative toxicity study in three strains of mice provided supplemental evidence of CYP2E1 and depleted GSH levels contributing to sperm abnormalities [Liu et al. 2009]. Although limited, the available data indicate that metabolic activation of CYP2E1 and depletion of GSH contribute to the reproductive toxicity of 1-BP in male rodents. The available data are insufficient to characterize potential MOAs for reproductive toxicity in female animals or humans exposed to 1-BP.

## 6.6 CARCINOGENICITY

The various genotoxicity studies summarized in Chapter 5 provide conflicting findings. Overall, the results are negative for genotoxicity, but some positive genotoxic data in *Salmonella* test strains that possess intrinsic GST activity have been reported [Barber et al. 1981]. However, later studies with the same *Salmonella* test strains have been negative [Elf Atochem 1994; NTP 2011]. Barber et al. [1981] suggest that 1-BP mutagenicity can be mediated by GSH conjugation; however, the failure of later studies to reproduce the mutagenicity casts doubt on this interpretation. Given the mixed and inconsistent results of 1-BP genotoxicity studies, no conclusions can be drawn regarding the possible role of genotoxicity in the induction of tumors by 1-BP in animals [NTP 2011].

NTP [2014] theorized numerous MOAs to explain the carcinogenicity of 1-BP, including oxidative stress; immunosuppression; chronic inflammation; GABA dysfunction; and bioactive metabolites. Morgan et al. [2011] reported that oxidative stress caused by cellular GSH depletion could contribute to the carcinogenicity of 1-BP. No studies demonstrating the possible relationship between GSH levels and oxidative stress in onset of 1-BP-induced cancers were identified. However, several published studies provide evidence of GSH depletion and oxidative stress in animals exposed to varying concentrations of 1-BP [Wang et al. 2002, 2003; Garner et al. 2007; Liu et al. 2009; Huang et al. 2011, 2012; Subramanian et al. 2012].. The second MOA focuses on immunosuppression, including changes in the number and type of T-cells, which has

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1 been documented in animals exposed to 1-BP [Anderson et al. 2010, Lee et al. 2007a,  
2 Lee et al. 2007b]. NTP [2011] documented increased incidences of chronic respiratory  
3 tract inflammation in rats and increased incidences of cytoplasmic vacuolization in the  
4 various sections of the respiratory tract in mice. NTP [2014] noted that local  
5 inflammation is a potential MOA for 1-BP-induced cancers, although no data are  
6 available that directly link these effects to onset of cancer. As previously noted, 1-BP has  
7 been demonstrated to cause GABA dysfunction. NTP [2014] reported that GABA is a  
8 strong inhibitor of cell proliferation and that the modified GABA-ergic signaling in tumor  
9 cells may lead to abnormal cell proliferation. Another potential MOA involves the  
10 metabolism of 1-BP into bioactive metabolites that are responsible for toxicity. NTP  
11 [2014] reported multiple metabolites associated with 1-BP that have been identified as  
12 *reasonably anticipated to be a human carcinogen*.

## 13 14 6.7 SUMMARY

15 The objective of an analysis of MOA is to identify the key events or processes that result  
16 in toxicity, with the goal of informing the modeling approaches in the dose-response  
17 analysis. The available data allow for the development of multiple potential MOAs for  
18 both non-cancer health endpoints and cancers associated with 1-BP exposures.  
19 However, they are insufficient to identify the key biological events that result in the onset  
20 of these adverse outcomes. Potential MOAs associated with the onset of non-cancer  
21 health endpoints include oxidative stress from GSH depletion and GABA dysfunction.  
22 NTP [2014] theorized several MOAs that may contribute to the onset of adverse effects  
23 associated with exposures to 1-BP including oxidative stress, immunosuppression,  
24 chronic inflammation, GABA dysfunction, and bioactive metabolites. The specific MOA of  
25 1-BP-induced toxicity is still unknown; further research is needed.

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## 1 CHAPTER 7: QUANTITATIVE RISK ASSESSMENT BASED ON CANCER 2 DATA IN ANIMALS

3 NIOSH used quantitative risk-assessment techniques to estimate the risk of developing  
4 adverse health effects due to occupational exposure to 1-BP. These estimates are  
5 based on mathematical models, known as exposure-response models, that describe the  
6 relationship between exposure to 1-BP and the development of any of several adverse  
7 health effects in animals. One approach that is used, known as the benchmark dose,  
8 estimates the dose or concentration that produces a specified percentage of adverse  
9 effects in exposed animals. The process of extrapolating exposure-response models  
10 from experimental animals to humans requires making assumptions about the precise  
11 mathematical form of the exposure-response relationship. These mathematical models  
12 are used to develop a range of risk estimates associated with a range of levels of  
13 occupational exposure to 1-BP.

14  
15 NIOSH used the best exposure-response data available as the basis for the  
16 development of the NIOSH REL. Available human data for 1-BP are observational  
17 studies and occupational exposure assessments that are inadequate for use in  
18 quantitative risk assessment (described in Chapter 2). Several animal toxicity studies  
19 have been identified with dose-response data for 1-BP that are suitable for extrapolation  
20 to human equivalent concentrations that allow determination of a REL, for both cancer  
21 and non-cancer endpoints. This chapter provides a description of the animal tumor data,  
22 the methods NIOSH applied for dose-response analysis, the results from the cancer risk  
23 assessment, and a comparison to the risk assessment results for non-cancer endpoints.

### 24 7.1 DATA SOURCES

25 NIOSH identified both cancer and non-cancer data that provide dose-response  
26 information suitable for quantitative risk assessment for occupational exposures to 1-BP.  
27 This chapter presents the best available animal tumor data [NTP 2011] and a  
28 quantitative risk assessment based on these data. For tumor endpoints, data were  
29 identified for alveolar/bronchiolar adenomas and carcinomas in female mice, adenomas  
30 of the large intestine in female rats, and keratoacanthoma/squamous cell carcinoma of  
31 the skin in male rats [NTP 2011]. The tumor data are summarized in Table 7-1.

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2 The data for non-cancer endpoints, BMD modeling for those endpoints, and  
3 extrapolation to occupational exposures are presented in Appendix B. Because the non-  
4 cancer risk assessment is discussed in detail in Appendix B, only summary results are  
5 presented here for comparison to the cancer modeling results.

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1 **TABLE 7-1 – SUMMARY OF 1-BP INHALATION DATA FROM NTP 2-YEAR BIOASSAY\* THAT PROVIDE DOSE-RESPONSE INFORMATION**  
 2 **SUITABLE FOR BENCHMARK CONCENTRATION ESTIMATION: DICHOTOMOUS ENDPOINTS**

<b>Health End (sex; species)</b>	<b>Exposure Concentration (ppm)</b>	<b>Sample size</b>	<b>Number of tumors</b>
Pulmonary adenomas + carcinomas (female; B6C3F1 mice)	0	50	1
	62.5	50	9
	125	50	8
	250	50	14
Large intestine adenomas (female; F344 rats)	0	50	0
	125	50	1
	250	50	2
	500	50	5
Dermal keratoacanthoma + squamous cell carcinoma (male; F344 rats)	ppm	Number of rats	No. of tumors
	0	50	1
	125	50	4
	250	50	6
	500	50	8

3 **Abbreviations: ppm = parts per million; SD = standard deviation.**

4 \*Source: NTP [2011].

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1 7.2 METHODS

2 7.2.1 Dose-response Modeling

3 The NIOSH quantitative risk assessment for 1-BP was conducted using benchmark  
4 concentration modeling. Dose-response modeling was done and benchmark  
5 concentrations were estimated with the U.S. EPA BMD software suite, version 2.12  
6 [EPA 2010]. The BMD (or in this case, the benchmark concentration) has been defined  
7 as "... a statistical lower confidence limit on the dose corresponding to a small increase  
8 in effect over the background level" [Crump 1984]. In current practice, and as used in  
9 this document, the BMC refers to the maximum likelihood estimate of the target  
10 response rate from the model; and the benchmark concentration lower-bound  
11 confidence limit (BMCL) is the 95% lower confidence limit of the BMC [Gaylor et al.  
12 1998], which is equivalent to the BMD as originally defined by Crump [1984].

13  
14 Benchmark dose methods used for modeling non-cancer endpoints are discussed in  
15 detail in Appendix B. For tumor responses, where no uncertainty factor is applied in  
16 extrapolating to humans, the benchmark response level was set at 0.1%, corresponding  
17 to 1 in 1000 lifetime excess risk of cancer. The models considered were the gamma,  
18 logistic, log-logistic, multistage, probit, log-probit, quantal-linear, and Weibull models.  
19 The quantal-linear model is a subset of the multistage and Weibull models, which can  
20 assume this form if it is appropriate for a given data set, but it was included as a  
21 separate model in order to assess the fit of a strictly low-dose linear model. Models with  
22 chi-square goodness of fit  $P$  values of 0.10 or greater were considered to fit the data  
23 adequately. Because model-based extrapolation to a 0.1% response level is sensitive to  
24 the choice of models, the BMD results for tumor endpoints were summarized by using a  
25 model-averaging (MA) technique [Wheeler and Bailer 2007], which weights several  
26 models on the basis of the model fit. A restricted version of the model-averaging  
27 software was used to avoid supralinear models, which have low-dose properties  
28 considered biologically implausible. It should be noted that the model-averaging  
29 procedure relies on a statistical method known as bootstrapping to obtain confidence  
30 limits, which may differ from the likelihood-based confidence limits estimated by the

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1 BMD software. A range of excess risk levels for workers, from 1 in 500 to 1 in 100,000,  
2 were also projected (see Table 7-6).

### 4 7.2.2 Extrapolation to Humans

5 Extrapolation from rats to humans is based on an estimate of the relative mg/kg-day  
6 metabolized dose of 1-BP in humans versus rats exposed to a given concentration. The  
7 duration-adjusted BMC and BMCL equivalent concentrations were converted to mg/kg-  
8 day inhaled values, assuming standard body weights and inhalation rate values for rats  
9 of the appropriate strains in subchronic studies [EPA 1988]. For humans, a body weight  
10 of 70 kg and total respiratory inhalation of 9.6 m<sup>3</sup> of air were assumed [ICRP 1975].

11 Metabolism and pharmacokinetics were assumed to extrapolate across species  
12 proportional to mg/kg-day scaled according to body weight to the 0.75 power [O'Flaherty  
13 1989; Travis et al. 1990]. For computational purposes, the net effect of such scaling can  
14 be calculated as a factor of (animal body weight/human body weight)<sup>0.25</sup> [EPA 1992].

15  
16 The NTP [2011] study of effects of 1-BP included a 2-year bioassay of B6C3F<sub>1</sub> mice.  
17 The model average BMCL for lung tumors in female B6C3F<sub>1</sub> mice was 0.64 ppm (Table  
18 7-5). The reference body weight for a female B6C3F<sub>1</sub> mouse in a chronic study is  
19 0.0353 kg [EPA 1988, Table 1-2]. Note that this is not simply the average body weight at  
20 the beginning or end of the study, but a representative average weight over the duration  
21 of the study. The corresponding reference inhalation rate for a male female B6C3F<sub>1</sub>  
22 mouse in a chronic study is 0.020 m<sup>3</sup>/day. The daily mg/kg inhaled dose in mice exposed  
23 to 0.41 ppm of 1-BP for a 6-hour day was estimated.

#### 24 **Equation 1:**

$$25 \quad 0.41 \text{ ppm} * 5.031 \text{ mg/m}^3 \text{ per ppm} * 0.020 \text{ m}^3/\text{day} * 6 \text{ hour}/24 \text{ hour} / 0.0353 \text{ kg}$$
$$26 \quad = \text{Mouse BMDL} = 1.3682 \text{ mg/kg-day}$$

27  
28 This was extrapolated to humans, assuming dose equivalence in units of mg/kg-day  
29 scaled according to body weight to the 0.75 power.

#### 30 **Equation 2:**

$$31 \quad \text{Mouse BMDL of } 1.3682 \text{ mg/kg-day} * (0.0353 \text{ kg}/70 \text{ kg})^{0.25} =$$

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1 Human BMDL = 0.205 mg/kg-day

2

3 The human mg/kg-day dose was then converted to ppm for an 8-hour work day.

4 **Equation 3:**

5  $0.205 \text{ mg/kg-day} * 70 \text{ Kg} / 9.6 \text{ m}^3 \text{ per day} * 1 \text{ ppm}/5.031 \text{ mg/m}^3 =$

6 Human BMCL = 0.297 ppm, rounded to 0.3 ppm<sup>1</sup>.

7 The human BMCL is the human equivalent to the BMCL for lung tumors in the female  
8 B6C3F<sub>1</sub> mouse (Table 7-5). Reference body weights and inhalation rates for the animal  
9 strains used in the NTP [2011] study of 1-BP are listed in Table 7-5.

10

### 11 7.3 RESULTS

12 As described in Section 7.2, benchmark dose modeling was conducted for 1-BP-induced  
13 tumors observed in the best available animal data, a chronic inhalation bioassay [NTP  
14 2011]. The tumor sites modeled were alveolar/bronchiolar adenomas and carcinomas in  
15 female mice, adenomas of the large intestine in female rats, and  
16 keratoacanthoma/squamous cell carcinoma of the skin in male rats. All models in the  
17 BMDS quantal modeling suite fit the skin and intestinal tumor data adequately. Model fits  
18 for the lung tumor data were not as good but were still considered adequate for the  
19 majority of models, based on the chi-square goodness of fit criterion described in section  
20 7.2.1. As summarized by the model-averaging procedure, the lung tumors gave the  
21 lowest BMC and BMCL estimates, compared to the skin and intestinal tumors. Table 7-  
22 2 lists benchmark concentration estimates (BMCs and BMCLs) for female mouse lung  
23 tumors, Table 7-3 lists estimates for female rat intestinal tumors, and Table 7-4 lists  
24 estimates for male rat skin tumors.

---

<sup>1</sup> A workweek of five 8-hour days has been assumed for calculation purposes; however, the same final answer is obtained if a workweek of four 10-hour days is assumed.

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1 **TABLE 7-2 – BMC AND BMCL ESTIMATES OF PPM 1-BP ASSOCIATED WITH A 0.1% ADDED RISK OF LUNG TUMORS IN FEMALE**  
 2 **B6C3F<sub>1</sub> MICE<sup>†</sup>**  
 3

<b>Model: BMDS [EPA 2010]</b>	<b>P value (goodness of fit)**</b>	<b>AIC</b>	<b>BMC</b>	<b>BMCL</b>
Gamma	0.2184	166.972	0.77	0.52
Logistic	0.0889	169.506	2.16	1.64
Log-logistic	0.2825	166.522	0.65	0.42
Multistage	0.2184	166.972	0.77	0.52
Probit	0.0956	169.232	1.94	1.47
Log-probit	0.0392	170.959	22.77	15.19
Quantal-linear	0.2184	166.972	0.77	0.52
Weibull	0.2184	166.972	0.77	0.52
MA*	0.1290	—	0.85	0.64

4 **Abbreviations: AIC = Akaike Information Criterion; BMC = maximum-likelihood estimate of benchmark dose; BMCL = benchmark dose**  
 5 **low (95% lower confidence limit for the benchmark dose); MA = model average; ppm = parts per million.**

6 <sup>†</sup>Source: NTP [2011]

7 \*Model Average, as described by Wheeler and Bailer [2007], based on the multistage, Weibull, and log-probit models.

8 \*\* A higher p-value indicates a better model fit

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1 **TABLE 7-3 – BMC AND BMCL ESTIMATES OF PPM 1-BP ASSOCIATED WITH A 0.1% ADDED RISK OF LARGE INTESTINE ADENOMAS IN**  
 2 **FEMALE FISCHER 344 RATS**  
 3

<b>Model: BMDS [EPA 20010]</b>	<b>P value (goodness of fit)**</b>	<b>AIC</b>	<b>BMC</b>	<b>BMCL</b>
Gamma	0.9899	63.127	12.23	3.13
Logistic	0.7221	64.145	21.92	11.40
Log-logistic	0.9893	63.128	12.49	2.97
Multistage	0.9989	63.109	6.56	3.14
Probit	0.7580	63.982	20.35	10.30
Log-probit	0.9787	63.150	22.54	3 x 10 <sup>-10</sup>
Quantal-linear	0.9886	61.234	5.27	3.10
Weibull	0.9907	63.126	11.77	3.13
MA*	0.8380	—	13.50	4.85

4 **Abbreviations: AIC = Akaike Information Criterion; BMC = maximum-likelihood estimate of benchmark dose; BMCL = benchmark dose**  
 5 **low (95% lower confidence limit for the benchmark dose); MA = model average; ppm = parts per million.**

6 †Source: NTP [2011]

7 \*Model average, as described by Wheeler and Bailer [2007], based on the multistage, Weibull, and log-probit models.

8 \*\* A higher p-value indicates a better model fit

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1 **TABLE 7-4 – BMC AND BMCL ESTIMATES OF PPM 1-BP ASSOCIATED WITH A 0.1% ADDED RISK OF KERATOACANTHOMAS AND**  
 2 **SQUAMOUS CELL CARCINOMAS IN MALE FISCHER 344 RATS**

Model: BMDS [EPA 2010]	P value (goodness of fit)**	AIC	BMC	BMCL
Gamma			2.96	1.78
Logistic	0.4707	123.99	7.54	5.31
Log-logistic	0.8950	124.36	0.21	Failed*
Multistage	0.8022	122.78	2.96	1.78
Probit	0.5034	123.82	6.80	4.76
Log-probit	0.9131	124.35	1.25	Failed*
Quantal-linear	0.8022	122.78	2.96	1.78
Weibull	0.8022	122.78	2.96	1.78
MA‡	0.5768	—	3.73	2.25

4 **Abbreviations: AIC = Akaike Information Criterion; BMC = maximum-likelihood estimate of benchmark dose; BMCL = benchmark dose**  
 5 **low (95% lower confidence limit for the benchmark dose); MA = model average; ppm = parts per million.**

6  
 7 †Source: NTP [2011]

8  
 9 \*Indicates that the model did not generate a BMCL estimate, because the lower limit includes zero.

10  
 11 ‡ Model average, as described by Wheeler and Bailer [2007], based on the multistage, Weibull, and log-probit models.

12 \*\* A higher p-value indicates a better model fit

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1 7.3.1 SELECTION OF TUMOR-BASED BMCs AND BMCLs FOR EXTRAPOLATION TO  
2 HUMANS

3 The selection of a specific BMC or BMCL for extrapolation to humans is dependent on  
4 the biological relevance of the tumor site, adequacy of the model fit, and the biological  
5 plausibility of the model in the low-dose region. Since the experimental exposures to 1-  
6 BP were via inhalation, which is also the major route of occupational exposure, and all of  
7 the sites where tumors were observed are sites where tumors occur in humans, all of the  
8 tumor sites are regarded as biologically relevant. Therefore, the choice is between  
9 selecting the best-fitting plausible model, the most health-protective plausible model, or  
10 a weighted average of several models that are each individually plausible. A model-  
11 averaging strategy has been shown to be generally superior to either picking the best-  
12 fitting model or picking the most health-protective model [Wheeler and Bailer 2007] and  
13 was the strategy adopted here. The model average rodent BMC and BMCL estimates  
14 were extrapolated to humans on the basis of the mg/kg-day dose, scaled by body weight  
15 to the 0.75 power, as described in Section 7.3.2. The human-equivalent BMC and BMCL  
16 values for the lung, skin, and intestinal tumors are shown in Table 7.7. Based on the  
17 most sensitive of the three tumorigenic endpoints, alveolar/bronchiolar adenomas +  
18 carcinomas, 45-year lifetime occupational exposures to concentrations of 0.3–0.4 ppm of  
19 1-BP are expected to produce approximately 1 in 1000 lifetime excess risk of lung  
20 cancer.

21  
22 7.3.2 EXTRAPOLATION OF TUMOR-BASED BMCs AND BMCLs TO A RANGE OF  
23 LEVELS OF LIFETIME EXCESS RISK

24  
25 Estimated occupational inhalational exposure concentrations corresponding to a range  
26 of lifetime excess risks from 1 in 500 to 1 in 100,000 are shown in Table 7-6. The 95%  
27 lower confidence limit (LCL) estimates of the occupational exposure concentrations  
28 expected to produce a given level of lifetime excess risk are shown in the right-hand  
29 column. The concentration shown in bold, 0.3 ppm, represents the 95% LCL estimate of  
30 the occupational exposure concentration expected to produce a 1 per 1,000 lifetime  
31 added risk. This concentration associated with a 1 in 1,000 lifetime excess risk was used  
32 as the basis for the NIOSH REL.

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**TABLE 7-5 – HUMAN-EQUIVALENT BMC AND BMCL ESTIMATES FOR 1-BP TOXICITY, EXTRAPOLATED FROM BMC AND BMCL ESTIMATES FOR TUMOR ENDPOINTS IN THE NTP [2011] STUDY. BENCHMARK RESPONSE RATE = 0.1% ADDED RISK.**

Endpoint	Rodent BMC (ppm)	Rodent BMCL (ppm)	Rodent strain, Sex	Reference BW (grams)*	8-hour m <sup>3</sup> inhaled <sup>†</sup>	Extrapolated human BMC (ppm)‡	Extrapolated human BMCL (ppm)‡
Alveolar/bronchiolar adenoma + carcinoma	0.85	0.64	B6C3F <sub>1</sub> mice, female	35.3	0.020	0.39	0.30
Large intestine adenoma	13.5	4.85	F344 rats, female	229	0.080	6.17	2.22
Keratoacanthoma +squamous cell carcinoma of skin	3.73	2.25	F344 rats, male	380	0.120	1.75	1.05

**Abbreviations: BMC = benchmark concentration; BMCL = benchmark concentration low (95% lower confidence limit for the benchmark concentration); BW = body weight; BW<sup>0.75</sup> = body weight to the three-fourths power; m<sup>3</sup> = cubic meter; ppm = parts per million; B6C3F<sub>1</sub> = F<sub>1</sub> generation hybrid of female C57BL/6 and male C3H; F344 = Fischer 344.**

**\*From: EPA [1988], Table 1-2.**

**†From: EPA [1988], Table 1-4.**

**‡Rodent BMCs or BMCLs were multiplied by 0.75 to adjust from a 30-hour/week experimental exposure to a 40-hour/week occupational exposure and then extrapolated on the basis of dose equivalency in units of mg/kg<sup>0.75</sup>, as described in Section 7.2.3.**

1 **TABLE 7-6 – ESTIMATED LIFETIME ADDED RISK OF LUNG TUMORS DUE TO OCCUPATIONAL EXPOSURE TO 1-BP, BASED ON LUNG**  
 2 **TUMORS IN FEMALE B6C3F<sub>1</sub> MICE**

Lifetime added risk	Rodent BMC (ppm)	Rodent BMCL (ppm)	Reference BW (grams)*	8-hour m <sup>3</sup> inhaled <sup>†</sup>	Extrapolated human BMC (ppm)‡	Extrapolated human BMCL (ppm)‡
1 in 500	1.70	1.27	35.3	0.020	0.79	0.59
1 in 1,000	0.85	0.64	35.3	0.020	0.39	<b>0.30</b> <sup>§</sup>
1 in 2,000	0.42	0.32	35.3	0.020	0.20	0.15
1 in 5,000	0.17	0.13	35.3	0.020	0.079	0.060
1 in 10,000	0.085	0.064	35.3	0.020	0.039	0.030
1 in 20,000	0.042	0.032	35.3	0.020	0.020	0.015
1 in 50,000	0.017	0.013	35.3	0.020	0.0079	0.006
1 in 100,000	0.0085	0.0064	35.3	0.020	0.0039	0.003

4  
 5 **Abbreviations: BMC = benchmark concentration; BMCL = benchmark concentration low (95% lower confidence limit for the benchmark**  
 6 **concentration); BW = body weight; m<sup>3</sup> = cubic meter; ppm = parts per million; B6C3F<sub>1</sub> = F<sub>1</sub> generation hybrid of female C57BL/6 and**  
 7 **male C3H.**

8 \*From: EPA [1988], Table 1-2.

9 †From: EPA [1988], Table 1-4.

10 ‡Rodent BMCs or BMCLs were multiplied by 0.75 to adjust from a 30-hour/week experimental exposure to a 40-hour/week occupational  
 11 exposure and then extrapolated on the basis of dose equivalency in units of mg/kg<sup>0.75</sup>, as described in Section 7.2.3.

12 §The exposure level shown in boldface is the 95% LCL estimate of the concentration of 1-BP considered appropriate for establishment  
 13 of a REL.

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1 7.3.3 Sensitivity Analysis

2

3 This analysis explores the impact of alternative models and assumptions on the  
4 quantitative risk estimate for 1-BP. The assumptions explored are the choice of the  
5 tumor endpoint on which to base extrapolation from animals to human, the decision to  
6 base recommendations on a model average rather than the best-fitting individual model,  
7 and the use of the (body weight)<sup>0.75</sup> procedure for extrapolation of mouse lung tumors to  
8 humans. The analysis explores the quantitative impact of each of these assumptions on  
9 the estimated concentration of 1-BP that is anticipated to produce a 1 in 1000 lifetime  
10 excess risk of cancer.

11

12 As shown in Table 7-5, lung tumors in female mice are clearly the tumor endpoint that  
13 leads to the lowest extrapolated human BMC and BMCL. Therefore, exposure  
14 recommendations based on this endpoint are expected to be health-protective for the  
15 other sites of tumor formation as well. However, if recommendations were based on the  
16 other tumor sites—skin tumors or intestinal tumors—then somewhat higher occupational  
17 exposure concentrations would be considered acceptable. Skin tumors in male rats  
18 resulted in the second-lowest BMC and BMCL of the three tumor sites, yielding  
19 estimated occupational exposure levels of 1.75 or 1.05 ppm, respectively. However, this  
20 would not be protective for lung tumors.

21

22 As shown in Table 7-2, the various benchmark dose models for lung tumors yield widely  
23 varying BMDL estimates. A possible alternative to the model-averaging procedure used  
24 above would be to select a single benchmark dose model and use it as the basis for  
25 extrapolation. As shown in Table 7-2, the best-fitting model by the chi-square goodness  
26 of fit criterion, as well as by AIC, is the log-logistic model. Extrapolation based on the  
27 log-logistic model rather than the model average would lead to occupational exposure  
28 concentration estimates of 0.2 ppm with use of the BMCL or 0.3 ppm with use of the  
29 BMC. These results, rounded to one significant figure, are similar (within a factor of 2) to  
30 the results obtained by model averaging.

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1

2 As noted in section 7.2.2, extrapolation of carcinogenicity from animals to humans is  
3 typically assumed to scale according to (body weight)<sup>0.75</sup>. This assumption is based on  
4 the expected cross-species scaling of the metabolism and pharmacokinetics of 1-BP.

5 An alternative assumption for 1-BP-induced lung tumors might be that they scale across  
6 species according to the inhaled concentration of 1-BP. As shown in Table 7-2, the  
7 model average BMC and BMCL for 1-BP lung tumors in mice are 0.85 and 0.64 ppm,  
8 respectively. These results were obtained using an experimental protocol in which the  
9 mice were exposed to 1-BP for 6 hours per day, 5 days per week. Assuming that  
10 occupational exposures would involve an 8 hour per day, 5 days per week exposure, the  
11 mouse BMC and BMCL can be adjusted to an occupational exposure scenario by  
12 multiplying by 6/8. Therefore, the estimated human BMC and BMCL for a 1 in 1000  
13 lifetime excess risk of lung cancer would be 0.6 or 0.5 ppm, respectively, when rounded  
14 to one significant figure.

15  
16 As shown in Table 7-5, the model average human-equivalent BMC and BMCL estimates  
17 for a 1 in 1000 lifetime excess risk of cancer are (when rounded) 0.4 and 0.3 ppm,  
18 respectively. The alternative assumptions explored here would yield BMC estimates of  
19 0.3-1.75 ppm, and BMCL estimates of 0.2-1.05 ppm. The sensitivity analysis indicates  
20 that the results obtained using alternative assumptions are similar to those obtained  
21 using model averaging.

22  
23  
24 The data for non-cancer endpoints, BMD modeling for those endpoints, and  
25 extrapolation to occupational exposures are presented in Appendix B. Because the non-  
26 cancer risk assessment is discussed in detail in Appendix B, only summary results are  
27 presented here for comparison to the cancer modeling results.

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1 7.4 DISCUSSION

2 One assumption made in this NIOSH analysis is that recommendations for occupational  
3 exposure levels should be based on the 95% lower confidence limit estimate of a  
4 benchmark concentration, that is, a BMCL, rather than the central estimate, the BMC.  
5 The rationale for this is that the BMCL reflects the statistical variability of the data and  
6 therefore is more likely to be health-protective than a central estimate such as a BMC.  
7 For the endpoint selected as the basis for development of the NIOSH REL,  
8 alveolar/bronchiolar adenomas and carcinomas in female mice, the BMC estimate  
9 (shown in Table 7-5) is approximately 33% higher than the corresponding BMCL;  
10 therefore, the REL would be 33% higher if a recommendation was based on the BMC  
11 rather than the BMCL.

12  
13 As discussed in Appendix B, the lowest duration-adjusted BMC and BMCL values for  
14 non-cancer endpoints were observed for the dichotomous endpoints of renal pelvic  
15 mineralization in the F<sub>0</sub> females in the WIL Research Laboratories [2001] study and  
16 hepatic cytosolic vacuolation in the F<sub>0</sub> males in the WIL Research Laboratories [2001]  
17 study. These endpoints were judged to be inappropriate for extrapolation to occupational  
18 exposures. However, if hypothetical recommendations were based on these endpoints  
19 for purposes of comparison with the cancer endpoints, then the extrapolated BMCL  
20 values would be 92 ppm for renal mineralization in the F<sub>0</sub> females and 103 ppm for  
21 hepatic cytosolic vacuolation in the F<sub>0</sub> males, yielding occupational exposure levels of  
22 approximately 1.2–1.4 ppm after application of a 75-fold UF. The lowest occupationally  
23 relevant human-equivalent non-cancer BMCL for 1-BP is 144 ppm, derived from effects  
24 on sperm morphology in the F<sub>0</sub> generation of the WIL Research Laboratories [2001]  
25 study. Application of the 75-fold UF yields an estimated occupational exposure  
26 concentration of approximately 1.9 ppm. Similarly, the 182 ppm human-equivalent BMCL  
27 for decreased hind limb grip strength in the Ichihara [2000b] study yields an estimated  
28 occupational exposure concentration of approximately 2.4 ppm. Thus, recommendations  
29 based on the non-cancer endpoints would lead to occupational exposure concentrations

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1 nearly an order of magnitude higher than the 0.2–0.4 ppm recommendations derived  
2 from alveolar/bronchiolar adenomas and carcinomas in female mice.

### 3 7.5 SUMMARY

4 Dose-response modeling was conducted on the best available 1-BP data [NTP 2011]  
5 with the use of benchmark dose methods. Existing human studies do not provide  
6 adequate data for quantitative dose-response analysis; therefore, the dose-response  
7 analysis was based on the best available animal data. BMD modeling was conducted on  
8 data from a NTP chronic inhalation bioassay for 1-BP [NTP 2011]. Extrapolation to  
9 humans of the toxicologically based BMCs and BMCLs for alveolar/bronchiolar  
10 adenomas and carcinomas suggests that occupational exposures to 1-BP should be  
11 limited to 8-hour TWA exposures in the range of 0.3 ppm (for recommendations based  
12 on the BMCL) to 0.4 ppm (for recommendations based on the BMC). Based on the  
13 results of this quantitative risk assessment, NIOSH recommends that workplace airborne  
14 exposure be limited to 0.3 ppm 1-BP 8-hour TWA over a 45-year working lifetime. This  
15 1-BP concentration is associated with a 1 in 1000 excess risk of lung cancer.

16

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1 **CHAPTER 8: BASIS FOR THE RECOMMENDED EXPOSURE LIMIT**

2 NIOSH is mandated under the authority of the Occupational Safety and Health Act of  
3 1970 (Public Law 91-956) to develop and recommend criteria for identifying and  
4 controlling workplace hazards that may result in occupational illnesses and injury. In  
5 fulfilling this mission, NIOSH began conducting research on 1-BP when it became an  
6 emerging hazard of occupational concern. NIOSH continues to investigate the potential  
7 health effects of exposure to 1-BP, because of the increased use of the brominated  
8 solvent in several industrial and commercial settings, including vapor degreasing,  
9 precision cleaning, dry cleaning, and spray applications during the manufacturing of  
10 foam cushions. The scientific literature was critically reviewed to identify epidemiologic,  
11 toxicologic, and industrial hygiene studies to be used as the basis of NIOSH  
12 recommendations for occupational exposure to 1-BP. This chapter summarizes the  
13 scientific information and data that are the basis of the NIOSH REL. More detailed  
14 information about the studies summarized here is provided in the respective document  
15 chapters.

16  
17 **8.1 BASIS FOR THE NIOSH REL**

18 NIOSH has proposed a REL for 1-BP of 0.3 ppm (1.5 milligrams per cubic meter of air  
19 [mg/m<sup>3</sup>]) for an 8-hour TWA exposure, during a 40-hour workweek. This  
20 recommendation is based on the results of a quantitative assessment of cancer risks  
21 (described in Chapter 7). Data on lung tumors in female mice were selected as the basis  
22 of the REL for 1-BP because lung cancer was identified as the most sensitive health  
23 endpoint [NTP 2011]. This value is associated with a 1 in 1,000 excess risk of lung  
24 cancer over a working lifetime (see Table 7-8). The NIOSH REL represents the  
25 maximum 8-hour TWA concentration to which a worker may be exposed and is intended  
26 to reduce workers' risk of lung cancer associated with occupational exposure to 1-BP  
27 over a 45-year working lifetime. NIOSH does not consider an exposure limit set at a risk  
28 level of 1 in 1,000 to be a safe level of exposure for workers because of the residual risk  
29 of lung cancer and other health effects at the REL. Therefore, exposures should always

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1 be kept below the proposed REL of 0.3 ppm. NIOSH recommends that all reasonable  
2 efforts be made to further reduce the risks from worker exposures to 1-BP to levels  
3 significantly below the REL through use of the hierarchy of controls, including  
4 elimination, substitution, engineering controls and, when those methods do not  
5 adequately reduce exposures, personal protective equipment. NIOSH also recommends  
6 that a comprehensive safety and health program be implemented that includes worker  
7 education and training, hazard communication and exposure monitoring. It is expected  
8 from the results of a supplemental risk assessment (summarized in Appendix B) that  
9 reducing airborne occupational exposures below the NIOSH REL will also reduce the  
10 non-cancer health outcomes of 1-BP exposure, including adverse neurological,  
11 reproductive, developmental, and hematological effects. The use of NIOSH Analytical  
12 Method 1026 is recommended for air sampling for 1-BP in the workplace.

13  
14 An in-depth assessment by NIOSH of the available human and animal data (see  
15 Chapters 2–5) indicates that 1-BP is capable of causing a wide spectrum of adverse  
16 health outcomes. This assessment revealed that human health effects and exposure  
17 were inadequate to serve as the basis of a quantitative risk assessment for 1-BP. In  
18 contrast, the animal toxicity datasets contained dose-response information suitable for  
19 quantitative risk assessment for occupational exposures to 1-BP [Ichihara et al. 2000b;  
20 WIL Research Laboratories 2001; NTP 2011]. The results of an NTP 2-year inhalation  
21 bioassay provided evidence of carcinogenicity of 1-BP [NTP 2011] and served as the  
22 basis of a quantitative risk assessment that evaluated cancer risks via BMD-modeling  
23 techniques (see Chapter 7.0). NIOSH considers these adverse health effects in 1-BP-  
24 exposed animals to be relevant to workers. Further analysis indicated that cancer  
25 endpoints were the most critical and sensitive health endpoints, and these were selected  
26 as the basis of the quantitative risk assessment. Human-equivalent risk estimates were  
27 derived from animal dose-response data (from rats and mice). Human-equivalent expo-  
28 sures over a 45-year working lifetime are associated with an added risk of cancer of 1 in  
29 1000. BMD modeling for the critical health endpoints yielded a relatively narrow range of  
30 extrapolated human equivalent BMCL values, which correspond with the 95% lower-

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1 bound estimates and represent the most conservative estimates. A model-averaging  
2 strategy was applied to estimate a BMCL that corresponded with a 0.1% response rate;  
3 this approach assumes a low-dose linear behavior for lower exposure concentrations.  
4 The extrapolated human BMCL estimates are in Table 7-7. Data on lung tumors in  
5 female mice were selected as the basis of the REL for 1-BP because lung cancer was  
6 identified as the most sensitive health endpoint.

7  
8 In addition to limiting airborne concentrations of 1-BP, NIOSH recommends that dermal  
9 exposure to 1-BP be prevented in the workplace to reduce the risk of adverse dermal  
10 health effects, including irritation. 1-BP may also be absorbed by the skin and contribute  
11 to systemic toxicity.

## 13 8.2 ANALYTICAL FEASIBILITY OF THE NIOSH REL

14 Two methods for quantifying airborne concentrations of 1-BP in the workplace have  
15 been developed and validated. NIOSH Analytical Method 1025 (see Attachment A) has  
16 an estimated limit of detection (LOD) of 1.0 microgram ( $\mu\text{g}$ ) per sample for 1-BP [NIOSH  
17 2003a]. This method has been demonstrated to reliably measure airborne  
18 concentrations of 1-BP as low as 0.01 ppm over a full work shift [NIOSH 2000]. OSHA  
19 has developed and partially validated PV2061 for 1-BP, which has an LOD of 0.13  $\mu\text{g}$   
20 per sample and a reliable quantitation limit of 0.007 ppm [OSHA 1999a]. The NIOSH and  
21 OSHA methods are capable of quantifying airborne concentrations below the NIOSH  
22 REL for 1-BP of 0.3 ppm.

## 23 8.3 ACTION LEVEL

24 NIOSH has historically recommended an action level (AL) with the primary consideration  
25 of protecting workers from exposures that exceed the REL [NIOSH 1975b]. Individual  
26 exposure concentration measurements at or above the AL were thought to indicate with  
27 a high degree of certainty that exposure concentrations could exceed the REL, which  
28 triggered additional controls and administrative actions to reduce worker exposures.  
29 NIOSH is in the process of re-evaluating its AL policy.

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Exposures to 1-BP are highly variable within jobs (see Chapter 2.0). It is not feasible to establish a specific AL for 1-BP on the basis of available data. Therefore, NIOSH is providing general exposure monitoring guidance for workplaces with 1-BP exposures rather than recommending a specific AL. This will allow each employer to determine a strategy for monitoring exposures that is specific to each workplace, to ensure that workers' exposures do not exceed the REL.

### 8.4 SUMMARY

The following points summarize the scientific information used as the basis of the NIOSH recommendations for occupational exposure to 1-BP:

- The REL for 1-BP of 0.3 ppm for an 8-hour TWA exposure in a 40-hour workweek is intended to be protective against lung cancer, which is identified as the most sensitive health endpoint. There is an excess risk of 1 in 1,000 associated with a 45-year working lifetime of exposure to 1-BP at the REL. The REL is also expected to reduce noncarcinogenic adverse health effects, such as neurotoxicity or hematotoxicity.
- The REL for 1-BP of 0.3 ppm is quantifiable by NIOSH analytical method 1025 and OSHA method PV2061.
- Exposure data are insufficient to assess whether the REL of 0.3 ppm for 1-BP is achievable in most workplaces. The hierarchy of controls (elimination, substitution, engineering controls, administrative controls, and use of personal protective equipment) has been applied to effectively lower airborne concentrations of other organic solvents—with physiochemical properties similar to those of 1-BP—in dry cleaning and vapor degreasing operations. The REL is intended to promote the proper use of existing control technologies and to encourage the research and development of new technologies where needed, in order to control workplace 1-BP exposures.

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1 The REL may not be sufficiently protective to prevent all occurrences of lung cancer and  
2 other adverse health effects among workers exposed for a working lifetime. The REL  
3 represents the upper limit of exposure for each worker during each work shift. Because  
4 of the residual risk of lung cancer and other health effects at the REL, NIOSH further  
5 recommends that all reasonable efforts be made to reduce 1-BP exposures to below the  
6 REL. NIOSH also recommends that a comprehensive safety and health program be  
7 implemented that includes worker education and training, exposure monitoring, and  
8 medical monitoring. A safety and health program designed to protect workers from  
9 adverse effects of exposure to 1-BP should include mechanisms to identify all risk  
10 factors for exposure.

11  
12 To be successful, safety and health programs should have strong management  
13 commitment, worker involvement, and occupational safety and health expertise. The  
14 program should include employee training on the health hazards of occupational 1-BP  
15 exposure, workplace monitoring of airborne 1-BP concentrations, and medical  
16 surveillance of workers exposed to 1-BP. These are the primary elements of such a  
17 comprehensive, effective safety and health program:

- 18 • hazard communication and training (Chapter 9)
- 19 • exposure control (Chapter 9)
- 20 • medical monitoring and surveillance (Chapter 10)
- 21 • biological monitoring (Chapter 10)
- 22 • exposure monitoring (Chapter 11).

23  
24 NIOSH recommends specific guidelines to control and minimize occupational exposures  
25 to 1-BP; application of the recommended controls (Chapter 9) should limit inhalation and  
26 skin exposures of workers to 1-BP. It is expected that a reduction in exposures to 1-BP  
27 will reduce the risk and incidence of adverse health effects, including lung cancer and  
28 non-cancer endpoints (that is, neurotoxicity, hepatotoxicity, hematotoxicity, and  
29 reproductive and developmental toxicity). Although settings in which workers are  
30 exposed to 1-BP above the REL warrant additional concern and attention, all workplaces

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- 1 should attempt to decrease workers' exposure to 1-BP to the lowest level that is
- 2 reasonably achievable, to minimize adverse health effects in workers.
- 3

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## CHAPTER 9: HAZARD PREVENTION AND CONTROL OF EXPOSURE TO 1-BROMOPROPANE

### 9.1 INTRODUCTION

Worker exposure to air contaminants can best be reduced by a combination of efforts that minimize air contaminant generation using good work practices and controlling emissions at their source through process changes or engineering controls. The hierarchy of controls, including elimination, substitution, engineering controls, administrative controls, and the use of personal protective equipment, has been applied to effectively lower airborne concentration of other organic solvents – which exhibit similar physiochemical properties as 1-BP – in dry cleaning and vapor degreasing operations [Earnest 2002; NIOSH 2002 c,d,e,f; EPA 2004]. These results suggest that airborne concentrations of 1-BP can be effectively lowered using available technology and by applying the hierarchy of controls. The REL is intended to promote the effective use of existing control technologies and to encourage the research and development of new control technologies where needed, in order to control workplace 1-BP exposures.

Traditionally, a hierarchy of controls has been used as a means of determining how to implement feasible, effective controls. One representation of this hierarchy can be summarized as follows:

- elimination and substitution,
- engineering controls,
- administrative controls and work practice controls, and
- personal protective equipment (PPE).

The idea behind this hierarchy is that the control methods at the top of the list are potentially more effective, protective, and economical (in the long run) than those at the bottom. Following the hierarchy normally leads to the implementation of inherently safer systems, where the risk of illness or injury has been substantially reduced. The hierarchy of controls mentioned above is discussed in more detail in this chapter for any industry

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1 using 1-BP as well as for specific industries (e.g., dry cleaning) and specific uses (e.g.,  
2 vapor degreasing).

### 3 9.2 ELIMINATION AND SUBSTITUTION

4 Elimination of a hazard from the workplace is the most effective control to protect worker  
5 health. The intention of eliminating a chemical in the workplace is to remove the  
6 exposure by removing the source. Elimination may be difficult to implement in an  
7 existing process; it may be easier to implement during the design or re-design of a  
8 product or process.

9  
10 If elimination is not possible, substitution is the next choice of control to protect worker  
11 health, using substitution of equipment, materials, or less hazardous processes.

12 Equipment substitution is the most common type of substitution [NIOSH 1973; Burton  
13 2011]. It is often less costly than process substitution, and it may be easier than finding  
14 a suitable substitute material. Examples that apply to 1-BP exposure reduction include  
15 (1) the substitution of an unenclosed, manual operated degreasing unit with an  
16 enclosed, automated degreasing unit [MTAP 2011] and (2) the substitution of an  
17 organic-solvent based dry cleaning unit with a unit that relies on aqueous or “wet  
18 cleaning” systems [NIOSH 1997a,b,c; MTAP 2010].

19  
20 Material substitution is the second most common type of substitution after equipment  
21 substitution. It has been used to improve the safety of a process or lower the intrinsic  
22 toxicity of the material being used. However, evaluation of the potential adverse health  
23 effects of the substitute material is essential to ensure that one hazard is not replaced  
24 with a different one [NIOSH 1973; Burton 2011]. Material substitution for 1-BP has been  
25 previously recommended at foam cushion manufacturers, where it was recommended  
26 that 1-BP based adhesive be replaced with a non-hydrocarbon solvent (water-based)  
27 adhesive mixture, thereby eliminating the risk of exposure to 1-BP [NIOSH 2002a,  
28 2002b, 2003b]. When no suitable substitute can be identified, NIOSH recommends using

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1 compounds that minimize the amount of 1-BP in their formulations, thereby limiting the  
2 potential for exposure.

3  
4 OSHA [2014b] has developed a web-based toolkit entitled, *Transitioning to Safer*  
5 *Chemicals: A Toolkit for Employers and Workers*, to assist both employers and workers  
6 with information, methods, tools, and guidance on using informed substitution in the  
7 workplace. This toolkit is available at  
8 [https://www.osha.gov/dsg/safer\\_chemicals/index.html](https://www.osha.gov/dsg/safer_chemicals/index.html) and contains resources and  
9 provides a step-by-step approach to allow for making informed decisions about chemical  
10 substitution, planning and assessment.

## 12 9.3 ENGINEERING CONTROLS

13 When it is not always possible to eliminate toxic substances from the workplace or  
14 replace them with less toxic substances, the use of engineering controls to minimize  
15 exposures is the next level of control for reducing exposure.

16 Insufficient exposure data are available to assess the extent to which the REL of 0.3  
17 ppm for 1-BP is achievable in various workplaces. The hierarchy of controls, including  
18 elimination, substitution, engineering controls, administrative controls, and the use of  
19 personal protective equipment, has been applied to effectively lower airborne  
20 concentration of other organic solvents – which exhibit similar physiochemical properties  
21 as 1-BP – in dry cleaning and vapor degreasing operations [Earnest 2002; NIOSH 2002  
22 c,d,e,f; EPA 2004]. These results suggest that airborne concentrations of 1-BP can be  
23 effectively lowered using available technology and by applying the hierarchy of controls.  
24 The REL is intended to promote the proper use of existing control technologies and to  
25 encourage the research and development of new control technologies where needed, in  
26 order to control workplace 1-BP exposures.

### 28 9.3.1 VENTILATION

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1 A properly designed supply air ventilation system can provide both plant ventilation and  
2 building zone pressurization. Ventilation may be defined as the strategic use of airflow to  
3 control the environment in a space—to provide thermal control of the space, remove an  
4 air contaminant near its source of release, or dilute the concentration of an air  
5 contaminant to an acceptable concentration [Soule 1978]. For controlling a workplace air  
6 contaminant such as 1-BP, a specific ventilation system or assembly may be designed  
7 primarily to provide local or general control, by means of air exhaust and/or supply air  
8 [Burton 2011].

9

10 Local exhaust ventilation (LEV) is primarily intended to capture the contaminant at  
11 specific points of release into the workroom air. This is done through the use of exhaust  
12 hoods, enclosures, or similar assemblies. LEV is appropriate for the control of stationary  
13 point sources of contaminant release. When LEV is installed in production areas, it is  
14 important to consider the need for replacement or make-up air. In general, it is  
15 necessary to balance the amount of exhausted air with a similar amount of supply air  
16 (slightly more or less depending upon pressurization requirements). Without  
17 replacement air, uncontrolled drafts may exist at doors, windows, and other openings;  
18 doors may become difficult to open because of the high pressure difference, and  
19 exhaust fan performance may degrade. Good supply air design consists of ducted  
20 supply with air discharge registers positioned to maximize air distribution within the  
21 assigned zone or to establish protective air current patterns within the working vicinity. It  
22 is important to confirm that the LEV system is operating as designed by documenting  
23 baseline performance metrics (volumetric flow, capture velocity, static pressure...) and  
24 periodically re-measuring the LEV system performance parameters for comparison  
25 against the baseline measurements. A standard measurement, called hood static  
26 pressure, provides important information on the hood performance, because any change  
27 in airflow results in a change in hood static pressure. For hoods designed to prevent  
28 exposures to hazardous airborne contaminants, the American Conference of  
29 Governmental Industrial Hygienists (ACGIH®) recommends the installation of a fixed  
30 hood static pressure gauge [ACGIH 2007].

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1 General ventilation, often called dilution ventilation, is primarily intended to dilute the  
2 concentration in the general workroom air. It controls widespread problems such as  
3 generalized or mobile emission sources [Burton 2011]. Whenever practicable, point-  
4 source emissions are most effectively controlled by LEV, which is designed to remove  
5 the contaminant at the source before it emanates throughout the workspace. Dilution  
6 ventilation is less effective because it merely reduces the concentration of the  
7 contaminant after it enters the workroom air, rather than preventing the contaminant  
8 from ever entering the workroom air. It is also much less efficient because of the high  
9 volumetric airflow rates required for adequate control. ACGIH [2007] has identified four  
10 factors that may limit the effectiveness of using dilution ventilation for health protection.  
11 These factors include: the quantity of contaminant generated must not be too great or  
12 the airflow rate required for dilution will be excessive; workers must be far enough away  
13 from the contaminant source or the source released in sufficiently low concentrations to  
14 maintain worker exposures below desired levels; the toxicity of the contaminant must be  
15 low; and the evolution of the contaminants must be uniform.

16  
17 It is important to recognize that LEV and general ventilation are connected. The air  
18 exhausted by a local exhaust system must be replaced, and the replacement or make-  
19 up air will usually be supplied by a general system that is not associated with any  
20 particular exhaust inlet and/or by simple infiltration through building openings. Whether  
21 exhausted air is replaced by infiltration or a mechanical supply-air system, replacement  
22 air usually provides a source of general ventilation to the space even if all the exhaust is  
23 considered local. The designation of a particular ventilation system as local, general,  
24 exhaust, or supply, is governed by the primary intent of the design [Burton 2011].

25  
26 LEV has been used to control airborne 1-BP concentrations in several different  
27 applications. In foam cushion fabricating, the installation and application of LEV hoods  
28 resulted in the reduction of the mean full shift TWA airborne concentrations during the  
29 various activities conducted to manufacture the cushion. For example, NIOSH [2002a]  
30 stated that the mean exposure levels were reduced from 168.9 ppm to 19.0 ppm after

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1 the installation of LEV. Specific changes noted included 1-BP exposures in the Sew and  
2 Saw departments have been reduced from over 100 ppm to less than 2 ppm, 1-BP  
3 exposures in the Assembly department have been reduced from a mean of 169.8 to 18.8  
4 ppm, and those in the Covers department from 197.0 to 29.2 ppm. In another workplace,  
5 installation of LEV, in addition to enclosure of a 1-BP vapor degreaser unit, resulted in  
6 low airborne concentrations of 1-BP at the degreaser (4.4 ppm) and in the degreaser  
7 room (1.7 ppm). Employee reports of irritation and other symptoms of exposure also  
8 decreased [NIOSH 2000]. While these reduced exposure levels may still exceed the  
9 REL for 1-BP, the reduced exposures are substantially easier to protect workers by  
10 applying additional engineering controls, as well as administrative and PPE control  
11 strategies.

12  
13 In addition to routine monitoring of the hood static pressure, additional system checks  
14 should be completed periodically to ensure adequate system performance, including  
15 smoke tube testing, hood slot/face velocity measurements, capture velocity  
16 measurements at the source generation point and duct velocity measurements. These  
17 system evaluation tasks are essential elements of a routine preventative maintenance  
18 schedule to check system performance. It is important to note that the collection and  
19 environmental release of air contaminants may be regulated; companies should contact  
20 agencies responsible for local air pollution to ensure compliance with emission  
21 requirements when installing new or modifying engineering controls.

### 22 9.3.1.1 DRY CLEANING

23 LEV captures vapor at or near its source of release. This ventilation technique reduces  
24 the vapor concentrations reaching the worker's breathing zone and minimizes vapor  
25 diffusion. Vapor diffusion is one cause of background ambient air solvent concentrations  
26 in a dry cleaning shop. For dry cleaning shops, the release of solvent vapors into the  
27 environment and subsequent worker exposure to solvent vapors is greatest during  
28 machine maintenance, loading and unloading, as well as, during machine maintenance.  
29 Dry cleaning machines that use LEV as a control should have an inward air velocity of  
30 30.6 meters per minute (m/min; 100 fpm) through the loading and unloading door

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1 (known as the door's face velocity). This velocity helps reduce solvent vapors escaping  
2 into the shop by providing a draft of clean air passing over the items being removed from  
3 the machine. Exhaust from the machine should be ducted to a point whose location and  
4 height is at least 1.5 meters (5 ft) above the roof to prevent reentry to the work  
5 environment or entry to adjacent establishments or occupied areas. Stack height design  
6 is discussed in detail in ACGIH [2007] and in the *Airflow Around Buildings* chapter in  
7 ASHRAE [2013]. LEV systems are typically activated by a door-interlocking switch  
8 [NIOSH 1997b,d].

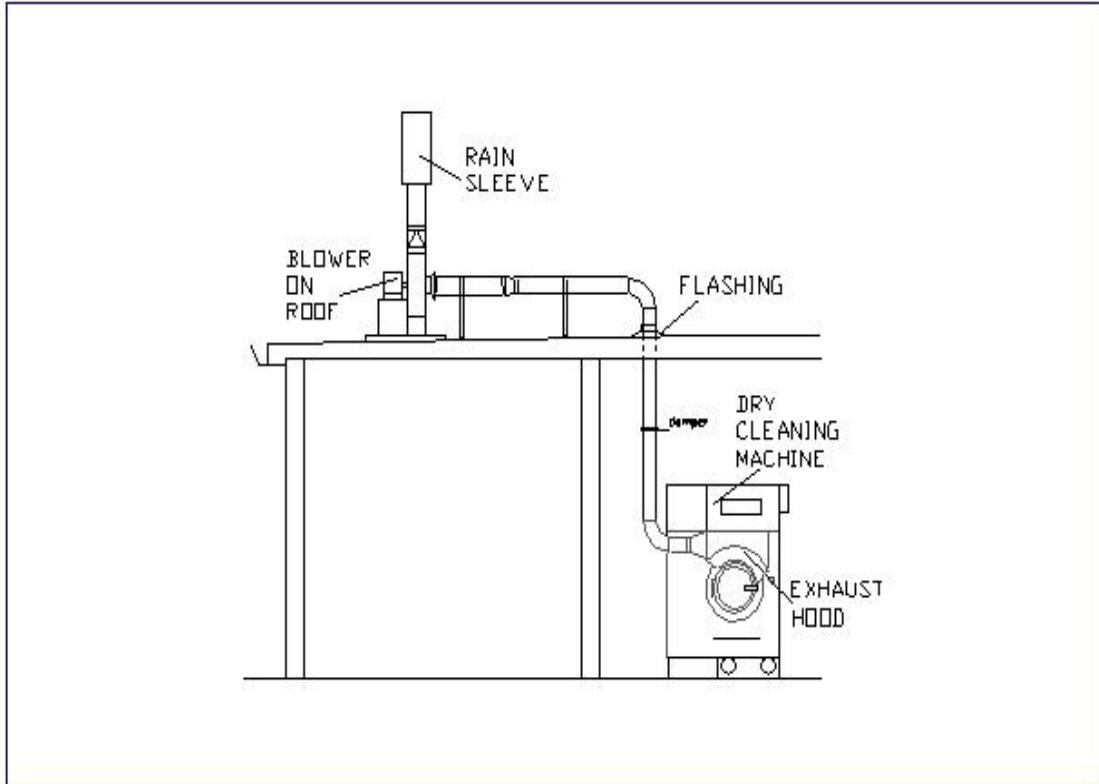
9

10 An alternative for older machines without built-in exhaust ventilation is to retrofit an  
11 external ventilation hood outside the machine door (see Figure 9-1). Airflow capacity in  
12 cubic meters per min ( $\text{m}^3/\text{min}$ ) through this retrofit hood should not be less than 100  
13 times the door opening area in square meters (i.e., a door opening with a surface area of  
14  $0.5 \text{ m}^2$  would need an exhaust hood flow rate at least  $50 \text{ m}^3/\text{min}$  [NIOSH 1997b,d]). The  
15 exhaust hood should be isolated from cross-drafts caused by general ventilation, floor or  
16 other shop fans, and high personnel traffic areas.

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1 **FIGURE 9-1 – LOCAL EXHAUST VENTILATION ADDED TO A DRY CLEANING MACHINE\***



3 **Reference: NIOSH[1997d]**

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1 General ventilation, also known as dilution ventilation, should be used to supply  
2 conditioned fresh air and to exhaust contaminated air from the general workroom area.  
3 This ventilation technique can provide temperature control and reduce background  
4 concentrations of PERC in the dry cleaning shop, and it may provide similar results with  
5 1-BP. Generally accepted guidelines recommend an air change in the workroom every 5  
6 minutes (12 air changes per hour) with a minimum of 0.85 m<sup>3</sup>/min (30 cfm) of outside air  
7 per person [NIOSH 1997d]. Supply and exhaust systems in the shop should move air  
8 from a clean area (e.g., offices, customer counters, etc.) towards a less-clean area  
9 (where the dry cleaning machine is located). This process reduces movement of  
10 contaminated air into other areas of the shop. Make-up or replacement air, which  
11 replaces the air being exhausted to the outside, enters naturally through windows and  
12 doors or through large louvers/fans in the ceiling or walls. Insufficient volumes of make-  
13 up air could cause undesirable migration of contaminated air from dirty-to-clean areas of  
14 the dry cleaning shop and hamper proper functioning of LEV devices. A qualified  
15 ventilation system contractor, with both general ventilation and LEV experience, should  
16 be contacted to assist with this work [NIOSH 1997d].

#### 18 9.3.1.2 Vapor Degreasing

19 Many open-top degreasers have lip vent exhaust systems designed to capture solvent  
20 vapors and direct them away from the operating personnel. Lip vents should be avoided  
21 if possible because they act like room drafts, disturbing the vapor layer and increasing  
22 solvent losses [Center for Emission Control 1992]. A degreaser without lip vents or with  
23 the vents turned off will release 15% less solvent emissions than a degreaser with a vent  
24 [MTAP 2011]. If lip vents are required in order to maintain worker exposures beneath  
25 applicable OELs during the work activity, then use covers on the degreaser when it is  
26 not in use and shut off the lip vent when the cover is closed. ACGIH [2007] provides  
27 detailed instructions for assisting in the design and operation of vapor degreasing  
28 operations.

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1 Room air velocity should be kept below 15 m/min (50 fpm) to eliminate external drafts  
2 around the degreaser. Repositioning fans and adding baffles or shield panels between  
3 the degreaser and draft source can also reduce emissions [MTAP 2011].

4 If monitoring results indicate that workers' exposures to 1-BP are above established  
5 limits when they are working on or near a specific operation and if new or improved  
6 controls are necessary, consider using one or more of the following ventilation control  
7 options:

- 8 • Install LEV systems wherever 1-BP is stored or use LEV to remove 1-BP vapors  
9 before they reach a worker.
- 10 • Increase the exhaust capacity of the LEV system. ACGIH® recommends a  
11 minimum duct velocity of 612 m/min (2000 fpm) for a solvent degreasing tank  
12 [ACGIH 2007].
- 13 • Install a remote electrical switch to turn on the LEV, rather than putting a switch  
14 on the unit. This way, workers can turn on the LEV without going near the 1-BP  
15 [OSHA 1998a].

### 17 9.3.2 ISOLATION

18 Isolation as an engineering control may involve the erection of a physical barrier  
19 between the worker and the hazard. Isolation may also be achieved by the appropriate  
20 use of distance or time [Soule 1978]. Examples of hazard isolation include separate  
21 structures, rooms, or cabinets and the isolation of potentially hazardous process  
22 equipment into dedicated areas or rooms that are separate from the general process  
23 areas [Burton 2011]. Separate ventilation of the isolated area(s) may be needed to  
24 maintain the isolation of the hazard from the rest of the facility [Soule 1978]. Complete  
25 isolation of an entire process also may be achieved by using automated, remote  
26 operation methods [Burton 2011]. Separating workers from the source of contamination  
27 is another recommended practice to reduce worker exposures to airborne  
28 concentrations of 1-BP.

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1 9.3.2.1 DRY CLEANING

2 Some dry cleaning establishments in large cities utilize a central plant, where the dry  
3 cleaning occurs, and satellite shops. Many facilities have established a location where  
4 garments are picked up and dropped off. The garments are transported to and from the  
5 central plant for dry cleaning. This approach isolates the dry cleaning process from the  
6 workers in the satellite shops, limiting solvent exposures.

7 9.3.2.2 VAPOR DEGREASING

8 The National Emissions Standard for Hazardous Air Pollutants (NESHAP) requires  
9 certain design features on vapor degreasers to reduce solvent emissions in the air [EPA  
10 2004]. One such requirement includes keeping the degreasing tank in an isolated area  
11 that is separate from other work areas, open windows or doors, heating or cooling  
12 equipment, or any device that may cause uncontrolled air movement, to minimize  
13 disturbance of the vapors. If the degreaser cannot be placed in an isolated area, then  
14 baffles should be installed on the windward side to divert drafts and the degreaser  
15 should be enclosed or, where possible, fans and vents that cause disruptive air currents  
16 should be redirected [MTAP 2011].

17  
18 9.3.3 CONTROL OF EXPOSURE BY PROCESS

19 Some primary processes may increase potential for a worker to be exposed to 1-BP,  
20 and changes in these processes may reduce the potential for exposure. This section  
21 details the processes for dry cleaning and vapor degreasing, as well as important design  
22 features for machines used in dry cleaning or vapor degreasing that may reduce  
23 workers' exposure to 1-BP.

24 9.3.3.1 DRY CLEANING

25 The typical dry cleaning process begins when garments are brought to the shop by  
26 customers and initially tagged for identification. Prior to spotting or being loaded into the  
27 dry cleaning machine, garments are typically inspected and sorted according to weight,  
28 color, and finish. Garments with visible stains are routinely treated at the spotting station,  
29 which involves the selective application of a wide variety of chemicals and steam to

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1 remove specific stains from the garments. The spotting chemicals, contained in small,  
2 plastic squeeze bottles, are applied to the stain. In addition to the spotting chemicals,  
3 spotting stations usually include a spotting board equipped with pressurized air, steam,  
4 and water guns designed to flush the chemicals and stains from the garment.

5  
6 Dry cleaning is a three-step process involving washing, extracting, and drying. Before  
7 washing, a worker adds detergent to the solvent. Water is added to the system before or  
8 during dry cleaning and aids in removing water-soluble soils from the fabric. To begin  
9 washing, clothes are manually loaded into the machine, followed by the solvent. The  
10 contents of the machine are then agitated for a period of time, allowing the solution to  
11 remove soils. Next, the clothes are spun at a high speed to extract the solvent [NIOSH  
12 1997a, b].

13  
14 After extraction, the fabric is tumble dried. The drying process may occur in the same  
15 machine or a different, dedicated dryer, depending on the system. Recirculated warm air  
16 vaporizes the residual solvent. Unheated air is then passed through the system during  
17 the cool-down cycle. This step reduces wrinkles. Following cool-down in vented  
18 machines, fresh air is passed through the system to freshen and deodorize the clothing  
19 during the aeration step. Garments are then removed from the machine prior to  
20 pressing. When a garment is placed on a pressing machine, it is pressed between two  
21 surfaces, at least one of which is heated to a temperature around 149°C (300°F).

#### 22 23 9.3.3.1.1 TYPES OF DRY CLEANING MACHINES

24 Dry cleaning machines have evolved over time to better protect worker safety and health  
25 and the environment. Dry cleaning machines encompass five “generations” that are  
26 used in the United States [NIOSH 1997e]:

- 27 • 1<sup>st</sup> Generation: transfer machines. These older, less expensive machines require  
28 manual transfer of solvent-laden clothing between a separate washer and dryer.  
29 Transfer machines were used exclusively until the late 1960s.

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- 1 • 2<sup>nd</sup> Generation: dry-to-dry (vented). These machines are nonrefrigerated, dry-to-  
2 dry machines, using a one-step process that eliminates clothing transfer. Clothes  
3 enter and exit the machine dry. The machines vent residual solvent vapors  
4 directly to the atmosphere or through a form of vapor recovery system during the  
5 aeration process.
- 6 • 3<sup>rd</sup> Generation: dry-to-dry (non-vented—drynonvented). Dry-to-dry machines with  
7 refrigerated condensers were introduced in the late 1970s and early 1980s.  
8 These non-vented machines are essentially closed systems, which are open to  
9 the atmosphere only when the machine door is opened. They recirculate the  
10 heated drying air through a vapor recovery system and back to the drying drum.  
11 These machines provide considerable solvent savings and reductions in  
12 emissions over their predecessors.
- 13 • 4<sup>th</sup> Generation: dry-to-dry (nonvented with secondary vapor control—"fourth  
14 generation" dry cleaning machines). These are essentially third-generation  
15 machines with controls to reduce residual solvent in the machine cylinder at the  
16 end of the dry cycle. They rely on both a refrigerated condenser and a carbon  
17 adsorber to reduce the solvent concentration at the cylinder outlet to <300 ppm at  
18 the end of the dry cycle. These machines are much more effective at recovering  
19 solvent vapors than machines equipped with a carbon adsorber or refrigerated  
20 condenser alone.
- 21 • 5<sup>th</sup> Generation: dry-to-dry (nonvented with secondary vapor control and drum  
22 monitor—"fifth generation" machines). Widely used in Germany but seldom in the  
23 United States, these have the same features as fourth-generation machines.  
24 However, they also have a monitor inside the machine drum and an interlocking  
25 system to ensure that the concentration is below approximately 300 ppm before  
26 the loading door can be opened.

#### 27 9.3.3.1.2 IMPORTANT MACHINE DESIGN FEATURES

28 The following machine design features are important for dry cleaning shop owners to  
29 consider when purchasing new equipment to minimize worker exposures:

- 30 • A dry-to-dry design that eliminates clothing transfer

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- 1 • Primary and secondary vapor control systems
- 2 • Secondary vapor control on each machine, with the following features:
  - 3 ○ A carbon adsorber capable of reducing the solvent vapor concentration in
  - 4 the cylinder at the end of the dry cycle to <300 ppm
  - 5 ○ Carbon adsorber capable of holding 200% of maximum quantity of
  - 6 solvent vapor that it is designed to capture
  - 7 ○ A drying sensor that automatically controls the dry cycle by monitoring the
  - 8 solvent recovery process
  - 9 ○ A door locking mechanism that prevents the loading and unloading door
  - 10 of the dry cleaning machine from opening before the end of the dry cycle

### 11 9.3.3.1.3 RETROFITTING MACHINES

12 Retrofitting is a less expensive option than purchasing new equipment, but it is not  
13 always practical and can be fairly difficult, depending on the machine. Some shop  
14 owners, particularly in New Jersey, are converting PERC dry cleaning machines so that  
15 they can use 1-BP. The cost of a retrofit is approximately \$4,000, whereas a new  
16 machine can cost \$30,000 to \$60,000 [NIOSH 2010]. A refrigerated condenser could be  
17 retrofitted on many machines currently using a water- or air-cooled condenser. This  
18 retrofit has been shown to lower short-term solvent exposures by approximately 50%  
19 and increases solvent mileage. A carbon adsorber could be retrofitted onto a third-  
20 generation machine. This retrofit has been shown to lower short-term exposures by  
21 approximately 90% [Earnest 2002].

22  
23 Other machine features that help reduce occupational exposures to solvent include:

- 24 • Safety switches to ensure closed-door operation
- 25 • Safety interlocks for heating
- 26 • Cooling and still system failures
- 27 • Emission-free still cleaning devices
- 28 • Regenerable solvent filtration systems
- 29 • Emission-free solvent filling devices

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- 1 • Seals and fittings with tighter tolerances that resist deterioration
- 2 • Process controls that lower solvent residuals within the garment after the drying
- 3 process
- 4 • Controls that reduce vapors escaping from the button and lint traps

#### 5 9.3.3.2 VAPOR DEGREASING

6 Vapor degreasing is an industrial process used to remove grease, oil, temporary  
7 coatings, dirt and other solids, where clean, dry surfaces are required. The process is  
8 commonly used to clean all types of metals, solvent resistant plastics, ceramics, glass,  
9 and other materials. Vapor degreasing can be used at any stage of a manufacturing  
10 process to clean parts of varying sizes and parts containing recesses, blind holes,  
11 perforations, crevices, or welded seams [Center for Emissions Control 1992; NIOSH  
12 2002 c,d,e,f]. Vapor degreasing may occur before painting, enameling, lacquering,  
13 electroplating, inspection, assembly, or packing. It can also be used before and after  
14 machining, before further metalwork, or before treatment or other special applications  
15 [NIOSH 2002 c,d,e,f].

16  
17 Certain workers at facilities that perform degreasing operations are at greater risk of  
18 being exposed to high levels of solvents. Facilities where degreasing is performed need  
19 to use engineering controls to reduce workers' exposures. Vapor emissions in  
20 degreasing are commonly caused by drag-out, diffusion, drafts, and sprays. There are  
21 several control-strategy options available for controlling solvent emissions. If monitoring  
22 results indicate that workers' exposures to 1-BP are above established limits when they  
23 are working near tanks, and if new or improved controls are necessary, then consider  
24 using one or more of the control options discussed in this section.

#### 26 9.3.3.2.1 TYPES OF VAPOR DEGREASERS

##### 27 9.3.3.2.1.1 OPEN-TOP VAPOR DEGREASERS

28 Open-top degreasers operate in batch mode. A cold metal part is lowered into the warm  
29 vapor zone either manually or mechanically to allow the solvent vapor to condense on

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1 the surface of the cold part. This allows the dirt to dissolve and provides a continuous  
2 rinse with the clean solvent. The part remains in the vapor zone until it reaches the  
3 solvent vapor temperature. The part is then removed from the degreaser. The built-in  
4 heat balance provides an equilibrium whereby the coil condenses vapors as fast as they  
5 are produced by the heaters in the boiling sump. The condensed vapors drip into the  
6 collection trough and course through the water separator to the rinse sump and back to  
7 the first sump to complete the “Distillate Turnover Cycle” [Center for Emissions Control  
8 1992; NIOSH 2002 c,d,e,f].

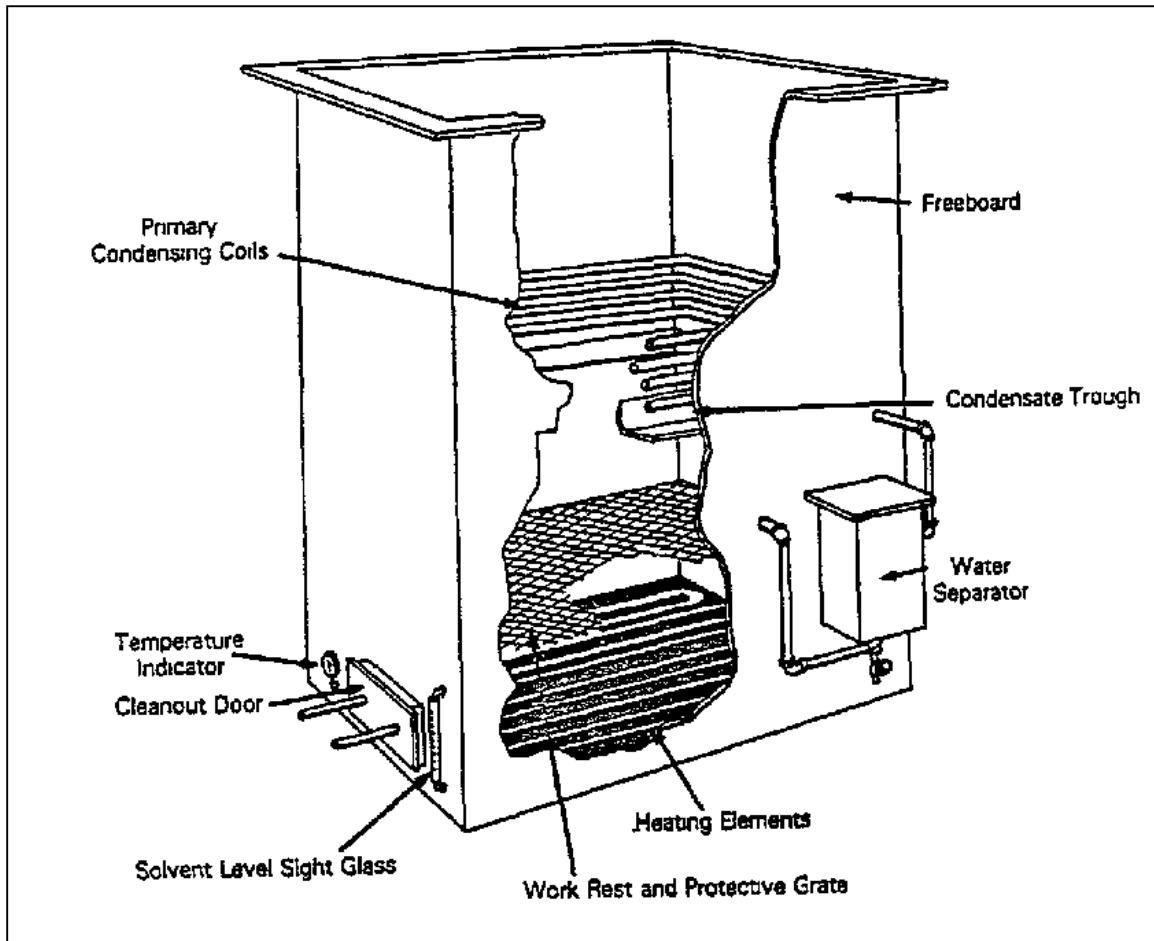
9  
10 Open-top vapor degreasers consist of several sections (see Figure 9-2):

- 11 • A tank, where solvent is heated to a boil
- 12 • The vapor zone, an area immediately above the heated tank, where vaporized  
13 solvent is present. The part(s) to be cleaned are held in the vapor zone until they  
14 reach the temperature of the vapor and surface contaminants are flushed off the  
15 part(s) by liquid solvent condensation. At this point, condensation or flushing  
16 ceases and cleaning is complete. The part is then removed from the unit, clean  
17 and dry.
- 18 • Condensation coils, where vapors are condensed and thereby prevented from  
19 escaping the degreaser. This forms a sharply defined interface between the  
20 solvent and air above the coils.
- 21 • The freeboard, an area between the condensation coils and the top of the  
22 degreaser, which provides additional control in containing the solvent vapor.

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1 **FIGURE 9-2 – OPEN-TOP DEGREASER\***



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3

\*Reference: NIOSH [2002c]

4

5 9.3.3.2.1.2 IN-LINE (CONVEYORIZED) VAPOR DEGREASER

6

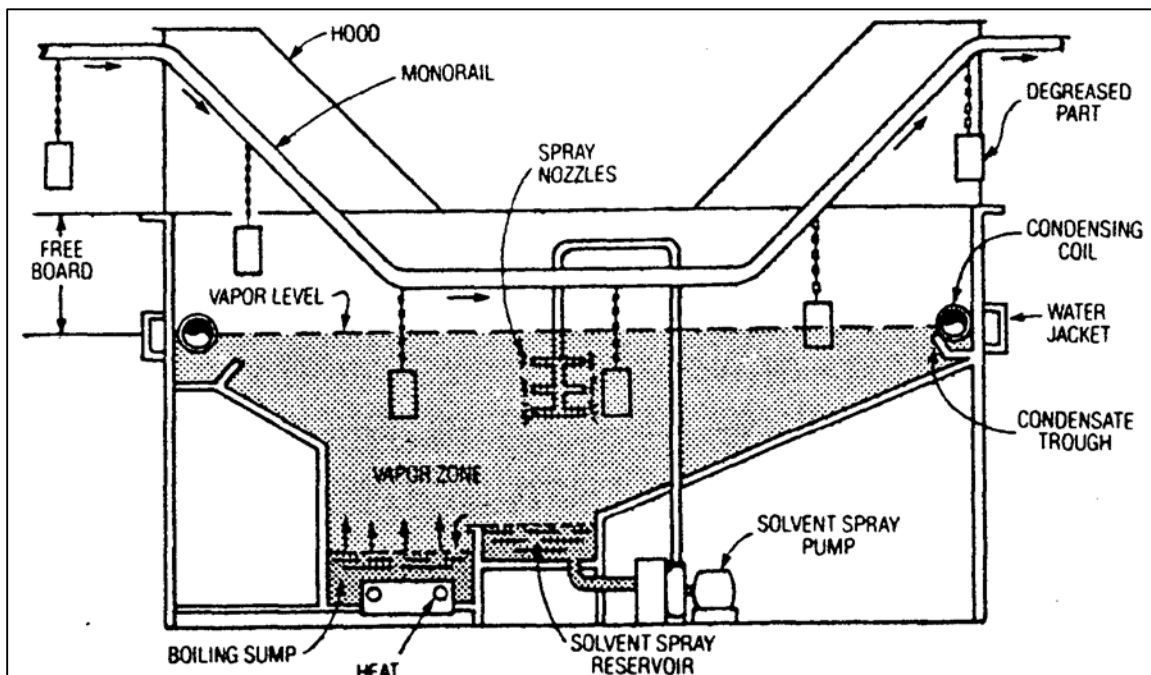
In-line or conveyORIZED vapor degreasers are usually enclosed (see Figure 9-3). Solvent emissions are generally well controlled for in-line vapor degreasers because these machines are mostly enclosed, except for the part entrance and exit ports [Center for Emissions Control 1992]. The components and cleaning process for the in-line degreaser are similar to those of the open-top degreaser. The in-line vapor degreaser is designed for continuous cleaning of parts [Center for Emissions Control 1992].

12

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1 **FIGURE 9-3 – IN-LINE (CONVEYORIZED) DEGREASER\***



2  
3 \*Reference: Center for Emissions Control [1992]

4  
5 **9.3.3.2.2 DESIGN FEATURES OF VAPOR DEGREASERS**

6 The Environmental Protection Agency (EPA) has regulations on vapor degreasing  
7 solvent emissions into the air that require certain design features and techniques be  
8 used with all existing and new degreasers when using traditional solvents [EPA 2007d;  
9 MTAP 2011]. Companies may choose to retrofit their existing vapor degreaser(s) to  
10 comply with the new regulations, rather than replacing their equipment. Retrofitting is not  
11 always practical and can be fairly difficult, depending on the machine. Be sure to check  
12 state and regional environmental regulations before making any changes to a machine.  
13 Below is a list of design recommendations that will help reduce solvent emissions:

- 14 • Add at least 75% freeboard height to degreaser width. The freeboard height is  
15 dependent upon the width of the degreaser. If the width of the degreaser  
16 increases, then the height of the freeboard should be proportionally increased.

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1 The NESHAP minimum requirement is 75%, but 100% is a control option  
2 [Center for Emissions Control 1992; EPA 1995; OSHA 1998a; MTAP 2011].

- 3 • Move parts at a rate no greater than 3.6 m/min (11 fpm). NESHAP limits speeds  
4 to 3.6 m/min (11 fpm) and requires a mechanical hoist to move parts (see  
5 Figure 9-4). Parts moving through the vapor zone at 3 m/min (10 fpm) vertically  
6 will have 30% fewer emissions than parts moving at 6 m/min (20 fpm) [MTAP  
7 2011].
- 8 • Use sliding or rolling covers on the degreaser unit to reduce drafts and  
9 turbulence (see Figure 9-5) [OSHA 1998a; MTAP 2011]. Covers that open  
10 upward on hinges can cause solvent vapors to be pulled out of the tank, which  
11 can expose workers to high levels of 1-BP. Note: If covers must open upwards,  
12 then they should be opened slowly to limit the amount of 1-BP pulled out.
- 13 • Add liquid and vapor level indicators that shut off sump heat [EPA 1995].
- 14 • Install freeboard cooling coils to provide a cool, dry layer of air above the vapor  
15 zone [MTAP 2011].
- 16 • Install third dehumidification coil. Adding a third dehumidification or freeboard  
17 coil at -18 °C (0°F) near the degreaser lip reduces idling losses by an additional  
18 80%. A main coil at 10 °C (50°F) condenses most solvent. A second coil at -18  
19 °C (0°F) overlaps or is slightly above the main coil to capture additional solvent.  
20 A third coil located near the lip of the unit dehumidifies the air, which prevents  
21 ice buildup on the secondary coil. It also eliminates convection currents in the  
22 freeboard. On the basis of these parameters, for higher boiling point  
23 halogenated solvents such as 1-BP the best coil configuration would be a  
24 dehumidification coil operating at the same temperature as the main condenser  
25 coil to eliminate internal convection currents [MTAP 2011].
- 26 • Use tanks with small openings so that cleaning does not necessitate entering  
27 the degreaser. This will prevent unnecessary worker exposure to confined-  
28 space hazards [OSHA 1998a].
- 29 • Use a closed-loop degreaser rather than an open-top degreaser (see Figure 9-  
30 6). These systems have the potential to reduce emissions up to 95% [MTAP

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- 1           2011; OSHA 1998a). Four NIOSH studies [NIOSH 2002a,b,c,d] evaluated open-  
2 top and airless vacuum vapor degreasers that used PERC as the solvent.  
3 Personal breathing zone concentrations were lower for the airless vacuum  
4 vapor degreaser (0.052 to 0.4 ppm) than for the open-top degreaser (0.9 to 17.1  
5 ppm).
- 6       • Install a secondary condenser (a primary condenser is required on vapor  
7 cleaning machines) [MTAP 2011; EPA 1995].
  - 8       • Use a carbon adsorber if lip vents are used [MTAP 2011].

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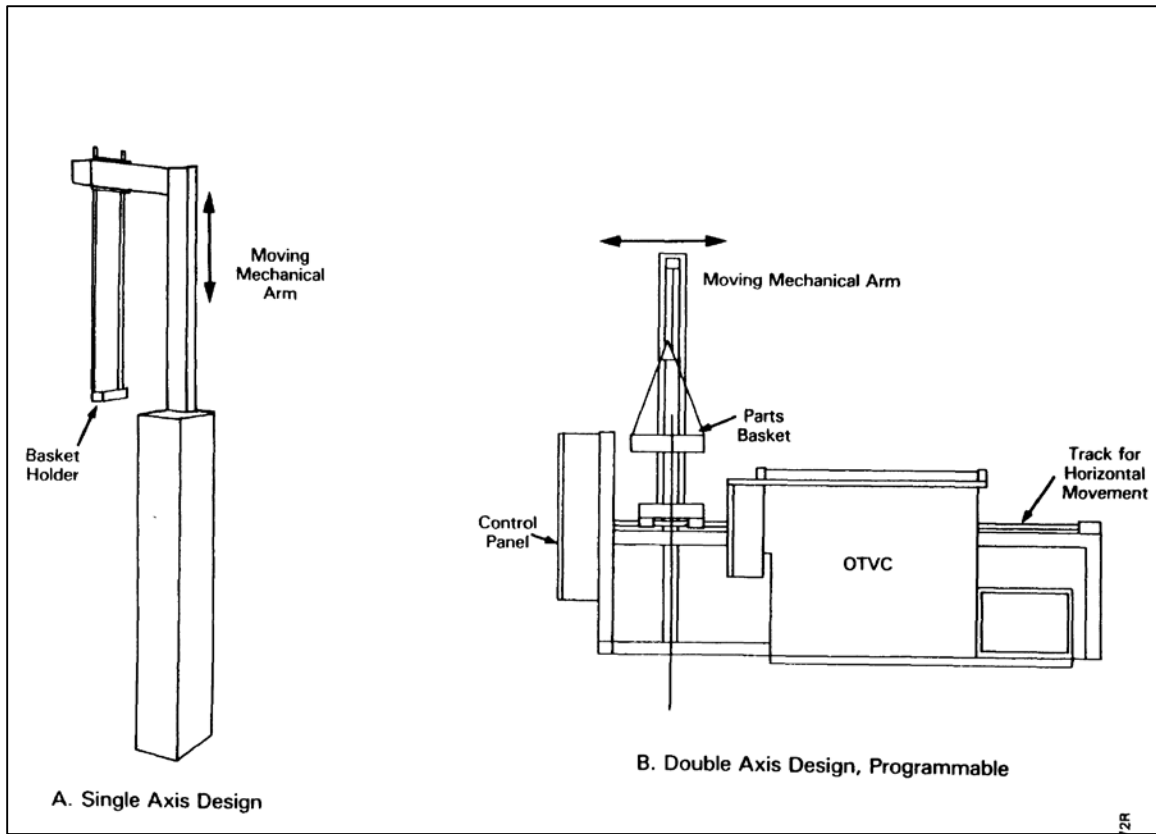
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1 **FIGURE 9-4 – AUTOMATED PARTS HANDLING SYSTEM\***



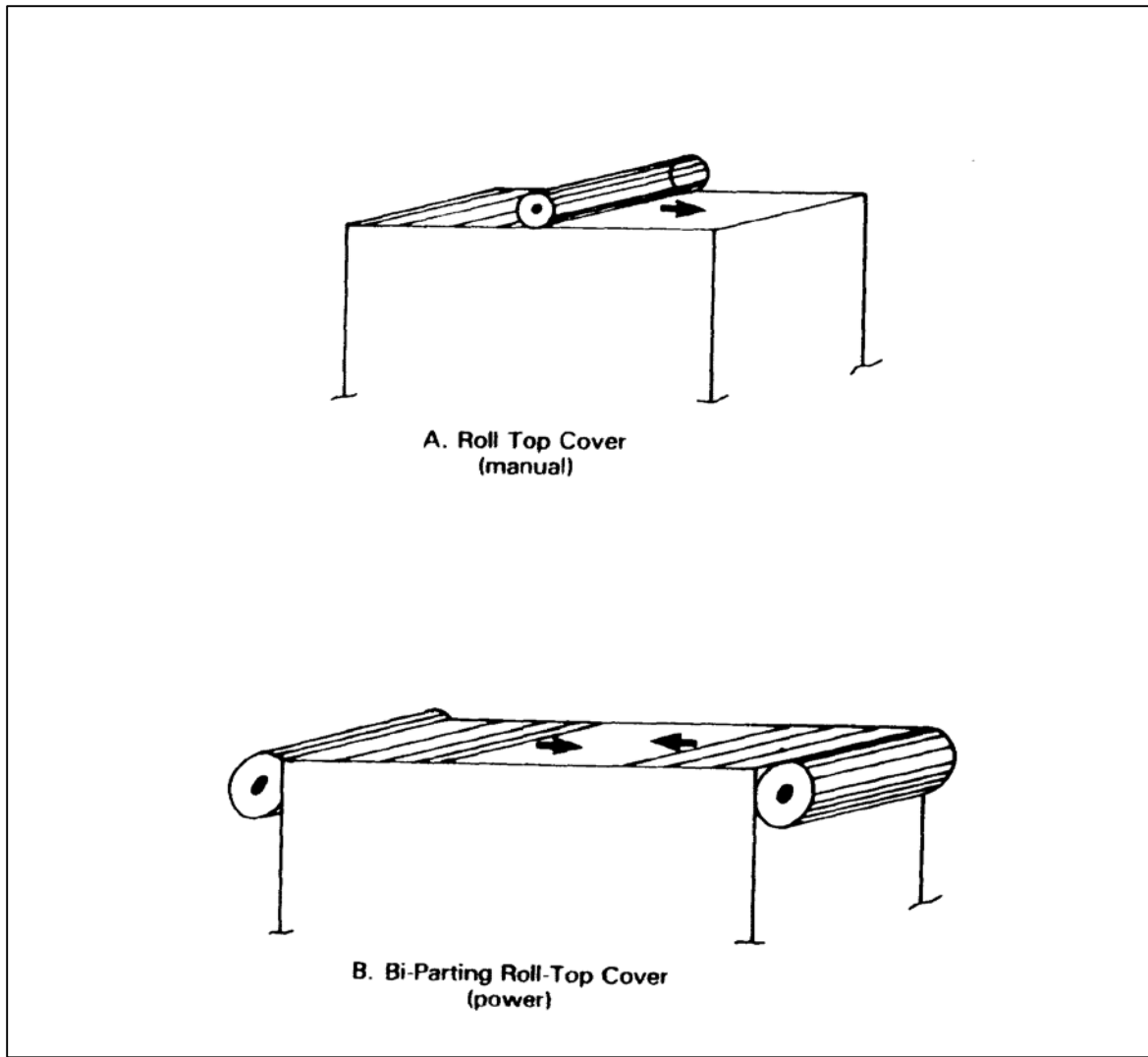
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\*Reference: EPA [1989]

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1 **FIGURE 9-5 – OPEN-TOP VAPOR DEGREASER COVER OPTIONS\***



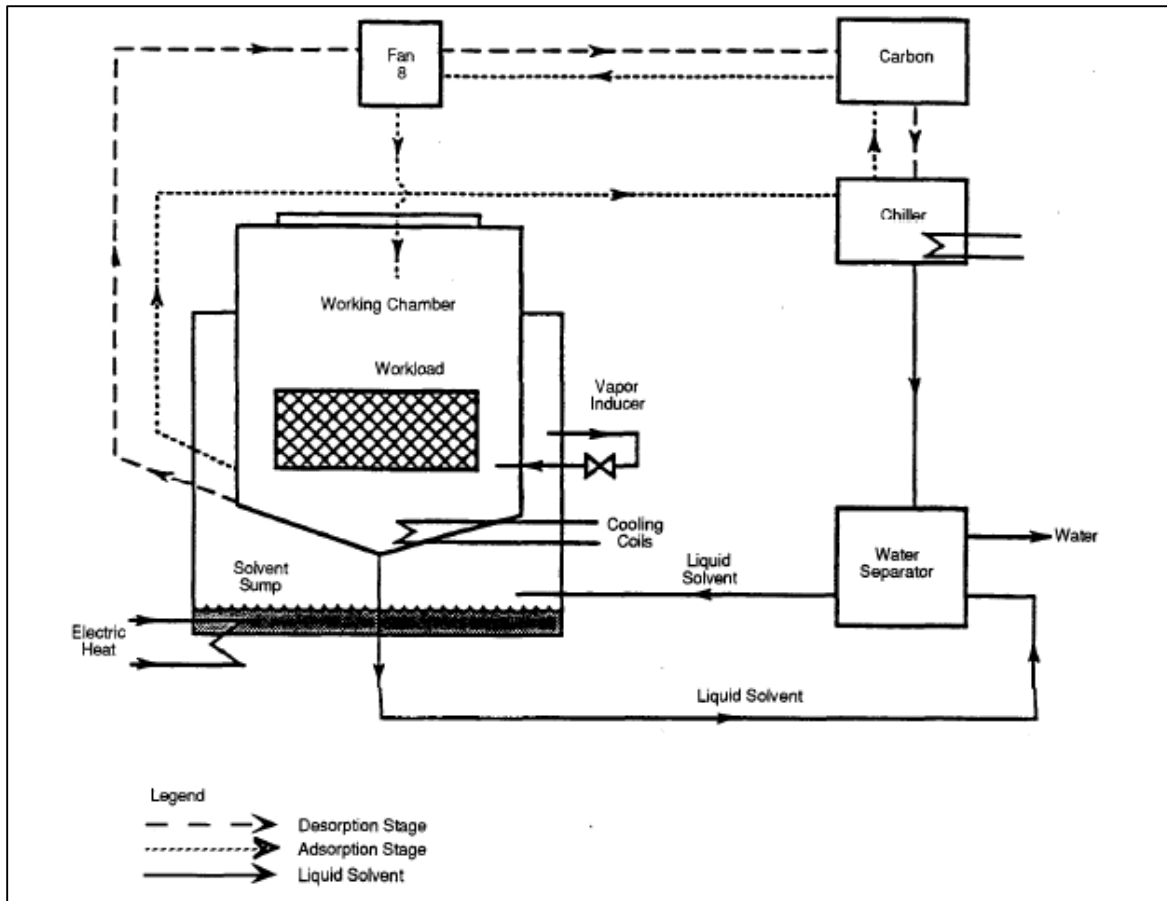
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\*Reference: EPA [1989]

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1 **FIGURE 9-6 – CLOSED-LOOP VAPOR DEGREASER\***



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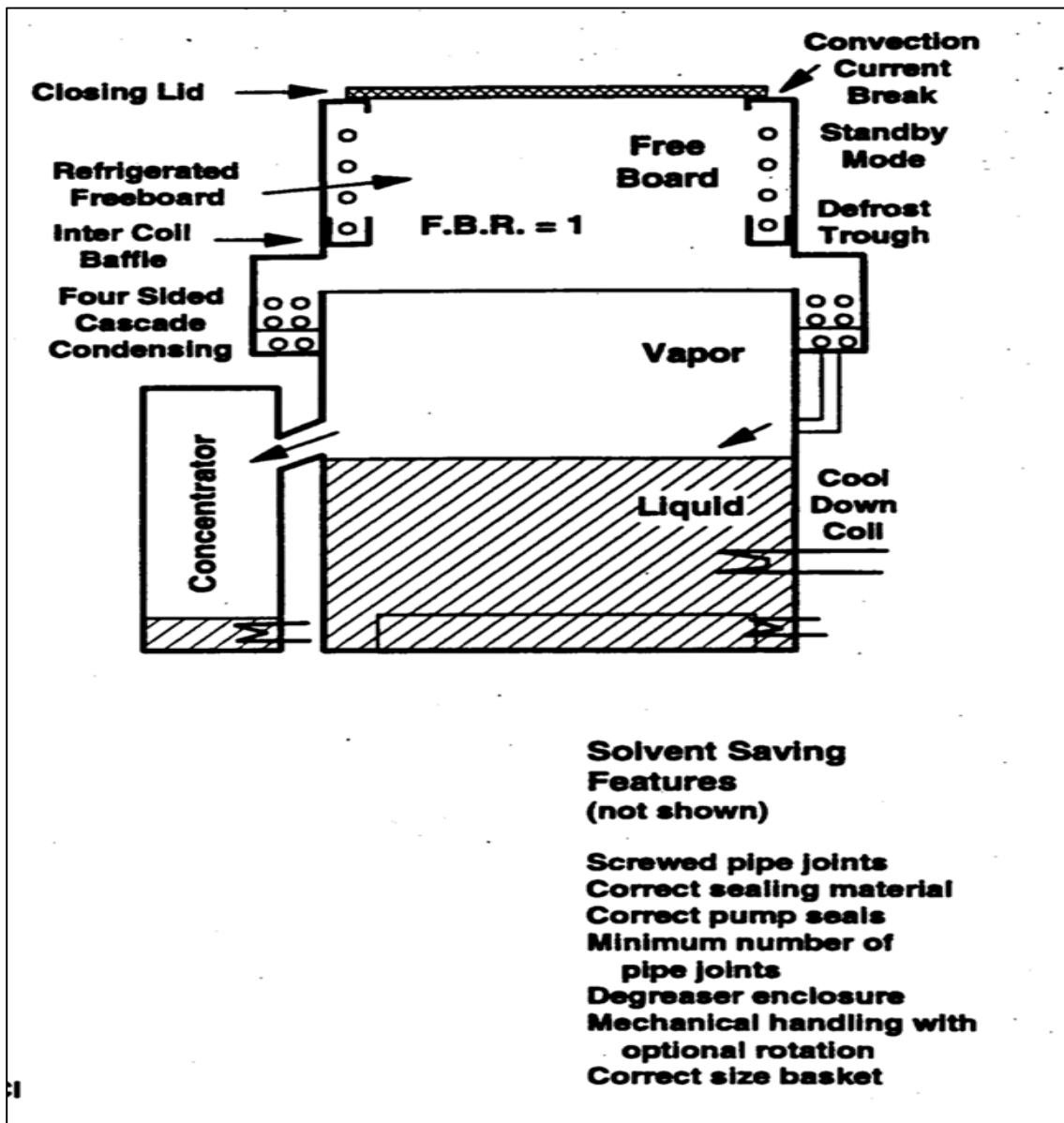
\*Reference: EPA [1994]

Figure 9-7 shows a vapor degreaser with available technology to reduce solvent emissions [Center for Emission Control; EPA 1991]. The degreaser is completely enclosed and automated. This particular design has been shown to reduce idling and working solvent losses by 90% [Center for Emissions Control 1992].

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1 **FIGURE 9-7 – VAPOR DEGREASER WITH SOLVENT REDUCTION EMISSIONS**  
2 **TECHNOLOGY\***  
3



4  
5 \*References: CENTER FOR EMISSION CONTROL [1992]; EPA [1991]

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1 9.4 ADMINISTRATIVE CONTROLS AND WORK PRACTICES

2 Solvent exposure can be reduced by proper work practices and procedures followed by  
3 employers and workers to control hazards in the workplace. When incorporated into the  
4 facility's standard operating procedures, good work practices can help reduce exposures  
5 to 1-BP while at the same time maximizing efficiency and product quality. Work practices  
6 include housekeeping and cleaning, storage and use procedures, work clothes, labels  
7 and postings, hazard awareness and communication training, and use of engineering  
8 controls.

9  
10 9.4.1 GOOD HOUSEKEEPING PRACTICES AND HYGIENE PROCEDURES

11 An organized, clean workplace improves quality assurance and reduces the potential for  
12 slips, trips, and falls. It is important to maintain good general housekeeping practices so  
13 that leaks, spills, and other problems are readily detected and corrected.

14  
15 Good personal hygiene is important to limit inhalation exposures to 1-BP and exposure  
16 from ingestion and dermal absorption. This includes hand washing and removal of  
17 contaminated clothing prior to eating, drinking, smoking or using a restroom. In addition,  
18 workers should not be allowed to smoke, eat, or drink in work areas where 1-BP is used  
19 or stored. Emergency showers and eyewash stations should be provided by the  
20 employer in areas where there is the potential for skin or eye contact with 1-BP [OSHA  
21 1982] . This equipment should be properly maintained and inspected and tested  
22 regularly. If 1-BP gets on the skin, then the affected area must be flushed promptly with  
23 large amounts of mild soap and running water for at least 15 minutes. If the eyes are  
24 contaminated with 1-BP, they should be flushed immediately for at least 15 minutes with  
25 a copious flow of water and promptly examined by a physician.

26  
27 Clean work clothing should be put on before each work shift. The clothing should be  
28 changed whenever it becomes wetted or grossly contaminated with compounds  
29 containing 1-BP. Work clothing should not be worn home. Workers should be provided  
30 with showering and changing areas free from contamination where they may store and

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1 change into street clothes before leaving the worksite. Employers should provide  
2 services for laundering work clothing so that contaminated clothes are not taken home.  
3 These precautions will protect the worker and people outside the workplace, including  
4 the worker's family, from being exposed to clothing contaminated with 1-BP. Laundry  
5 personnel should be informed about the potential hazards of handling contaminated  
6 clothing, and they should be instructed about measures to minimize their health risk.

### 8 9.4.2 HAZARD TRAINING AND COMMUNICATION

9 Workers should receive training as mandated by the OSHA Hazard Communication  
10 Standard (HCS) in the section titled "Employee Information and Training" [OSHA 2013].  
11 This training should include information and explanations about (1) how 1-BP exposure  
12 may occur; (2) the chemical and physical properties of 1-BP; (3) the corresponding  
13 safety data sheets (SDSs, formerly known as material safety data sheets or MSDSs); (4)  
14 appropriate routine and emergency handling procedures; and (5) recognition of the  
15 adverse health effects of 1-BP exposure. Workers should be trained in the appropriate  
16 use, maintenance, and storage of PPE to minimize 1-BP exposure. Workers should be  
17 trained to report promptly to their supervisor any leaks observed, failures of equipment  
18 or procedures, wet or dry spills, cases of gross contact, and instances of suspected  
19 overexposure to 1-BP. Workers should be trained to report to their supervisor or the  
20 director of the medical monitoring program any symptoms or illnesses associated with 1-  
21 BP exposure and any workplace events involving accidental or incidental exposures to  
22 1-BP. A medical monitoring and surveillance program should be in place for all workers  
23 exposed to 1-BP in the workplace (see Section 10.2).

24  
25 Safety and health programs should also include workers involved in cleaning, repair, and  
26 maintenance procedures that may cause exposure to 1-BP. Attempts should be made to  
27 minimize 1-BP exposures to these workers by the exposure control measures  
28 recommended in this chapter. When possible, these duties should be performed when  
29 the work area or facility is not in operation, to minimize these workers' airborne and  
30 dermal 1-BP exposures.

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### 1 9.4.2.1 GLOBALLY HARMONIZED SYSTEM OF CLASSIFICATION AND LABELING

2 In March 2012, OSHA revised the HCS to align with the United Nations Globally  
3 Harmonized System of Classification and Labeling of Chemicals (GHS). This revision  
4 provides detailed criteria for hazard classification as well as new label elements  
5 (pictograms, signal words, hazard statements, and precautionary statements) and  
6 establishes an SDS format. An SDS is a form that communicates the hazards of  
7 hazardous chemicals and mixtures and guidance for safe use. As of June 1, 2015,  
8 OSHA will require that SDSs adhere to a uniform format and include 16 sections that  
9 require specific information for the listed chemical or mixture. More information on SDSs  
10 can be found on the OSHA HCS website [<https://www.osha.gov/dsg/hazcom/index.html>].  
11 Employers should be aware of the changes, requirements, phase-in dates, and  
12 compliance-effective dates of the revised HCS standard. OSHA has provided additional  
13 information on the phase-in requirements and dates for transition to the revised HCS on  
14 its website [<http://www.osha.gov/dsg/hazcom/index.html>].

15  
16 NIOSH has provided (Table 9-1) the classification and labeling recommendations for 1-  
17 BP, according to the hazard classification and labeling elements outlined in the HCS  
18 [OSHA 2013]. These classifications are based on human data (Chapter 2) and data from  
19 experimental toxicology studies (Chapter 4). The classifications included in Table 9-1 are  
20 those GHS designations applicable to occupational hazards associated with inhalation  
21 and dermal hazards. Other exposure routes (e.g., oral) are not represented in this table.

22  
23 Table 9-2 provides a summary of GHS designations assigned to 1-BP by other  
24 authoritative organizations, including the European Parliament [2008] and GESTIS  
25 [2012]. The primary differences between the NIOSH GHS designations and the GHS  
26 designations provided by these other organizations include:

- 27 • European Parliament [2008] and GESTIS [2012] have designated 1-BP as a  
28 Category 2 flammable liquid, which is accompanied by *Hazard Statement 225:*  
29 *Highly flammable liquid and vapor*. The bases of these assignments are

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1 unknown. Due to an absence of primary data, this GHS designation has not been  
2 assigned to 1-BP by NIOSH.

- 3 • European Parliament [2008] and GESTIS [2012] have designated 1-BP as a  
4 Category 3 specific target organ toxicant after single exposure via inhalation  
5 route, which is accompanied by *Hazard Statement 335: May cause respiratory*  
6 *irritation* and by *Hazard Statement 336: May cause drowsiness or dizziness*. The  
7 bases of these assignments are unknown.
- 8 • NIOSH has designated 1-BP as a Category 1B carcinogen, which is  
9 accompanied by the *Hazard phrase: May cause cancer via inhalation exposures*.  
10 The basis of this assignment is studies by NTP [2011, 2014] and Morgan et al.  
11 [2011]. European Parliament [2008] and GESTIS [2012] have not classified 1-BP  
12 with this GHS designation.

13

14 The HCS indicates that mixtures containing compounds that require classification and  
15 labeling can be evaluated under a set of bridging principles if no toxicological data are  
16 available for the mixture itself. These bridging principles can be applied when there are  
17 “sufficient data on both the individual ingredients and similarly tested mixtures to  
18 adequately characterize the hazards of the mixture” [OSHA 2013]. If these bridging  
19 principles cannot be applied, the HCS provides specific cut-off values/concentration  
20 limits that are specified for each health hazard class and category. Most of these  
21 specific cut-off values/concentration limits are either  $\geq 0.1\%$  or  $\geq 1\%$ , under which  
22 mixtures containing classified compounds should be labeled accordingly. However, a  
23 few endpoints have different specific cut-off value/concentration limits specified. For  
24 most of the chemical hazards for which NIOSH has made classifications (see Table 9-1),  
25 the specific cut-off values/concentration limits specified by the HCS are  $\geq 1\%$ . An  
26 exception is for “flammable liquids,” for which HCS does not have a cut-off  
27 value/concentration limit. If these mixtures contain classified compounds below the  
28 specified HCS cut-off values/concentration limits, classification and labeling of those  
29 mixtures is not usually required. However, the HCS indicates that “while the adopted  
30 cut-off values/concentration limits adequately identify the hazard for most mixtures, there

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1 may be some that contain hazardous ingredients at lower concentrations than the  
2 specified cut-off values/concentration limits that still pose an identifiable hazard” [OSHA  
3 2013]. This is an important consideration for mixtures containing 1-BP.

4

5 The data summarized in Chapter 2 on workplace exposures to 1-BP indicate that  
6 commercially available products containing 1-BP typically do not contain concentrations  
7 less than the GHS cutoff values (i.e.,  $\geq 0.1\%$  or  $\geq 1\%$ ) for chemical mixtures. Because of  
8 this, the exposure characteristics and health risks associated with products containing  
9 low concentrations of 1-BP are unknown. NIOSH recommends that further evaluation  
10 be conducted for mixtures containing low concentrations of 1-BP to determine if  
11 exposure concentrations are capable of approaching or exceeding the NIOSH REL.  
12 Results of such evaluations that demonstrate concentrations of 1-BP exceeding the REL  
13 or that reveal a health risk should carry the appropriate pictogram, hazard statement,  
14 and signal word provided in Table 9-1 on labels and SDSs.

15





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1 **TABLE 9-1 – NIOSH GHS HAZARD CLASSIFICATIONS OF 1-BP**

GHS endpoint	Hazard category [Criteria]	Rationale (Species)	References	Pictogram	Hazard phrase	Signal word†
Acute toxicity	Category 4, inhalation [LC <sub>50</sub> value range: >2,500 and ≤ 20,000]	4-hour LC <sub>50</sub> value -- 6,957 ppm (rats)	Elf Atochem [1997] Kim et al. [1999b]		Harmful if inhaled	Warning
Eye irritation	Category 2B [Human data demonstrating eye irritation]	Irritation of the eyes and mucous linings (humans)	Ichihara et al. [2004a]		Causes serious eye damage	Warning
Skin irritation	Category 2 [Pronounced variability of response among animals, with very definite positive effects related to chemical exposure]	Erythema and edema (rabbits)	Jacobs et al. [1987] Pálovics [2004]		Causes skin irritation	Warning
Carcinogen	Category 1B [Presumed to have carcinogenic potential for humans]	Evidence of multisite tumors occurring following inhalation of 1-BP (rats; mice)	NTP [2011, 2014] Morgan et al. [2011]		May cause cancer via inhalation exposures	Danger

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<b>GHS endpoint</b>	<b>Hazard category [Criteria]</b>	<b>Rationale (Species)</b>	<b>References</b>	<b>Pictogram</b>	<b>Hazard phrase</b>	<b>Signal word†</b>
Reproductive	Category 1B [Suspected human reproductive toxicant]	Morphological abnormalities in the reproductive systems of male and female animals  Sperm morphological and motility abnormalities; <i>(Continued)</i>  Irregularities in menstrual cycles  (rats; mice; humans)	WIL Research Laboratories [2001] Yamada et al. [2003] Ichihara et al. [2000a, 2004a] Liu et al. [2009] NTP [2001]		May damage fertility or the unborn children via inhalation exposure	Danger
Specific target organ toxicity-repeated exposure	Category 1	Neurotoxicity  (rats; mice; humans)  Hepatotoxicity (liver)  (rats; mice; humans)	Ichihara et al. [2000a, 2004a,b] WIL Research Laboratories [2001] Majersik et al. [2007] Li et al. [2010]  ClinTrials BioReasech [1997b] Ichihara et al. [2004b] Li et al. [2010] NTP [2011]		Causes damage to nervous system, liver and blood through prolonged or repeated exposure if inhaled  <i>(Continued)</i>	Danger

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<b>GHS endpoint</b>	<b>Hazard category [Criteria]</b>	<b>Rationale (Species)</b>	<b>References</b>	<b>Pictogram</b>	<b>Hazard phrase</b>	<b>Signal word†</b>
Germ cell mutagens	Category 2	Direct acting mutagen in bacteria  DNA damage in in vitro assay (human leukocytes)	Barber et al. [1981]  Toraason et al. [2006]		Suspected of causing genetic defects	Warning

\*Precautionary statements for the health and physical hazard classifications presented can be found in Appendix C of the hazard communication standard [OSHA 2013].

†Appendix C of the hazard communication standard [OSHA 2013] provides several precedence rules regarding the application of pictograms and signal words as well as rules for combining or omitting hazard and precautionary statements. These precedence rules save space on the label and improve readability.






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1 **TABLE 9-2 – GHS CLASSIFICATION ESTABLISHED BY OTHER AUTHORITATIVE ORGANIZATIONS**



Reference	Hazard category	Pictogram	Hazard statement	Signal word
European Parliament[2008] GESTIS [2012]	Flammable liquid; Category 2		Highly flammable liquid and vapor	Warning
	Skin irritation; Category 2		Causes skin irritation	Warning
	Eye irritation; Category 2		Causes serious eye irritation	Warning
	Specific target organ toxicity after single exposure via inhalation route; Category 3		May cause respiratory irritation	Warning
	Specific target organ toxicity after single exposure via inhalation route; Category 3		May cause drowsiness or dizziness	Warning

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Reference	Hazard category	Pictogram	Hazard statement	Signal word
	Reproductive Category 1B		May damage fertility. May damage the unborn child	Danger
	Specific target organ toxicity after repeated exposure; Category 2		May cause damage to organs through prolonged or repeated exposure.	Warning

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### 1 9.4.2.2 LABELING AND POSTING

2 Appropriate labeling is required on all containers, according to the HCS requirements  
3 [OSHA 2013]. To communicate hazard information effectively to workers, employers  
4 should:

- 5 • Post appropriate labeling on all containers according to the HCS requirements  
6 [OSHA 2013]. In this document, NIOSH is providing the recommended label  
7 elements, including signal word, hazard statements, and pictograms, that should  
8 be included for labeling of 1-BP on SDSs and labels for shipping containers [See  
9 Table 9-1]. The precautionary statements that are also required can be found in  
10 Appendix C to the HCS [OSHA 2013].
- 11 • Post warning labels and signs describing the health risks associated with  
12 exposures at entrances to work areas and inside work areas where 1-BP is used.
- 13 • Receptacles containing used or stored 1-BP located in the workplace should  
14 carry a permanently attached label that is readily visible.
- 15 • Post warning labels and signs describing any needs for PPE in the work area.
- 16 • If respiratory protection is required, post the statement: “Wear Respiratory  
17 Protection in this Area.”
- 18 • Information on emergency first-aid procedures and the locations of emergency  
19 showers and eyewash fountains should also be provided where needed.  
20 Instruction on the content and instructions on any written signs.
- 21 • Print all labels and warning signs in both English and the predominant language  
22 of workers who do not read English.
- 23 • Verbally inform workers about the hazards and instructions printed on the labels  
24 and signs if they are unable to read them.
- 25 • Follow the requirements of the HCS for classifying and labeling 1-BP.

26

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### 1 9.4.2.3 EMERGENCY PROCEDURES

2 Emergency plans and procedures should be developed for all work areas where there is  
3 a potential for exposure to 1-BP. Workers should be trained in the effective  
4 implementation of these plans and procedures. These plans should be reviewed  
5 regularly for their effectiveness and updated when warranted because of changes in the  
6 facility, operating procedures, or chemical types or uses. Necessary emergency  
7 equipment, including appropriate respiratory protective devices, should be kept in readily  
8 accessible locations. Appropriate respirators (see Section 9.5) should be available for  
9 use during evacuation. Any spills of 1-BP should be promptly cleaned by means that  
10 minimize the inhalation of, or contact with, the spilled material. Spills should be  
11 channeled for appropriate treatment or collection for disposal. They should not be  
12 channeled directly into the sanitary sewer system.

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1 9.4.3 GOOD WORK PRACTICES: DRY CLEANING

2 Good work practices are needed more to reduce exposures associated with the  
3 traditional, less automated dry cleaning machines than with more modern dry cleaning  
4 machines. Many of the modern machines have design features that will compensate for  
5 poor work practices which may cause high exposures. For example, operators should  
6 not exceed the machine's rated capacity, shorten the drying cycle, or open machine  
7 doors while the machine is operating because each of these activities will increase their  
8 exposure. Modern, fifth-generation machines are designed so that the dry cycle cannot  
9 be shortened, and if the machine is overloaded, the dry cycle will run longer to  
10 compensate. Furthermore, many of the machine doors are automatically locked and  
11 cannot be opened while the machine is in operation. The following is a list of  
12 recommendations related to work practices needed to minimize exposures [NIOSH  
13 1997]:

- 14 • Solvents or hazardous waste should never be left in an open container.
- 15 • Dry cleaning machines should never be loaded beyond the manufacturer's  
16 capacity rating. Drying times and temperatures should be regularly monitored.
- 17 • All ventilation systems in the dry cleaning room should be operating when the dry  
18 cleaning machine is in operation.
- 19 • All doors on dry cleaning machines should be opened for a minimal amount of  
20 time.
- 21 • Operators should not open the door of the dry cleaning machine while it is  
22 running. The drying period should not be cut short.

23 The operator should keep his or her head out of the machine and should stay as far  
24 away from the door during loading and unloading as possible. A tool with a long handle  
25 should be used to retrieve clothes at the back of the drum.

26  
27 Proper maintenance is important for reducing exposures and increasing the life and  
28 performance of the machine. Both routine and as-needed maintenance should be done  
29 properly to prevent the performance of the dry cleaning machine from degrading, which  
30 might result in increased solvent exposures. Maintenance activities that are particularly

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1 important in reducing solvent exposures include ensuring vapor recovery systems are in  
2 good working order and checking for liquid and vapor leaks on equipment piping and  
3 ductwork and on the machine. When available, follow the maintenance  
4 recommendations from the manufacturer. Recommendations related to proper work  
5 practice and maintenance for dry cleaning machines include [NIOSH 1997]:

- 6 • All forms of machine maintenance should be performed when the machine and  
7 solvent are under cold conditions. Machine maintenance, such as cleaning the  
8 button/lint trap, should never be performed when the machine is in operation.
- 9 • Machine maintenance should be performed on a routine basis, in accordance  
10 with the manufacturer's guidelines.
- 11 • Leak checks should be regularly performed, and any leak should be immediately  
12 repaired.

### 13 14 9.4.4 GOOD WORK PRACTICES: VAPOR DEGREASING

15 Workers should be trained in the operation of the degreaser (if required, take and pass  
16 the operator test) and how to recognize when maintenance is required [EPA 1995]. The  
17 degreaser operator should receive annual training to ensure that their work practices  
18 maintain degreaser operation at maximum efficiency [NIOSH 2002 c,d,e,f]. The following  
19 is a list of other work practices recommended to reduce solvent exposure in degreasing:

- 20 • Maintain equipment as recommended by the manufacturer.
- 21 • When degreaser cover is open, control room drafts.
- 22 • Minimize emission loss due to external drafts (e.g., drafts from fans and  
23 ventilators).
- 24 • Store solvent waste in closed containers.
- 25 • Minimize spray use, keep spray nozzle below the cooling coils, and use short  
26 spray bursts.
- 27 • Remove parts from degreaser once dripping stops completely.
- 28 • Reduce the pooling of solvent on and in parts.
- 29 • During shutdown, turn sump heater off before the primary condenser.

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- 1 • Do not clean absorbent materials in a vapor degreaser (e.g., sponges, paper,  
2 wood, etc.).
- 3 • Do not fill cleaning machine above fill line [EPA 1995; OSHA 1998a; MTAP  
4 2011].

5

6 Preventive maintenance, routine maintenance, and comprehensive employee education  
7 are key to proper operation and maintenance of the vapor degreaser. The following list  
8 should be included in the maintenance schedule.

- 9 • Check cooling coils on a daily basis by measuring the cooling water  
10 volume/flow and the outlet and inlet temperature.
- 11 • Keep condensing coils clean to ensure efficient heat transfer.
- 12 • Check ventilation system (e.g., duct work, vent slot) regularly and repair any  
13 damage or blockage promptly. Hood and duct static pressure monitors can  
14 assist in monitoring ventilation exhaust systems.
- 15 • Check for leaks from pipe joints, pump parts or sump door gaskets.
- 16 • Visually check solvent level daily, or more frequently when the work  
17 throughput is heavy.
- 18 • Maintain vapor degreaser covers so that they are always in efficient working  
19 order.
- 20 • Drain water separators at frequent intervals, usually daily [HSE 2003a, b].

21

### 22 9.5 PERSONAL PROTECTIVE EQUIPMENT

23 The use of protective clothing and PPE is another way to create a physical barrier  
24 between the worker and the hazard. The PPE discussed in this chapter includes  
25 protective clothing and gloves; skin, face, and eye protection; and respiratory protection  
26 (with a NIOSH-certified “gas mask”). The use of different types of protective clothing and  
27 PPE, such as respirators and chemically impervious gloves and clothing, may be  
28 appropriate. Employers are responsible for ensuring PPE is used in the context of a

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1 comprehensive safety and health program. The basic elements of a PPE program, as  
2 described by OSHA [1994], include the following:

- 3 • Assigning management responsibility and conducting an initial hazard  
4 assessment
- 5 • Identifying PPE needs and properly selecting them
- 6 • Establishing inspection, cleaning, maintenance, and storage procedures
- 7 • Training workers about use of PPE and ensuring proper fit
- 8 • Reviewing the PPE program periodically

9  
10 Medical evaluation and clearance may be required for some types of PPE (e.g.,  
11 respirators). Employers should also be responsible for providing and paying for all  
12 required PPE [NIOSH 1999]. The use of PPE is considered a last resort for cases where  
13 substitution, engineering, administrative control, and other measures cannot provide  
14 sufficient control of exposures.

15  
16 Workers and persons responsible for worker health and safety should be informed that  
17 protective clothing may interfere with the body's heat dissipation, especially during hot  
18 weather or in hot-work situations. Additional monitoring is required to prevent heat-  
19 related illness when protective clothing is worn in these conditions [NIOSH 1986].  
20

### 21 9.5.1 PROTECTIVE CLOTHING AND GLOVES

22 NIOSH recommends the use of gloves and chemical protective clothing (CPC) with  
23 maximum body coverage for all workers exposed to 1-BP. While the selection of this  
24 CPC is based on permeation properties, other selection factors such as size, dexterity,  
25 and cut and tear resistance should be considered as well. Contaminants on reusable  
26 CPC, gloves, and shoes must be removed and the items must be decontaminated with  
27 proper methods before reuse [AIHA 2005]. Further information on CPC can be obtained  
28 on the NIOSH Protective Clothing topic page:

29 <http://www.cdc.gov/niosh/topics/protclothing/>. Additional information is also available in

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1 the *OSHA Technical Manual*, Section VIII, Chapter 1, “Chemical Protective Clothing”  
2 [OSHA 1999b].

3

#### 4 9.5.2 SKIN, FACE, AND EYE PROTECTION

5 1-BP causes irritation of the skin and eyes, and it may be absorbed via the skin following  
6 contact. In workplaces where skin or mucous membrane contact with 1-BP is possible,  
7 exposures should be prevented by full-body nonpermeable, disposable, or reusable  
8 CPC consisting of head, neck, and face protection; coveralls, aprons, or similar  
9 protective body clothing; chemical-resistant gloves and shoes. CPC, including gloves  
10 and aprons, made from flexible laminates (such as Viton™, 4H™ [PE/EVAL], or Silver  
11 Shield™) should be used [EnviroTech International, Inc. 2005]. Other materials, such as  
12 nitrile, neoprene, or butyl gloves, offer less protection and should be used for splash  
13 protection only [EnviroTech International, Inc. 2005].

14

15 The proper use of this protective clothing requires that all openings, seams, and  
16 interfaces be appropriately sealed and closed when the wearer is in an exposure area.  
17 Exercise care to keep work clothing separate from street clothing to avoid contamination.  
18 Properly maintain all protective clothing in an uncontaminated environment following  
19 proper decontamination procedures. Protective clothing should be inspected prior to  
20 each use and cleaned or replaced regularly.

21

22 Eye protection should be provided by the employer and used by the workers where eye  
23 contact with 1-BP is possible. Selection, use, and maintenance of eye-protective  
24 equipment should be in accordance with the provisions of the American National  
25 Standard Practice for Occupational and Educational Eye and Face Protection, ANSI  
26 Z87.1-1989 [ANSI 1989]. In work environments where 1-BP levels are above the NIOSH  
27 REL and respiratory protection is required, NIOSH recommends that eye protection be  
28 incorporated into PPE by the use of tight-fitting full-facepiece respirators or tight-fitting  
29 half-mask respirators used in conjunction with safety spectacles or goggles.

30

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1 9.5.3 RESPIRATORY PROTECTION

2 When respiratory protection is needed, the employer should establish a comprehensive  
3 respiratory protection program as described in the OSHA respiratory protection standard  
4 [OSHA 1998b]. Elements of a respiratory protection program should be established and  
5 described in a written plan that is specific to the workplace, and it must include the  
6 following:

- 7 • Procedures for selecting respirators
- 8 • Medical evaluations of workers required to wear respirators
- 9 • Fit-testing procedures
- 10 • Routine-use procedures and emergency respirator use procedures
- 11 • Procedures and schedules for cleaning, disinfecting, storing, inspecting,  
12 repairing, discarding, and maintaining respirators

13  
14 Training in respiratory hazards should include the following:

- 15 • Proper use and maintenance of respirators
- 16 • Program evaluation procedures
- 17 • Procedures for ensuring that workers who voluntarily wear respirators comply  
18 with the medical evaluation and cleaning, storing, and maintenance requirements  
19 of the standard
- 20 • A designated program administrator who is qualified to administer the respiratory  
21 protection program

22  
23 The written program should be updated as necessary to account for changes in the  
24 workplace that affect respirator use. All equipment, training, and medical evaluations  
25 required under the respiratory protection program should be provided at no cost to  
26 workers.

27  
28 Workers may voluntarily choose to use respiratory protection even when airborne 1-BP  
29 concentrations are below the NIOSH REL or other applicable federal or state  
30 occupational safety and health standards. When respirators are used voluntarily by

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1 workers, employers need to establish only those respiratory protection program  
2 elements necessary to ensure that the respirator itself is not a hazard [OSHA 1998b].  
3 Filtering facepiece particulate respirators do not provide any protection against 1-BP.  
4 Their voluntary use without a respiratory protection program should be discouraged.

5  
6 For information and assistance in establishing a respiratory protection program and  
7 selecting appropriate respirators, employers are directed to the OSHA Respiratory  
8 Protection eTool [OSHA 2011]. Additional information is also available from the NIOSH  
9 respirators topic page [NIOSH 2010b], the *NIOSH Guide to Industrial Respiratory*  
10 *Protection* [NIOSH 1987], and *NIOSH Respirator Selection Logic* [2005].

11  
12 NIOSH recommends respirator use during any task for which the exposure level either is  
13 unknown or has been documented to be higher than the NIOSH REL for 1-BP. An IDLH  
14 value of 464 ppm has been proposed for 1-BP [NIOSH 2013b; NIOSH 2015]. For  
15 exposures above the IDLH value, air purifying respirators are prohibited. Only air-  
16 supplied respirators should be used in IDLH atmospheres. For escape from  
17 atmospheres that may be IDLH, use a gas mask with a full facepiece and OV canister or  
18 pressure –demand self-contained breathing apparatus with a full facepiece

19  
20 For many exposure scenarios involving 1-BP, adequate respiratory protection should  
21 include appropriate half-mask (with gas-tight goggles to prevent eye irritation) or full-  
22 facepiece respirators (depending on worker's exposure levels) with organic vapor  
23 cartridges (OVCs) [NIOSH 2002a; NIOSH 2003b; NIOSH 2005]. Selection of the most  
24 appropriate respiratory protection equipment should be based on consideration of site-  
25 specific conditions. Table 9-3 indicates which types of respirators are recommended for  
26 use against 1-BP and the maximum use concentrations for 1-BP calculated using the  
27 NIOSH REL for this compound and the OSHA-assigned protection factors for each type  
28 of respirator listed [29 CFR 1910.134 (d)(3)(i)(A)].

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1 **TABLE 9-3 – OSHA ASSIGNED PROTECTION FACTORS AND MAXIMUM USE CONCENTRATIONS OF RESPIRATORS FOR 1-BP**

<b>Type of Respirator</b>	<b>OSHA Assigned Protection Factor*</b>	<b>Maximum Use Concentration for 1-BP†</b>
Full facepiece air purifying, w/OV cartridge(s) or canister(s)	50	15 ppm
PAPR, full facepiece w/OV cartridge(s) or canister(s)	1,000	300 ppm
PAPR, hood or helmet w/O cartridge(s) or canister(s)	25/1,000‡	7.5/300 ppm
PAPR, loose fitting facepiece w/OV cartridge(s) or canister(s)	25	7.5 ppm
SAR, continuous flow or positive pressure mode, full facepiece	1,000	300 ppm
SAR, continuous flow mode, hood or helmet	25/1,000†	5/300 ppm
SAR, continuous flow mode, loose fitting facepiece	25	7.5 ppm
SCBA, full facepiece, pressure-demand or other positive pressure mode	10,000	3,000

- 2 **Abbreviations: PAPR = powered, air-purifying respirator; ppm = parts per million; OV = organic vapor; SAR = supplied-air respirator; SCBA = self-**  
3 **contained breathing apparatus.**  
4 **\*APFs based on [29 CFR 1910.134 (d)(3)(i)(A)].**  
5 **†Maximum use concentrations will be lower than shown when those concentrations are equal to or exceed immediately dangerous to life and health**  
6 **levels.**  
7 **‡The employer should have evidence provided by the respirator manufacturer that testing of these respirators demonstrates performance at a level of**  
8 **protection of 1,000 or greater to receive an APF of 1,000. Absent such evidence, these respirators receive an APF of 25.**

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1 **CHAPTER 10: MEDICAL MONITORING AND BIOLOGICAL MONITORING**

2 **10.1 MEDICAL MONITORING**

3 The goal of a medical monitoring program for workers is the early identification of adverse  
4 health effects that may be related to workplace exposures to hazardous agents or conditions.  
5 The epidemiological and toxicological evidence summarized in this document indicate that  
6 workers exposed to 1-BP may be at risk of numerous adverse health outcomes. Early detection  
7 of adverse health effects, subsequent treatment, and workplace interventions may minimize the  
8 effects of 1-BP exposure. Medical monitoring data may also be used for the purposes of  
9 medical surveillance to identify work areas, tasks, and processes that require additional primary  
10 prevention efforts. A medical monitoring and surveillance program should be established for  
11 workers exposed to 1-BP at concentrations that exceed the REL. Such workers may benefit  
12 from inclusion in a medical monitoring and surveillance program designed to aid in protecting  
13 their health.

14  
15 **10.1.1 MEDICAL MONITORING PROGRAM DIRECTOR**

16 The employer should assign responsibility for the medical monitoring program to a qualified  
17 physician or other qualified health-care provider (as determined by appropriate state laws and  
18 regulations) who is informed and knowledgeable about the following:

- 19 • Administration and management of a medical monitoring program for occupational  
20 hazards.
- 21 • Establishment of a respiratory protection program, based on an understanding of the  
22 requirements of the OSHA respiratory protection standard and types of respiratory  
23 protection devices available at the workplace.
- 24 • Identification and management of occupational health effects, such as skin diseases and  
25 respiratory, neurological, reproductive, and developmental effects.

26  
27 **10.1.2 WORKER PARTICIPATION**

28 Workers who could receive the greatest benefit from medical monitoring include the following:

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- 1 • Those exposed to concentrations of 1-BP in excess of the REL (i.e., workers exposed to  
2 airborne 1-BP at concentrations above 0.3 ppm as 8-hour TWA)
- 3 • Those in areas or jobs qualitatively determined (by the person charged with program  
4 oversight) to have the potential for exposure to intermittent elevated airborne  
5 concentrations of 1-BP (i.e., those at risk of being exposed if they are involved in the  
6 production, distribution, or handling of 1-BP or in other tasks nearby).

7

### 8 10.1.3 WORKER EDUCATION

9 All workers in the medical monitoring program should be provided with information sufficient to  
10 allow them to understand the nature of potential workplace exposures, routes of exposure, and  
11 how to report health symptoms. The information should include these elements:

- 12 • The purposes of the program, the potential health benefits of participation, and program  
13 procedures
- 14 • Training in the potential symptoms, findings, and health effects associated with 1-BP  
15 exposure
- 16 • Training in procedures to avoid and minimize exposure to 1-BP
- 17 • Instructions for informing their supervisor or the medical director of any symptoms or  
18 effects consistent with 1-BP exposure
- 19 • Instructions for reporting any accidental exposures to 1-BP or incidents involving  
20 potentially high exposure levels.

21

### 22 10.1.4 MONITORING ELEMENTS

#### 23 10.1.4.1 INITIAL MEDICAL EXAMINATIONS

24 An initial examination should be conducted on all workers included in the medical monitoring  
25 program. This medical examination should include the following:

- 26 • A standardized occupational history questionnaire that gathers information on past jobs,  
27 a description of duties and potential exposures for each job, and a description of  
28 protective equipment the worker has used

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- 1 • A medical history focusing on conditions, such as respiratory, ophthalmologic (eye),  
2 dermatologic (skin), respiratory, or neurological symptoms or disorders, that may be  
3 exacerbated by exposure to 1-BP
- 4 • A physical examination of all systems, with careful inspection of the respiratory system,  
5 neurologic system, and skin and mucous membranes for evidence of irritation or other  
6 conditions
- 7 • For a worker who performs tasks potentially requiring respiratory protection, an  
8 evaluation of his or her ability to use negative- or positive-pressure respirators

### 9 10.1.4.2 PERIODIC MEDICAL EXAMINATIONS

10 All workers in the medical monitoring program should undergo follow-up  
11 medical examinations conducted by a physician or other qualified health-care provider, at a  
12 frequency deemed appropriate for the individual workers by that professional. Factors to help  
13 determine the frequency of periodic examinations include data gathered in the initial  
14 examination, ongoing work history, and changes in or worsening of symptoms that may be  
15 work-related. Any worker with adverse health effects potentially associated with 1-BP should be  
16 examined immediately.

### 17 10.1.4.3 WRITTEN REPORTS OF MEDICAL FINDINGS

18 The health-care professional should give each worker a written report containing the following:

- 19 • The worker's medical examination results
- 20 • Medical opinions and/or recommendations concerning any relationships between the  
21 worker's medical conditions and occupational exposures, any special instructions on the  
22 exposures and/or use of personal protective equipment, and any further evaluation or  
23 treatment

24 For each examined worker, the health-care professional should also give the employer a written  
25 report, specifying the following:

- 26 ○ Any work or exposure restrictions, based on the results of the medical  
27 evaluations
- 28 ○ Any recommendation concerning use of personal protective equipment

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- 1           ○ A medical opinion as to whether any of the worker's medical conditions is likely to
- 2           have been caused or aggravated by occupational exposures
- 3 Findings from the medical evaluations that have no bearing on the worker's ability to work with
- 4 1-BP should not be included in any reports to employers. Confidentiality of the worker's medical
- 5 records should be enforced in accordance with all applicable regulations and guidelines.

6 **10.1.5 EMPLOYER ACTIONS**

7 The employer should ensure that recommendations concerning restriction of a worker's

8 exposure to 1-BP or other workplace health hazards are followed and that the REL for 1-BP is

9 not exceeded without requiring the use of PPE. Efforts to encourage worker participation in the

10 medical monitoring program and to report any symptoms promptly to the program director are

11 important to the program's success. Medical evaluations performed as part of the medical

12 monitoring program should be provided by the employer at no cost to the participating workers.

13 Where medical removal or job reassignment is indicated, the affected worker should not suffer

14 loss of wages, benefits, or seniority. The employer should ensure that the program director

15 regularly collaborates with the employer's safety and health personnel (e.g., industrial

16 hygienists) to identify and control work exposure and activities that pose a risk of adverse health

17 effects.

18

19 Findings from the medical monitoring and surveillance program should be periodically

20 aggregated and evaluated to identify patterns of worker health that may be linked to work

21 activities and practices that require additional primary prevention efforts. This analysis should be

22 performed by a qualified health-care professional or other knowledgeable person. Confidentiality

23 of workers' medical records should be enforced in accordance with all applicable regulations

24 and guidelines.

25

26 Employers should periodically evaluate the elements of the medical monitoring program to

27 ensure that the program is consistent with current knowledge related to exposures and health

28 effects associated with occupational exposure to 1-BP.

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1 10.1.6 RECORD KEEPING

2 Employers should keep employee records on exposure and medical monitoring according to the  
3 requirements of 29 CFR 1910.20(d), Preservation of Records [OSHA 1996]. Accurate records of  
4 all sampling and analysis of airborne 1-BP conducted in a workplace should be maintained by  
5 the employer for at least 30 years. These records should include the name of the worker being  
6 monitored, duties performed and job locations, dates and times of measurements, sampling  
7 and analytical methods used, type of PPE used, and number, duration, and results of samples  
8 taken. Accurate records of all medical monitoring conducted in a workplace should be  
9 maintained by the employer for 30 years beyond the worker's termination of employment.

10 10.2 BIOLOGICAL MONITORING

11 This section summarizes available information on biomonitoring for 1-BP and its metabolites.  
12 Biomarkers for 1-BP are currently of uncertain value as early indicators of potential health  
13 effects related to 1-BP exposure. The metabolism of 1-BP is complex, occurring through  
14 multiple metabolic pathways, including the excretion of unaltered 1-BP via urine and exhaled  
15 breath, debromination, oxidation via CYP450, and conjugation with GSH [Cheever et al. 2009].  
16 Each pathway may result in the formation of metabolites that have the potential to serve as  
17 biomarkers of exposure. Several investigations have attempted to identify and quantify potential  
18 biomarkers for 1-BP [Kawai et al. 2001; B'Hymer and Cheever 2004; Hanley et al. 2006, 2009,  
19 2010; Valentine et al. 2007; Cheever et al. 2009; Mathias et al. 2012]. The results of these  
20 studies have demonstrated that urinary concentrations of particular metabolites, more  
21 specifically Br and AcPrCys, may serve as reliable biomarkers of exposures for 1-BP. Other  
22 metabolites, such as 3-bromopropionic acid (3-BPA) and n-propanal, have been identified as  
23 alternative metabolites of interest [Cheever et al. 2009].

24 Biological monitoring of workers exposed to 1-BP could assist in characterizing complex  
25 exposure scenarios, such as multiple exposure routes (i.e., inhalation and dermal contact), or  
26 assessing temporal patterns. Additional research efforts are needed to develop biomonitoring  
27 indices for 1-BP and its metabolites that would allow for the interpretation of quantitative data.  
28 Until biomonitoring indices for 1-BP are developed, NIOSH is not recommending routine  
29 biomonitoring because it is unclear how to interpret the quantitative data.

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1 10.2.1 1-BROMOPROPANE (1-BP)

2 Available data demonstrate that a large portion (>60%) of the absorbed dose of 1-BP in rodents  
3 is exhaled from the lungs and excreted in urine unchanged [Jones and Walsh 1979; Garner et  
4 al. 2006]. Measurements of exhaled 1-BP or excreted 1-BP in urine have been proposed as  
5 potential biomarkers. Numerous studies have attempted to quantify the concentration of 1-BP  
6 in exhaled air or biological media [Kawai et al. 2001; Ishidao et al. 2002; Garner et al. 2006].  
7 The use of urinary 1-BP levels as a biomarker has been recommended primarily because it  
8 would confirm 1-BP exposure, in addition to providing a quantified estimate of the magnitude of  
9 exposure [Kawai et al. 2001]. One benefit of the monitoring of urinary 1-BP levels includes  
10 limiting the impact of confounders associated with other potential biomarkers, such as urinary  
11 Br<sup>-</sup>. Kawai et al. [2001] suggested the use of end-of- shift urine sampling with use of a head-  
12 space technique and analysis via GC-FID to measure 1-BP concentration. Because of the  
13 volatile nature of 1-BP, analysis should be conducted immediately following collection to  
14 minimize possible loss of 1-BP from the urine samples [Kawai et al. 2001]. The need for  
15 immediate analysis makes this method impractical in field settings.

16 10.2.2 URINARY BROMIDE (Br<sup>-</sup>)

17 Urinary Br<sup>-</sup> levels have been investigated as a potential biomarker of exposure for 1-BP [Kawai  
18 et al. 2001; Hanley et al. 2006, 2009, 2010; Mathias et al. 2012]. The results of these studies  
19 have revealed that urinary Br<sup>-</sup> may be a useful biomarker in cases where exposures to 1-BP are  
20 anticipated to be relatively high [Mathias et al. 2012]. At low-level exposures to 1-BP, urinary  
21 Br<sup>-</sup> is not a reliable indicator of exposure to 1-BP because of interferences from non-  
22 occupational sources, such as brominated vegetable oils, seafood, and brominated drugs  
23 [Horowitz 1997; Zhang et al., 2001; Mathias et al. 2012]. In cases of elevated urinary Br<sup>-</sup> levels  
24 when airborne 1-BP concentrations have been determined to be relatively low, the potential for  
25 dietary or drug-related intake of bromine should be considered as a potential source of  
26 interference. The monitoring of urinary Br<sup>-</sup> level is a well-established process, and commercial  
27 methods are available that are relatively inexpensive [Allain et al. 1990; Kawai et al. 1997,  
28 2001]. The monitoring of urinary Br<sup>-</sup> is a practical biomarker for 1-BP when confounding  
29 exposures can be controlled and exposures are relatively high [Hanley et al. 2010].

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1 10.2.3 URINARY N-ACETYL-S-(N-PROPYL)-L-CYSTEINE (ACPRCYS)

2 Urinary AcPrCys is the primary mercapturate metabolite identified in the urine of workers  
3 exposed to 1-BP [Hanley et al. 2009, 2010]. The application of AcPrCys as a biomarker for 1-  
4 BP exposure has been demonstrated to represent a viable option in settings where air  
5 concentrations of 1-BP vapors are relatively low [Hanley et al. 2006, 2009, 2010; Cheever et al.,  
6 2009; Mathias et al. 2012]. Garner et al. [2006] reported the formation of AcPrCys from the  
7 conjugation of 1-BP with GSH. Cheever et al. [2009] confirmed the presence of mercapturic  
8 acid conjugates, including AcPrCys, in urine specimens collected from 1-BP-exposed workers.  
9 These findings indicate that AcPrCys may represent a feasible and specific biomarker for 1-BP.  
10 In comparison with urinary Br<sup>-</sup>, the monitoring of urinary AcPrCys is approximately 10 times  
11 more sensitive and specific because there are fewer interfering factors (such as dietary or drug-  
12 related intake of bromine). The LOD was reported at 0.01 µg/mL AcPrCys in urine. Despite the  
13 increased sensitivity and specificity of this method, the use of urinary AcPrCys as a biomarker of  
14 exposure for 1-BP is inhibited by the increased cost, the requirement of special analytical  
15 instrumentation, and the absence of an established commercial method. The biomonitoring of  
16 urinary AcPrCys is described in detail in Cheever et al. [2009].

17 10.2.4 URINARY 3-BROMOPROPIONIC ACID (3-BPA)

18 Urinary 3-BPA has been investigated as a potential biomarker of exposure [B'Hymer and  
19 Cheever 2004; Mathias et al. 2012]. 3-BPA is a product of P450 oxidative metabolism, and  
20 previous investigations have identified it as a potential metabolite of 1-BP in rodents [Tachizawa  
21 et al. 1982]. Few brominated chemicals are anticipated to yield 3-BPA as a metabolite; as a  
22 result, it represents a specific biomarker for 1-BP. Also, it is less volatile than 1-BP, indicating  
23 that it more likely will be present in urine in detectable concentrations. B'Hymer and Cheever  
24 [2004] conducted an experimental study to develop a method based on urinary 3-BPA levels.  
25 This experimental method was determined to be highly specific and sensitive, with a calculated  
26 LOD of 0.01 µg/mL equivalent. A subsequent study using urine samples collected from workers  
27 exposed to 1-BP revealed that 3-BPA was not detected in any of the collected samples (n = 50)  
28 [Mathias et al. 2012]. The authors indicated that unlike in rodents, P450 oxidation is not a major  
29 metabolic pathway, resulting in the formation of GSH conjugates instead of 3-BPA. Until further

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1 investigations of the metabolism of 1-BP are conducted, 3-BPA is not a recommended  
2 biomarker for 1-BP.

### 3 10.2.5 SUMMARY

4 Numerous potential biomarkers of exposure for 1-BP have been identified. Despite the absence  
5 of a standardized biological monitoring technique, methods have been developed to provide  
6 quantified estimates of the identified biomarkers for 1-BP [Kawai et al. 2001; B'Hymer and  
7 Cheever 2004; Hanley et al. 2006, 2009, 2010; Valentine et al. 2007; Cheever et al. 2009;  
8 Mathias et al. 2012]. These studies have primarily focused on methods that rely on the  
9 monitoring of urinary 1-BP levels or specific metabolites formed via debromination (Br), GSH  
10 conjugation (AcPrCys) or P450 oxidation (3-BPA). Urinary 1-BP, Br, and AcPrCys have been  
11 identified as potentially reliable biomarkers of exposure to 1-BP. However, biomarkers for 1-BP  
12 are currently of uncertain value as early indicators of potential health effects related to 1-BP  
13 exposure. Additional research is needed to develop biomonitoring indices for 1-BP and its  
14 metabolites that would allow for the interpretation of quantitative data.

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## CHAPTER 11: EXPOSURE MONITORING IN OCCUPATIONAL SAFETY AND HEALTH PROGRAMS

Employers should develop and implement comprehensive occupational safety and health programs to prevent occupational injuries, illnesses, and deaths. To be successful, safety and health programs should be developed and implemented as part of an employer's management system, with strong management commitment, worker involvement, and occupational safety and health expertise. A safety and health program designed to protect workers from the adverse effects of exposure to 1-BP should include mechanisms to identify all risk factors for exposure to the organic solvent. Just as medical monitoring is part of an overall OSH program, so is exposure monitoring. Exposure monitoring should be established whenever there is workplace exposure to 1-BP. This monitoring should (1) determine workers' exposure to 1-BP used in the workplace, (2) evaluate the effectiveness of work practices and engineering controls, and (3) facilitate selection of appropriate personal protective equipment.

### 11.1 EXPOSURE MONITORING GOALS AND STRATEGY

A workplace exposure monitoring program should have clear, stated goals [Mulhausen and Damiano 1998]. In addition to routine monitoring of airborne contaminant concentrations, the monitoring strategy should assess the effectiveness of engineering controls, work practices, PPE, training, and other factors in controlling exposures. The monitoring program should also identify areas or tasks that are associated with higher exposures to 1-BP where additional control efforts and/or sampling are needed. The program should also determine how changes in production (processes used; chemicals and other substances used; and products made) affect worker exposures.

A strategy to monitor exposure should be developed and implemented for each specific process and group of workers potentially exposed to 1-BP. The details of the plan will depend on a number of factors, including the number of workers in the group and variability in exposure within the group. Airborne concentrations of 1-BP vary daily and typically exhibit log normal distribution. Exposure concentrations will all vary according to the level of control implemented in each workplace. Well-controlled processes and environmental conditions vary less than

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1 poorly controlled processes and locations where environmental conditions change. Greater  
2 day-to-day variability in full work shift (8- or 10-hour) TWA exposures necessitates more daily  
3 assessments of exposure over the full shift, to achieve the specified level of confidence in the  
4 sampling results.  
5

## 6 11.2 EXPOSURE MONITORING PROGRAM ELEMENTS

7 Effective measurement of contaminants in the environment involves a variety of program  
8 elements. The sampling and analytical methods referred to in this chapter include an outline of  
9 tested and validated procedures that produce statistically reliable data when used in the manner  
10 prescribed. Several of the more significant elements of a monitoring program are described below  
11 [Gross and Pechter 2002; Milz et al. 2003; Soule 2000].

12 Where possible, a written sampling strategy or protocol should be developed prior to sampling;  
13 this protocol should guide all aspects of the sampling process. The protocol should describe (1)  
14 the objectives of sampling; (2) what to sample; (3) whom and where to sample; (4) how to  
15 sample; (5) when to sample; (6) how long to sample; (7) how many samples to collect; and (8)  
16 how to handle, store, and ship samples [Gross and Pechter 2002; Milz et al. 2003; Soule 2000].  
17 A walk-through survey or preliminary worksite visit is often useful in developing the sampling  
18 strategy [Jennison et al. 1996], as is knowledge of the data-keeping system to be used to store  
19 and retrieve information.  
20

21 The sampling and analytical methods recommended in this chapter include NIOSH Analytical  
22 Method 1025, which is used for 1-BP analysis in the laboratory and field settings [NIOSH  
23 2003a], and OSHA Method PV2061, which is a standardized method for 1-BP analysis [OSHA  
24 1999a].  
25

### 26 11.2.1. OBJECTIVES OF SAMPLING

27 Sampling as part of an exposure monitoring program for 1-BP has several objectives. Often, this  
28 sampling is part of a comprehensive assessment to identify and quantify exposure hazards  
29 throughout a designated plant or work area to protect workers' health. The frequency of

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1 monitoring will depend on the purpose and rationale of the sampling campaign. Specific  
2 sampling objectives might include these:

- 3 1. Characterizing (qualitatively or quantitatively) 1-BP present in workplace air or in bulk  
4 materials
- 5 2. Ensuring compliance with existing OELs
- 6 3. Assessing the effectiveness of engineering controls, work practices, PPE, training, or  
7 other methods used for exposure control
- 8 4. Identifying areas, tasks, or jobs with higher exposures that require additional exposure  
9 control
- 10 5. Evaluating exposures related to production process changes and to changes in  
11 products made or materials used
- 12 6. Evaluating specific high-risk job categories to ensure that exposures do not exceed  
13 exposure standards or guidelines
- 14 7. Measuring exposures of workers who report symptoms or illnesses.

15  
16 Sampling can also be used to assess any fugitive emissions from plant processes into the  
17 surrounding community.

18  
19 Exposure monitoring should be conducted by qualified professionals. The sampling strategy  
20 should provide an opportunity to determine each worker's exposure, either by direct measure  
21 (using personal breathing zone samples) or through reasonable estimates based on the  
22 sampling of similar work tasks or jobs. Sampling strategies that group workers according to  
23 exposure zones, uniform job titles, or functional job categories have been used in some  
24 industries to reduce the number of required samples while increasing the confidence that all  
25 workers at similar risk will be identified [Mulhausen and Damiano 1998]. Area sampling may  
26 also be useful in exposure monitoring for determining sources of airborne contaminants and  
27 assessing the effectiveness of engineering controls.

28  
29 For determining whether worker exposures are below an OEL, a focused sampling strategy that  
30 targets workers perceived to have the highest exposure concentrations may be more useful

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1 than random sampling. A focused strategy is most efficient for identifying exposures above the  
2 OEL if maximum-risk workers and time periods are accurately identified.

### 3 11.2.2 WHOM AND WHERE TO SAMPLE 4

5 Selecting whom or where to sample depends in part on the sampling objectives, as previously  
6 described. Targeting workers for sampling may be efficient if maximum-risk workers and time  
7 periods can be accurately identified. Focused sampling, including personal breathing zone  
8 sampling, may also help identify short-duration tasks (involving high 1-BP concentrations, for  
9 instance) that could result in peak exposures or contribute to elevated exposures over a full  
10 work shift. The sampling protocol should include sampling during the production of 1-BP.  
11 Sampling considerations include (1) distance from a 1-BP exposure source; (2) worker mobility;  
12 (3) air movement patterns; (4) specific tasks or work patterns; (5) individual work habits; and (6)  
13 exposure controls [NIOSH 1977]. When a sampling strategy is selected that groups workers  
14 according to similar exposure potential, uniform job titles, or functional job categories, the  
15 industrial hygienist should select at random a predetermined number of workers from each  
16 group for personal air sampling, to represent the exposures of those groups [Mulhausen and  
17 Damiano 1998; NIOSH 1977]. Area sampling may also be useful for determining sources of  
18 airborne contaminants and identifying the worst-case chemical concentrations in various  
19 locations or processes. Logic should dictate the selection of which workers or work locations are  
20 selected for other sampling.  
21

### 22 11.2.3 HOW TO SAMPLE 23

24 NIOSH and OSHA have developed sampling and analytical methods for 1-BP in the work  
25 environment. These methods include recommendations on sampling media, flow rate, duration,  
26 storage, shipment, sampling and analytical equipment, and procedures. The following  
27 paragraphs describe the methods in greater detail.  
28

29 NIOSH Method 1025 (Appendix A) has been developed to quantify airborne concentrations of 1-  
30 BP and 2-BP in the workplace [NIOSH 2003a]. The method requires the collection of PBZ air

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1 samples on a charcoal tube (Anasorb coconut shell charcoal, 100/50 milligram [mg] sections) at  
2 a sampling rate ranging from 0.01 to 0.2 liters of air per minute (L/min) and a recommended  
3 sample volume of 0.1 to 12 liters (L). The sample, which is stable for 30 days at 5°C, is analyzed  
4 following desorption of the specimen with 1 milliliter of carbon disulfide (CS<sub>2</sub>), by means of a GC  
5 unit equipped with a flame ionization detector (GC-FID). For a 12-L sample, the LOD is 1 µg  
6 (0.05 ppm) 1-BP, and the limit of quantification (LOQ) is 3 µg (0.05 ppm). This method has been  
7 partially validated. It was field tested in an industrial setting as part of a NIOSH HHE, in which 1-  
8 BP was used in the application of adhesive to foam strips [NIOSH 2003b]. This method can be  
9 applied to any process in which 1-BP may be volatilized.

10  
11 OSHA has developed sampling and analytical methods for 1-BP and 2-BP. The methods are  
12 partially validated and are available for information and trial use [OSHA 1999a]. Both method  
13 PV2061 for 1-BP and method PV2062 for 2-BP involve sample collection in which a known  
14 volume of air is drawn through charcoal tubes, which are then desorbed with a mixture of CS<sub>2</sub>  
15 and dimethylformamide (DMF) and analyzed by means of a GC-FID. The target concentration  
16 for 1-BP and 2-BP is 5 ppm. An air volume of 12 L and sampling rate at 0.1 L/min are  
17 recommended for both methods. The LOD is estimated as 0.13 µg per sample; the reliable  
18 quantification limit (RQL) for 1-BP is 0.007 ppm, and that for 2-BP is 0.004 ppm.

19  
20 To minimize the likelihood of inaccurate results, sampling equipment should be maintained in  
21 reliable working order through proper care and maintenance. All equipment should be regularly  
22 inspected and cleaned; sampling pumps should be calibrated before and after each use.  
23 Because differences in pressure drops across the sampler affect flow rate, each sampling pump  
24 should be precalibrated and postcalibrated with the specific type of sampling medium used for  
25 sampling.

26  
27 Careful record keeping in the field is also important. A detailed description of the work tasks  
28 conducted and the processes and materials involved is essential. Pertinent information such as  
29 sampling location, job category or task, air temperature, relative humidity, and possible  
30 interfering compounds in air should be documented. To avoid confusion in the laboratory,

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1 samples should be carefully labeled and accompanied by accurate paperwork. The exact  
2 sampling duration should be known to accurately calculate the sampled volume. Determining  
3 the sampling duration from the recorded start and stop times assumes that the pump functions  
4 properly over the entire sampling period. Occasional spot checks to verify proper sampler  
5 operation should be made throughout the sampling period.

6

7 Personnel performing field sampling should not overlook quality assurance procedures. The  
8 field sampling parameters, such as calibration checks and accurate timing, often affect the  
9 precision and accuracy of the final result more than the measurement's parameters. Field  
10 personnel should devote time to learning the sampling and analytical methods and sampling-  
11 equipment operation procedures prior to arriving at the sampling site. These methods usually  
12 specify the proper sampling medium, the correct flow rate and sample volume, any special  
13 precautions for sample handling and shipping, and possible interferences.

14

15 Because many modern analytical techniques are extremely sensitive, contamination of field  
16 samples should be carefully avoided. Samples should not be stored or shipped with bulk  
17 materials that might spill or otherwise contaminate them. The glassware or other containers  
18 used in sampling and shipping should be cleaned as recommended in the analytical method.

19 For many sampling methods, the analytical laboratory requires submission of a specific number  
20 of blank samples with each set of samples to be analyzed; this number of samples is specific to  
21 the method. Blanks are used to mitigate the potential for unrecognized contamination due to  
22 media or sample handling [NIOSH 1994]. The two types of sample blanks are field blanks and  
23 media blanks. Field blanks are unopened new samplers or media taken to the sampling site and  
24 handled in every way like the actual samples, except that no air is drawn through them. Media  
25 blanks are simply unopened new samplers or media that are submitted to the laboratory with  
26 the samples (these blanks are not usually taken to the field). Additional blind field blanks,  
27 labeled as field samples, should be sent along with the field samples as a further check on the  
28 analysis. Another occasionally used quality control practice is to include spiked samples—  
29 samples with known amounts of 1-BP added—along with the other field samples sent to the  
30 laboratory for analysis. These spiked samples are often prepared by a separate laboratory and

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1 then included with the other field samples sent to the analytical laboratory. They are labeled as  
2 field samples so that the analytical laboratory is blinded to their identity as spiked samples.

3  
4 The variety of types of direct-reading methods available for monitoring specific gases and  
5 vapors, as well as general contaminant concentration, is large and expanding. Detector tubes  
6 (short-term and long-term), also referred to as colorimetric indicator tubes, are widely used  
7 sampling devices for obtaining immediate, quantitative measures of gas or vapor concentrations  
8 in air. Aerosol monitors, integrating passive monitors for certain gases, and portable  
9 instrumentation for gas chromatography or infrared spectroscopy are becoming more commonly  
10 used for measuring exposures for organic solvents [ACGIH 2001; Soule 2000]. Many direct-  
11 reading instruments now used for personal or area measurements have evolved from laboratory  
12 or process control instruments. These types of monitoring techniques have significant  
13 advantages, although to date none of these methods has been validated for monitoring 1-BP in  
14 the work environment.

#### 16 11.2.4 WHEN TO SAMPLE

17 Because of the considerable variation in exposure to 1-BP, individuals conducting air sampling  
18 should coordinate with management to ensure that sampling is conducted when the organic  
19 solvent is being manufactured or used. Sampling several tasks that involve the manufacturing or  
20 use of 1-BP may be necessary to better characterize exposures. Additionally, some tasks may  
21 be conducted infrequently, and schedules may change rapidly, so the timing of sampling can be  
22 challenging. Exposure monitoring should be conducted whenever changes in processes,  
23 controls, work practices, or other conditions indicate a potential change in exposure conditions.

#### 25 11.2.5 HOW LONG TO SAMPLE

26 In general, TWA exposures should be determined from samples collected over a full work shift,  
27 for comparison with OELs and other toxicological data. Information on allowable sampling  
28 duration is given in validated sampling and analytical methods; depending on the method, in  
29 some instances it is necessary to collect multiple shorter-term samples to obtain an integrated  
30 full-work-shift sample. Work shifts that exceed 8 hours require extended sampling duration.

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1  
2 If the potential for exposure to 1-BP is sporadic throughout a work shift, then short-term or task-  
3 based sampling may be needed to replace or supplement full-shift sampling. Short-term  
4 samples for 1-BP can be collected for a duration of 15 minutes. Data from these short-term  
5 measurements and other task-based sampling can provide valuable perspective on task-based  
6 exposures and on the effectiveness of various control techniques. They can also be used to  
7 evaluate exposures relative to a short-term exposure limit [Milz et al. 2003].

#### 8 9 11.2.6 HOW MANY SAMPLES TO COLLECT

10 The numbers of samples to collect is important in that it relates to the degree of confidence set  
11 in the exposure estimate. The number of samples needed for an accurate and reliable exposure  
12 assessment depends on the purpose of the sampling; the number of processes, work tasks, or  
13 jobs to be evaluated; the variability inherent in the measured contaminant concentrations;  
14 sampling and analytical variability; and other factors. In most instances, time and budget  
15 constraints are major factors determining sample size. Statistical methods are available for  
16 calculating the minimum sample size needed to characterize a maximum-risk employee  
17 exposure subgroup or to achieve a set degree of statistical confidence in the representativeness  
18 of an exposure measurement [NIOSH 1977, 1994; Snedecor and Cochran 1967; Soule 2000].  
19 Recently, exposure control banding and Bayesian decision analysis have been used to help  
20 support exposure assessment decisions with more limited sample numbers [Hewett et al. 2006].

#### 21 22 11.2.7 SAMPLE HANDLING, STORAGE, AND SHIPMENT

23 Following sampling, appropriate handling, storage, and shipping methods should be used.  
24 Experiments demonstrated higher recovery percentages of 1-BP from samples that were  
25 refrigerated after collection [OSHA 1999a]. Attempts should be made to store and ship samples  
26 under refrigeration to ensure sample stability; this necessitates access to field refrigeration  
27 dedicated to sample storage. Working closely with the analytical laboratory before sampling to  
28 determine the handling, storage, and shipping methods required for each analyte is advised. An  
29 American Industrial Hygiene Association or other accredited analytical laboratory should  
30 analyze collected samples. Consulting with the analytical laboratory before sampling is essential

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1 to ensure that the measurement methods available can meet the defined sampling needs.

## 3 11.3 OUTCOMES OF EXPOSURE MONITORING

### 4 11.3.1 INTERPRETATION

5 As stated above, a monitoring strategy should assess the effectiveness of various methods  
6 used to control airborne 1-BP concentrations and to identify areas or tasks that are associated  
7 with higher exposures to the organic solvent. A common technique for evaluating the  
8 effectiveness of controls is to compare the outcome of environmental measurements made prior  
9 to the installation of those controls with measurements made following that installation. A control  
10 technique can be judged, for example, to be 50% efficient if the post-installation contaminant  
11 concentration is half of the pre-installation concentration.

12  
13 The TWA measurements of exposure to 1-BP, made with the collection of PBZ air samples, can  
14 be used to assess workers' exposures relative to an OEL. As discussed in the section of this  
15 document describing the development of the RELs, an 8-hour TWA measurement in excess of  
16 0.3 ppm 1-BP indicates that the worker in question was at a greater risk of developing  
17 occupationally induced cancer.

18  
19 If monitoring indicates that exposures have increased over past measurements or exposures  
20 exceed the selected OELs, then a thorough investigation of controls is needed to identify  
21 problems and guide remedial actions. Regular routine monitoring (yearly, for example) will help  
22 ensure the continued effectiveness of controls.

### 24 11.3.2 NOTIFICATION OF WORKERS

25 Employers should establish procedures for the timely notification of workers of their  
26 environmental monitoring results, any identified exposure hazards, and any subsequent actions  
27 taken to reduce their exposures. Workers should be informed about any products or processes  
28 that may generate high concentrations of 1-BP and any PPE and changes in work practices  
29 needed in response. Employers should ensure that workers understand this information and

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1 their role in helping to maintain a healthful workplace. Information should be conveyed in  
2 English and other languages as needed to ensure that all workers receive and comprehend this  
3 information.

4

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## 1 CHAPTER 12: SURVEILLANCE AND RESEARCH NEEDS

2 In this chapter, information gaps pertaining to characterizing and controlling the health risks  
3 associated with occupational exposures to 1-BP are identified. General areas of need include  
4 additional information about (1) exposure assessments, epidemiological studies, and  
5 surveillance studies; (2) exposure and hazard controls; (3) toxicological studies concerning the  
6 etiology of related diseases; and (4) best medical monitoring practices and surveillance  
7 practices for 1-BP-exposed workers.

8

9 There is a need for exposure assessments, epidemiological studies, and surveillance  
10 investigations designed specifically to characterize workplace exposures to 1-BP in commercial  
11 and industrial settings and to identify patterns of usage, exposed worker cohorts, and incidence  
12 of 1-BP-related diseases in exposed workers. Surveillance and Research in this area should  
13 address questions such as the following:

- 14 • What industries, jobs, and tasks use 1-BP?
- 15 • What are the exposure characteristics (i.e., magnitude, duration, and frequency)  
16 associated with these jobs and tasks?
- 17 • What worker cohorts have historically used or are currently using 1-BP?
- 18 • What are the historic and current trends in the production and use of 1-BP?
- 19 • What are the incidences of adverse effects, such as neurotoxicity and cancers, are  
20 associated with workplace exposures to 1-BP?
- 21 • What proportions of excess cases of adverse effects, such as neurotoxicity and cancers,  
22 are associated with workplace exposures to 1-BP?

23

24 Another need is the development and validation of additional control measures to reduce or  
25 eliminate exposures to 1-BP in various occupational settings. Research in this area should  
26 address questions such as the following:

27

- 28 • What jobs and tasks are the highest priority for developing engineering controls?
- 29 • What work practice interventions most effectively reduce worker exposure?

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- 1 • What other chemicals or processes could be used as a substitute for 1-BP? In which
- 2 industries, jobs, or tasks would substitutes be feasible?
- 3 • What engineering controls should be tested or implemented to eliminate or reduce
- 4 workplace exposures to 1-BP?
- 5 • What guidance is available on the selection and applicability of charcoal adsorbers
- 6 equipment to control exposures to 1-BP? Can such equipment originally developed
- 7 specifically for PERC be adapted for 1-BP-based tasks?
- 8 • What administrative controls should be tested or implemented to eliminate or reduce
- 9 workplace exposures to 1-BP?
- 10 • Which chemical protective clothing should be tested or recommended to eliminate or
- 11 reduce workplace exposures to 1-BP?

12

13 Regarding the health effects of 1-BP, unanswered questions include the following:

- 14 • What are the potential toxicological mechanisms by which 1-BP may cause carcinogenic
- 15 and noncarcinogenic effects?
- 16 • What is the role of metabolism in 1-BP toxicity?
- 17 • What is the role of oxidative stress in 1-BP toxicity?
- 18 • Is dermal contact and uptake a significant exposure route for 1-BP? If so, under what
- 19 conditions?
- 20 • What is the toxicity of substitutes for 1-BP?
- 21 • Are peak exposures or low-level repeated exposures responsible for the onset of 1-BP-
- 22 related adverse effects?
- 23 • Can a biological indices or reference value be developed to increase the utility of
- 24 biomonitoring data by linking biomarker concentrations with adverse health effects or
- 25 allow for the interpretation of quantitative data?

26

27 Also needed is further research on the flammability and volatility of 1-BP. Specific questions

28 include:

- 29 • Are primary data available to assist in characterizing the flammability and volatility of 1-
- 30 BP?

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- 1       • What are the risks to workers associated with the flammability of 1-BP in liquid or vapor  
2       form?  
3       • What other safety hazards (i.e., reactivity) should be taken into consideration when  
4       producing, using or handling 1-BP containing materials?  
5

6 Further research is needed for developing guidance pertaining to medical monitoring and  
7 surveillance of workers potentially exposed to 1-BP. Specific questions include these:

- 8       • What are the specific diagnostic tests, guidelines, and metrics that should be considered  
9       as part of a medical monitoring and surveillance program for 1-BP-exposed workers?  
10      • What is the most appropriate biomarker of 1-BP that can confirm and quantify magnitude  
11      of exposure?  
12      • Do biomarkers of effects exist that would be useful in worker monitoring or diagnosis?  
13      • Are there genetic markers for susceptibility to 1-BP-related adverse effects?  
14

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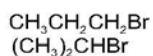
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## 1 APPENDIX A: ANALYTICAL METHOD

## 1- and 2-BROMOPROPANE

1025

MW: 123.00  
123.00CAS: 106-94-5  
75-26-3RTECS:TX4110000  
TX4111000

METHOD: 2552, ISSUE 1		EVALUATION: PARTIAL		Issue 1: 15 March 2003	
OSHA: None		PROPERTIES: 1-BP: liquid; d= 1.354 g/mL @ 20 °C; BP= 71 °C; MP = -110 °C; FP= 25 °C.			
NIOSH: None		2-BP: liquid; d= 1.310 g/mL @ 20 °C; BP= 59 °C; MP= -89 °C; FP= 19 °C.			
ACGIH: None					
NAMES & SYNONYMS: 1-Bromopropane: Propyl bromide, 1-BP. 2-Bromopropane: Isopropyl bromide, 2-BP.					
SAMPLING			MEASUREMENT		
SAMPLER:	Solid Sorbent Tube [1] (Anasorb CSC, 100/50 mg) Alternative sampler (Anasorb CMS, 150 mg/75 mg)		TECHNIQUE:	GAS CHROMATOGRAPHY, FID	
FLOW RATE:	0.01 to 0.2 L/min		ANALYTE:	1-Bromopropane and 2-Bromopropane	
VOL-MIN:	0.1L		DESORPTION:	1-mL CS <sub>2</sub> for 30 minutes with agitation.	
-MAX:	12 L		INJECTION VOLUME:	1-µL	
SHIPMENT:	Routine		TEMPERATURE:		
SAMPLE STABILITY:	30 days at 5°C		-INJECTION:	200°C	
BLANKS:	10% of field samples		-DETECTOR:	250°C	
			-COLUMN:	35°C (3 min) to 150°C (8°C/min)	
			CARRIER GAS:	Helium	
			COLUMN:	Capillary, fused silica, 30-m x 0.32-mm ID; 1.8-µm film phenyl/methyl polysiloxane, Rtx-502.2 or equivalent	
ACCURACY			CALIBRATION:	Standard solutions of analytes in CS <sub>2</sub> .	
RANGE STUDIED:	Not determined.		RANGE:	1-BP: 3.0 to 406.0 µg per sample [1] 2-BP: 4.5 to 393.0 µg per sample [1]	
BIAS:	Not determined.		ESTIMATED LOD:	1-BP: 1.0 µg per sample [1] 2-BP: 1.0 µg per sample [1]	
OVERALL PRECISION (S <sub>n</sub> ):	Not determined.		PRECISION (S <sub>n</sub> ):	1-BP: 0.015 [1] 2-BP: 0.022 [1]	
ACCURACY:	Not determined.				
APPLICABILITY: Method can be applied to any process where bromopropanes are volatilized. The method was field tested in an industrial setting where 1-bromopropane was used in the application of adhesive to foam strips [2].					
INTERFERENCES: Any compounds with similar retention times.					
OTHER METHODS: None.					

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2

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1- and 2-BROMOPROPANE: METHOD 1025, Issue 1, dated 15 March 2003 - Page 2 of 4

## REAGENTS:

1. 1-Bromopropane, GC grade.
2. 2-Bromopropane, GC grade.
3. Carbon disulfide, GC grade.
4. Helium, prepurified and filtered.
5. Hydrogen, prepurified and filtered.
6. Air, compressed, purified, filtered.
7. Calibration stock solution: Add known amounts of analytes to carbon disulfide in 10-mL volumetric flask.

\* See SPECIAL PRECAUTIONS

## EQUIPMENT:

1. Sampler: glass tube, 7 cm long, 4-mm ID, flame-sealed ends with plastic caps, containing two sections of Anasorb® CSC or equivalent (100/50 mg) separated by a 2-mm urethane plug. A silylated glass wool plug precedes the front section and a 3-mm urethane foam plug follows the back section.
2. Alternative sampler: glass tube, 7 cm long, 4-mm ID, flame-sealed ends with plastic caps, containing two sections of Anasorb® CMS or equivalent (150/75 mg) separated by a 2-mm urethane plug. A silylated glass wool plug precedes the front section and a 3-mm urethane foam plug follows the back section.
3. Personal sampling pump, 0.01 to 0.2 L/min, connected with flexible tubing.
4. Gas chromatograph equipped with FID, integrator and capillary column (see page 2552-1).
5. Autosampler vials, 2-mL, glass, with PTFE-lined crimp caps.
6. Syringes, 10- $\mu$ L, 25- $\mu$ L, and 1-mL.
7. Pipettes, 3-mL and 5-mL.
8. Volumetric flasks, 10-mL.

**SPECIAL PRECAUTIONS:** Carbon disulfide is toxic, explosive, and a fire hazard (FP= -30°C). Work with carbon disulfide in a well ventilated hood.

## SAMPLING:

1. Calibrate each sampling pump with a representative sampler in line.
2. Break the ends of sampling tube immediately before sampling. Attach sampling tube to personal sampling pump with flexible tubing.
3. Sample at an accurately known flow rate between 0.01 and 0.2 L/min for a total sample size of 12 L.
4. Cap the samplers with plastic caps and pack securely for shipment.

## SAMPLE PREPARATION:

5. Place the front and back sorbent sections of the sampler tube in separate vials. Place the glass wool preceding the front section into the vial containing the front sorbent section. Discard the urethane foam plugs.
6. Add 1.0 mL of carbon disulfide into each vial. Attach crimp caps to each vial.
7. Allow to stand for 30 minutes with occasional agitation.

## CALIBRATION AND QUALITY CONTROL:

8. Calibrate daily with at least six working standards from below the LOD to 10 times the LOQ. If necessary, additional standards may be added to extend the calibration curve.
  - a. Add known amounts of analytes to carbon disulfide solvent in a 10-mL volumetric flask and dilute to the mark. Prepare additional standards by serial dilution in 10-mL volumetric flasks.
  - b. Analyze together with samples and blanks (steps 11 and 12).
  - c. Prepare calibration graph (peak area vs  $\mu$ g analyte).

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1- and 2-BROMOPROPANE: METHOD 1025, Issue 1, dated 15 March 2003 - Page 3 of 4

9. Determine desorption efficiency (DE) at least once for each lot of Anasorb CSC or Anasorb CMS used for sampling in the calibration ranges (step 8).
  - a. Prepare three tubes at each of five levels plus three media blanks.
  - b. Inject a known amount of DE stock solution (5 to 25  $\mu\text{L}$ ) directly onto the front sorbent section of each tube with a microliter syringe.
  - c. Allow the tubes to air equilibrate for several minutes, then cap the ends of each tube and allow to stand overnight.
  - d. Desorb (steps 5-7) and analyze together with standards and blanks (steps 11 and 12).
  - e. Prepare a graph of DE vs  $\mu\text{g}$  analyte recovered.
10. Analyze a minimum of three quality control blind spikes and three analyst spikes to ensure that the calibration graph and DE graph are in control.

## MEASUREMENT:

11. Set gas chromatograph according to manufacturer's recommendations and to conditions given on page 1025-1. Inject a 1- $\mu\text{L}$  sample aliquot manually using the solvent flush technique or with an autosampler.  
NOTE: If peak area is above the linear range of the working standards, dilute with solvent, reanalyze, and apply the appropriate dilution factor in the calculations.
12. Measure peak areas.

## CALCULATIONS:

13. Determine the mass,  $\mu\text{g}$  (corrected for DE), of analyte found in the sample front ( $W_f$ ) and back ( $W_b$ ) sorbent sections, and in the average media blank front ( $B_f$ ) and back ( $B_b$ ) sorbent sections. NOTE: If  $W_b > W_f/10$ , report breakthrough and possible sample loss.
14. Calculate concentration, C, of analyte in the air volume sampled, V(L):

$$C = \frac{(W_f + W_b - B_f - B_b)}{V}, \text{mg} / \text{m}^3$$

## EVALUATION OF METHOD:

Desorption efficiency was checked for 1- and 2-bromopropane by spiking known amounts (in  $\text{CS}_2$ ) on 2 different sorbents, Anasorb CSC and Anasorb CMS. The effect of volatility on sample recovery was also determined for each analyte spiked on Anasorb CSC and Anasorb CMS sorbent tubes using GelAir portable pumps to pull air through each tube at 0.2 L/min for 60 minutes (total volume was 12 L). Storage stability was determined for each analyte after 7, 14, and 30 days.

The average DE determined for 1-bromopropane from Anasorb CSC was 96.8% (RSD = 0.015) and for 2-bromopropane was 101.0% (RSD = 0.020). When air was pulled through spiked sorbent tubes to determine the effects of volatility on sample recovery, the average DE determined for 1-bromopropane was 103.7% (RSD = 0.013) and for 2-bromopropane was 99.7% (RSD = 0.026).

The average 30-day storage stability recovery for 1-bromopropane on Anasorb CSC was 106.9% (RSD = 0.009) and for 2-bromopropane was 98.2% (RSD = 0.013). The 30 day storage recovery using Anasorb CMS was 106% (RSD = 0.014) for 1-Bromopropane and 100.6% for 2-Bromopropane.

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1- and 2-BROMOPROPANE: METHOD 1025, Issue 1, dated 15 March 2003 - Page 4 of 4

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## REFERENCES:

- [1] Pendergrass, SM [1998]. 1- & 2-Bromopropane Backup Data Report for method development, National Institute for Occupational Safety and Health, DART, Cincinnati, OH. Unpublished report.
- [2] Pendergrass, SM [1998]. Analytical Report for Sequence 9015 - 1-Bromopropane, National Institute for Occupational Safety and Health, DART, Cincinnati, Ohio, September.

**METHOD WRITTEN BY:** Stephanie M. Pendergrass, NIOSH/DART

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## APPENDIX B: QUANTITATIVE RISK ASSESSMENT BASED ON NON-CANCER DATA FROM ANIMALS

The quantitative risk assessment conducted for development of the NIOSH REL for 1-BP is based on lung tumors observed in a long-term NTP bioassay (see Chapter 7: Quantitative Risk Assessment Based on Cancer Data from Animals). However, several animal toxicity studies of shorter duration have been identified with 1-BP dose-response data for non-cancer endpoints, which are potentially suitable for extrapolation to human equivalent concentrations that support the determination of the REL. This chapter provides a description of the non-cancer animal dose-response data, the methods applied, and a non-cancer quantitative risk assessment, for comparison to the risk estimates based on tumor endpoints.

### B.1 DATA SOURCES

NIOSH has identified the following data as providing non-cancer dose-response information potentially suitable for quantitative risk assessment for occupational exposures to 1-BP:

- Liver vacuolation in male rats [ClinTrials BioResearch 1997b].
- Seminal vesicle relative weight [Ichihara et al. 2000a].
- Hind limb grip strength [Ichihara et al. 2000b].
- Liver vacuolation in F<sub>0</sub> male and female rats [WIL Research Laboratories 2001].
- F<sub>0</sub> sperm motility [WIL Research Laboratories 2001].
- F<sub>0</sub> sperm morphology [WIL Research Laboratories 2001].
- F<sub>0</sub> estrous cycle length [WIL Research Laboratories 2001].
- Renal pelvic mineralization in F<sub>0</sub> male and female rats [WIL Research Laboratories 2001].
- F<sub>1</sub> decreased live litter size [WIL Research Laboratories 2001].
- F<sub>1</sub> male fetal body weight [WIL Research Laboratories 2001].
- F<sub>1</sub> female fetal body weight [WIL Research Laboratories 2001].
- Decreased antral follicle counts [Yamada et al. 2003].

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1 The data are summarized in Table B-1 (continuously variable endpoints) and Table B-2  
2 (dichotomous endpoints). Not all of these data sets could be adequately modeled for risk  
3 estimation purposes, but modeling was at least attempted for all of them.

4

5 Non-cancer data from the 13-week and 2-year bioassays for 1-BP were also examined [NTP  
6 2011]. Although these data were not suitable for dose-response modeling, NTP [2011] was  
7 examined in order to evaluate the consistency of toxicological responses across studies and to  
8 assess the likelihood that effects seen in subchronic studies would occur at lower exposure  
9 concentrations in a chronic study. Additional detail about the individual studies is in Chapter 4:  
10 Studies of Non-Cancer Endpoints in Experimental Animals.

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1 **TABLE B-1 – SUMMARY OF 1-BP INHALATION STUDIES THAT PROVIDE DOSE-RESPONSE INFORMATION SUITABLE FOR BENCHMARK**  
 2 **CONCENTRATION ESTIMATION: CONTINUOUSLY VARIABLE ENDPOINTS\***

Continuously variable endpoints	Reference	Concentration	Sample size	Results	SD
F <sub>0</sub> estrous cycle length	WIL Research Laboratories [2001]	ppm	Number of rats	Days	SD
		0	25	4.2	0.49
		100	25	4.5	1.05
		250	25	4.7	0.9
		500	23	5.5	2.17
		750	22	5.6	1.79
F <sub>0</sub> sperm morphology	WIL Research Laboratories [2001]	ppm	Number of rats	% Normal	SD
		0	25	99.7	0.6
		100	25	99.7	0.52
		250	25	99.3	0.83
		500	24	98.2	2.59
		750	24	90.6	8.74

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<b>Continuously variable endpoints</b>	<b>Reference</b>	<b>Concentration</b>	<b>Sample size</b>	<b>Results</b>	<b>SD</b>
F <sub>0</sub> sperm motility	WIL Research Laboratories [2001]	ppm	Number of rats	% Motile	SD
		0	25	86.8	11.9
		100	25	88.8	7.22
		250	25	83.4	10.41
		500	23	71.9	9.27
		750	15	53.2	19.59
F <sub>1</sub> decreased live litter size	WIL Research Laboratories [2001]	ppm	Number of litters	Number of live pups	SD
		0	23	14.4	2.21
		100	25	13.3	3.72
		250	22	12.3	4.47
		500	11	8.3	4.1
		F <sub>1</sub> female fetal body weight	WIL Research Laboratories [2001]	ppm	Number of pups
0	23			6.9	0.59
100	24			6.7	0.64
250	21			6.9	0.61

*(Continued)*

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<b>Continuously variable endpoints</b>	<b>Reference</b>	<b>Concentration</b>	<b>Sample size</b>	<b>Results</b>	<b>SD</b>
F <sub>1</sub> male fetal body weight	WIL Research Laboratories [2001]	ppm	Number of rats	Mean	SD
		0	23	7.3	0.57
		100	24	7.1	0.63
		250	21	7.1	0.54
		500	10	8	0.91
Seminal vesicle relative weight	Ichihara et al. [2000a]	ppm	Number of rats	Mean	SD
		0	8	4.35	0.62
		200	9	3.23	0.55
		400	9	3.17	0.67
		800	9	2.62	0.87
Hind limb grip strength	Ichihara et al. [2000b]	ppm	Number of rats	Mean	SD
		0	8	353	69
		200	9	275	67
		400	9	248	69
		800	9	156	74

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Continuously variable endpoints	Reference	Concentration	Sample size	Results	SD
Antral follicle count	Yamada et al. [2003]	ppm	Number of rats	Mean	SD
		0	8	30.1	22.4
		200	9	12.6	4.82
		400	9	7.44	6.52
		800	9	3.78	3.87

---

1 Abbreviations: ppm = parts per million; SD = standard deviation.

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1 **TABLE B-2 – SUMMARY OF 1-BP INHALATION STUDIES THAT PROVIDE DOSE-RESPONSE INFORMATION SUITABLE FOR BENCHMARK**  
 2 **CONCENTRATION ESTIMATION: DICHOTOMOUS ENDPOINTS\***

---

<b>Dichotomous endpoints</b>	<b>Study</b>	<b>Concentration</b>	<b>Sample size</b>	<b>Results</b>
Hepatic vacuolation (F <sub>0</sub> males)	WIL Research Laboratories [2001]	ppm	Number of rats	Vacuolated
		0	25	0
		100	25	0
		250	25	7
		500	25	22
		750	25	24
Hepatic vacuolation (F <sub>0</sub> females)	WIL Research Laboratories [2001]	ppm	Number of rats	Vacuolated
		0	25	0
		100	25	0
		250	25	0
		500	25	6
		750	25	16

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<b>Dichotomous endpoints</b>	<b>Study</b>	<b>Concentration</b>	<b>Sample size</b>	<b>Results</b>
Renal pelvic mineralization (F <sub>0</sub> males)	WIL Research Laboratories [2001]	ppm	Number of rats	Mineralized
		0	25	1
		100	25	0
		250	25	1
		500	25	2
		750	25	6
Renal pelvic mineralization (F <sub>0</sub> females)	WIL Research Laboratories [2001]	ppm	Number of rats	Mineralized
		0	25	2
		100	25	3
		250	25	5
		500	24	12
		750	25	14
Hepatic vacuolation (male)	ClinTrials BioResearch [1997b]	ppm	Number of rats	Vacuolated
		0	15	0
		100	15	0
		200	15	0
		400	15	3
		600	15	6

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1 **Abbreviations: ppm = parts per million; SD = standard deviation.**

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1 B.2 METHODS

2 B.2.1 DOSE-RESPONSE MODELING

3 The risk assessment for 1-BP is based on benchmark concentration modeling. Dose-  
4 response modeling was done and benchmark concentrations estimated using the U.S.  
5 EPA benchmark dose (BMD) software suite, version 2.12 [EPA 2010]. The BMD (or in  
6 this case, concentration) has been defined as “. . . a statistical lower confidence limit on  
7 the dose corresponding to a small increase in effect over the background level” [Crump  
8 1984]. In current practice, and as used in this document, the benchmark concentration  
9 (BMC) refers to the maximum likelihood estimate (MLE) of the target response rate from  
10 the model; and the benchmark concentration lower-bound confidence limit (BMCL) is the  
11 95% lower confidence limit of the BMC [Gaylor et al. 1998], which is equivalent to the  
12 BMD as originally defined by Crump [1984].

13  
14 For dichotomous non-cancer responses, where uncertainty factors are customarily  
15 applied when extrapolating to humans, the benchmark response level was set at 10%  
16 added risk. The models considered were the gamma, logistic, log-logistic, multistage,  
17 probit, log-probit, quantal-linear, and Weibull models. The quantal-linear model is a  
18 subset of the multistage and Weibull models, which can assume this form if it is  
19 appropriate for a given data set, but it was included as a separate model in order to  
20 assess the fit of a strictly low-dose linear model. Models with chi-square goodness of fit  
21 *P* values of 0.10 or greater were considered to fit the data adequately.

22  
23 The benchmark response level used in this analysis for continuous responses was one  
24 standard deviation from the mean control response level. Models were selected for  
25 extrapolation to humans based on a combination of model fit and plausibility of low-dose  
26 model behavior. A minimum chi-square goodness of fit *P* value of 0.10 criterion was  
27 used for model fit; models with lower *P* values were not considered to have adequate fit  
28 and were not further considered. In one case ( $F_0$  sperm morphology), the high-dose  
29 group was dropped in order to obtain an adequate fit [WIL Research Laboratories 2001].

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1 For continuous response models the BMD software also provides an analysis of the  
2 adequacy of the model's variance structure, and a  $P$  value of 0.10 was used as a  
3 criterion of adequate variance structure fit. Among models with adequate fits to the data  
4 and adequate variance structure, models that exhibited behavior judged to be  
5 biologically implausible because of extreme non-linearity in the low-dose region were  
6 rejected in favor of more plausible models. Such behavior was observed with the power  
7 model when fitted using powers less than one; therefore, the power model was restricted  
8 to powers greater than or equal to one, in all cases. Finally, among biologically plausible  
9 continuous response models with adequate model fit, the model with the lowest Akaike  
10 Information Criterion (AIC) was selected for extrapolation to humans, on grounds of  
11 model parsimony.

#### 12 13 B.2.2 ADJUSTMENT FOR DIFFERENCES IN EXPERIMENTAL EXPOSURES

14 The BMCs and BMCLs estimated from the various studies are dependent on the specific  
15 exposure regimen employed in each study. These ranged from 6 hours/day and 5  
16 days/week [ClinTrials BioResearch 1997b] to 8 hours/day and 7 days/week [Ichihara et  
17 al. 2000a, 2004b]. The BMCs and BMCLs were adjusted to reflect a 40-hour workweek  
18 under the assumption that they are inversely proportional to exposure duration at a given  
19 concentration. For example, the BMCs and BMCLs calculated based on the results  
20 reported in Ichihara et al. [2004a, 2004b] were multiplied by 1.4 ( $7*8/40$ ) to derive  
21 adjusted BMCs appropriate to occupational exposure conditions. The adjustments  
22 applied to each BMC and BMCL are shown in Table B-3, for models that fit the data  
23 adequately.

#### 24 25 B.2.3 EXTRAPOLATION TO HUMANS

26 Animal-based BMC and BMCL estimates reflect the conditions used in the individual  
27 study they are derived from, including the number of hours per day and number of days  
28 per week that the animals were exposed. These animal-based estimates were then  
29 linearly extrapolated to duration-adjusted equivalent concentrations for a 40-hour  
30 workweek.

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1 Extrapolation from rats to humans is based on an estimate of the relative mg/kg-day  
2 metabolized dose of 1-BP in humans versus rats exposed to a given concentration. The  
3 duration-adjusted BMC and BMCL equivalent concentrations were converted to mg/kg-  
4 day inhaled values, assuming standard body weights and inhalation rate values for rats  
5 of the appropriate strains in subchronic studies [EPA 1988]. For humans, a body weight  
6 of 70 kg and total respiratory inhalation of 9.6 m<sup>3</sup> of air were assumed [ICRP 1975].  
7 Metabolism and pharmacokinetics were assumed to extrapolate across species  
8 proportional to mg/kg-day scaled according to body weight to the 0.75 power [O'Flaherty  
9 1989; Travis et al. 1990]. For computational purposes, the net effect of such scaling can  
10 be calculated as a factor of (animal body weight/human body weight)<sup>0.25</sup> [EPA 1992].

11  
12 For example, the Ichihara et al. [2000b] study of 1-BP effects on hind limb grip strength  
13 was a 12-week study using male Wistar rats. The reference body weight for a male  
14 Wistar rat in a subchronic study is 0.217 kg [EPA 1988, Table 1-2]. Note that this is not  
15 simply the average body weight at the beginning or end of the study, but a  
16 representative average weight over the duration of the study. The corresponding  
17 reference inhalation rate for a male Wistar rat in a subchronic study is 0.23 m<sup>3</sup>/day. The  
18 daily mg/kg inhaled dose in rats exposed to 400 ppm of 1-BP for an 8-hour day was  
19 estimated (Equation 1).<sup>2</sup>

20 **Equation 1:**

21  $400 \text{ ppm} * 5.031 \text{ mg/m}^3 \text{ per ppm} * 0.23 \text{ m}^3/\text{day} * 8 \text{ hour}/24 \text{ hour} / 0.217 \text{ kg} = 711$   
22  $\text{mg/kg-day}$

23  
24 This was extrapolated to humans, assuming dose equivalence in units of mg/kg-day  
25 scaled according to body weight to the 0.75 power (Equation 2).

26 **Equation 2:**

---

<sup>2</sup> A workweek of five 8-hour days has been assumed for calculation purposes; however, the same final answer is obtained if a workweek of four 10-hour days is assumed in both Equation 1 and Equation 3.

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1 Rat BMD of 711 mg/kg-day \* (0.217 kg/70 kg)<sup>0.25</sup> = Human BMD = 168 mg/kg-  
2 day

3

4 The human mg/kg-day dose was then converted to ppm (Equation 3).

5 **Equation 3:**

6  $168 \text{ mg/kg-day} * 70 \text{ Kg} / 9.6 \text{ m}^3 \text{ per day} * 1 \text{ ppm}/5.031 \text{ mg/m}^3 = 243 \text{ ppm}$

7

8 Reference body weights and inhalation rates for the animal strains used in the various  
9 toxicological studies of 1-BP are listed in Table B-4.

10

#### 11 B.2.3.1 EXTRAPOLATION OF NON-CANCER ENDPOINTS

12 The human-equivalent BMCs and BMCLs for non-cancer endpoints are estimates of  
13 frankly toxic exposure levels, and they must be adjusted by the application of uncertainty  
14 factors (UFs) to allow for uncertainty in animal-to-human extrapolation and interindividual  
15 variability. In general, these UFs are assumed to be 10-fold for animal-to-human  
16 extrapolation and another 10-fold for interindividual variability. The animal-to-human  
17 extrapolation can be subdivided into a factor of 4 for pharmacokinetics and a factor of  
18 2.5 for interspecies variability in susceptibility [WHO 1994]. In this case, the interspecies  
19 pharmacokinetic factor is replaced by the use of body weight to the 0.75 power  
20 pharmacokinetic scaling [O'Flaherty 1989; Travis et al. 1990] leaving an interspecies UF  
21 of 2.5. In addition, a factor of 3 is applied for conversion from subchronic to chronic  
22 inhalation exposure. When the three factors (10-fold for interindividual variability, 2.5-fold  
23 for interspecies variability, and 3-fold for subchronic to chronic) are multiplied, the  
24 resulting total UF is 75.

### 25 B.3 RESULTS

#### 26 B.3.1 BENCHMARK CONCENTRATION ESTIMATES FOR NON-CANCER ENDPOINTS

27 Benchmark concentration estimates (BMCs and BMCLs) for non-cancer endpoints are  
28 listed in Table B-4. Four of the models used to obtain the estimates shown in Table B-3  
29 were inadequate in terms of variance structure, and they were not further considered;

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1 these were the models for F<sub>0</sub> estrous cycle length and F<sub>0</sub> sperm motility [WIL Research  
2 Laboratories 2001], decreased antral follicle counts [Yamada et al. 2003], and F<sub>1</sub>  
3 decreased live litter size [WIL Research Laboratories 2001].

4

5 The BMC and BMCL values in Table B-4 that were derived from models with at least a  
6 marginally adequate fit were then adjusted for experimental exposure duration, as  
7 described in Section B.2 Methods, assuming an occupational exposure of 40  
8 hours/week. The duration-adjusted BMCs and BMCLs are shown in Table B-4, and they  
9 range from 195 to 568 ppm for the BMCs and from 142 to 450 ppm for the BMCLs.

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1 **TABLE B-3 – BMC MODEL FIT STATISTICS FOR NON-CANCER ENDPOINTS FROM INHALATION STUDIES OF 1-**  
 2 **BP IN RATS\***  
 3

<b>Continuously variable endpoints</b>					
	<b>Study</b>	<b>Model</b>	<b>Variance model</b>	<b>Model fit P</b>	<b>Variance fit P</b>
Estrous cycle length (F <sub>0</sub> )	WIL Research Laboratories [2001]	Linear	Homogeneous	0.7699	<.0001
Sperm morphology (F <sub>0</sub> )	WIL Research Laboratories [2001]	Polynomial	Nonconstant	0.3642	0.8531
Sperm motility (F <sub>0</sub> )	WIL Research Laboratories [2001]	Polynomial	Nonconstant	0.3742	0.04262
Decreased live litter size (F <sub>1</sub> )	WIL Research Laboratories [2001]	Linear	Nonconstant	0.4333	0.05343
Fetal body weight (F <sub>1</sub> female)	WIL Research Laboratories [2001]	Polynomial	Homogeneous	0.4636	0.3008
Fetal body weight (F <sub>1</sub> male)	WIL Research Laboratories [2001]	Polynomial	Homogeneous	0.9423	0.2362
Seminal vesicle relative weight	Ichihara et al. [2000a]	Polynomial	Homogeneous	0.12	0.5425
Hind limb grip strength	Ichihara et al. [2000b]	Linear	Homogeneous	0.6025	0.9917
Antral follicle count	Yamada et al. [2003]	Polynomial	Homogeneous	0.43	<.0001
<b>Dichotomous endpoints</b>					
	<b>Study</b>	<b>Model</b>	<b>Variance model</b>	<b>Model fit P</b>	<b>Variance fit P</b>
Liver vacuolation (F <sub>0</sub> males)	WIL Research Laboratories [2001]	Log-logistic	N/A*	0.9391	N/A
Liver vacuolation (F <sub>0</sub> females)	WIL Research Laboratories [2001]	Log-probit	N/A	0.9879	N/A
Renal pelvic mineralization (F <sub>0</sub> males)	WIL Research Laboratories [2001]	Logistic	N/A	0.6294	N/A
Renal pelvic mineralization (F <sub>0</sub> females)	WIL Research Laboratories [2001]	Log-probit	N/A	0.7346	N/A
Liver vacuolation (male )	ClinTrials BioResearch [1997b]	Multistage	N/A	0.9552	N/A

4 **Abbreviations: BMC = benchmark concentration; N/A = not applicable.**

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1 **TABLE B-4 – BMC AND BMCL ESTIMATES FOR NON-CANCER TOXICITY OBSERVED IN INHALATION STUDIES OF 1-BP IN RATS**

<b>Continuously variable endpoints</b>								
<b>[reference]</b>	<b>Endpoint</b>	<b>BMC*</b>	<b>BMCL*</b>	<b>Animal hours/day</b>	<b>Animal days/wk</b>	<b>Duration Adjustment</b>	<b>Adjusted BMC</b>	<b>Adjusted BMCL</b>
Ichihara et al. [2000a]	Seminal vesicle relative weight	175.8	108.2	8	7	1.4	246	152
Ichihara et al. [2000b]	Hind limb grip strength	285.7	213.8	8	7	1.4	400	299
WIL Research Laboratories [2001]	Sperm morphology (F <sub>0</sub> )	304.7	225.0	6	7	1.05	320	236
WIL Research Laboratories [2001]	Fetal body weight (F <sub>1</sub> female)	497.8	403.6	6	7	1.05	523	424
WIL Research Laboratories [2001]	Fetal body weight (F <sub>1</sub> male)	486.0	421.6	6	7	1.05	510	443
<b>Dichotomous endpoints</b>								
<b>[reference]</b>	<b>Endpoint</b>	<b>BMC</b>	<b>BMCL</b>	<b>Animal hours/day</b>	<b>Animal days/wk</b>	<b>Duration Adjustment</b>	<b>Adjusted BMC</b>	<b>Adjusted BMCL</b>
ClinTrials BioResearch [1997b]	Liver vacuolation (Male rats)	345.7	226.1	6	5	0.75	259	170
WIL Research Laboratories [2001]	Liver vacuolation (F <sub>0</sub> males)	187.6	143.5	6	7	1.05	197	151
WIL Research Laboratories [2001]	Liver vacuolation (F <sub>0</sub> Females)	415.4	322.1	6	7	1.05	436	338
WIL Research Laboratories [2001]	Renal pelvic mineralization (F <sub>0</sub> males)	541.3	428.3	6	7	1.05	568	450
WIL Research Laboratories [2001]	Renal pelvic mineralization (F <sub>0</sub> females)	185.4	135.0	6	7	1.05	195	142

2 **Abbreviations: BMC = benchmark concentration; BMCL = benchmark concentration low (95% lower confidence limit for the benchmark**  
3 **concentration).**

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1 B.3.2 SELECTION OF NON-CANCER ENDPOINTS FOR EXTRAPOLATION TO HUMANS

2 Two types of endpoints were modeled to generate the benchmark concentrations shown  
3 in Tables B-3 and B-4: continuously variable endpoints and dichotomous endpoints. The  
4 lowest duration-adjusted BMC and BMCL values were observed for the dichotomous  
5 endpoint of renal pelvic mineralization in the F<sub>0</sub> females [WIL Research Laboratories  
6 [2001]. The BMC and BMCL for hepatic cytosolic vacuolation in the F<sub>0</sub> males were  
7 similar [WIL Research Laboratories 2001]. The WIL Research Laboratories [2001] study  
8 was primarily a reproductive toxicity study, and exposures to the F<sub>0</sub> generation were  
9 limited to 10 weeks of exposure. The reproducibility of the renal and hepatic pathology  
10 observed in the WIL Research Laboratories [2001], and the long-term consequences to  
11 these organs of continued exposure to 1-BP were assessed by comparison to the results  
12 of the 13-week ClinTrials BioResearch [1997b] study, and preliminary reports of the NTP  
13 13-week and 2-year bioassays for 1-BP [NTP 2011].

14  
15 Renal pelvic mineralization was not reported in the ClinTrials BioResearch [1997b]  
16 study, or in the 13-week NTP bioassay [NTP 2011]. Only a low and sporadic incidence  
17 of renal pelvic mineralization was seen in the 2-year NTP bioassay [NTP 2011], and no  
18 significant long-term kidney pathology. Thus the renal pelvic mineralization observed in  
19 the WIL Research Laboratories [2001] study was judged to be nonreproducible and of  
20 minimal toxicological significance, and not an appropriate endpoint for extrapolation to  
21 occupational exposures.

22  
23 Hepatic cytosolic vacuolation was reported in the ClinTrials BioResearch [1997b] study  
24 and the 13-week NTP bioassay [NTP 2011], so this pathological endpoint was consistent  
25 among the various subchronic studies. However, the NTP 2-year bioassay results  
26 demonstrated hepatic cytosolic vacuolation in approximately 70% of the rats, with no  
27 clear dose-response and no obvious relationship to other hepatic pathology. This lesion  
28 appears to be an effect of aging in rats, without clear pathological significance, and it  
29 was thus also considered to be an inappropriate endpoint for extrapolation to  
30 occupational exposures. Although renal pelvic mineralization and hepatic cytosolic

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1 vacuolation were considered inappropriate to serve as the bases for occupational  
2 exposure recommendations, extrapolation of these endpoints to humans was carried  
3 forward as a sensitivity analysis.

4  
5 The lowest duration-adjusted BMC and BMCL (from an adequate model) among the  
6 continuous endpoints reported in Table B-4 were for decreased seminal vesicle weight  
7 [Ichihara et al. 2000a]. The larger WIL Research Laboratories [2001] study also  
8 examined this endpoint, and researchers saw some effects on the absolute seminal  
9 vesicle weight, but not on the relative weight. Since absolute weights may be  
10 confounded by changes in body weight at the higher dose levels, toxicity evaluation  
11 should focus on the relative weights. The WIL Research Laboratories [2001] study  
12 (Table 125) shows no major effects on seminal vesicle relative weight, up to 750 ppm.  
13 The NTP 13-week and 2-year bioassays did not report seminal vesicle weights;  
14 however, the 2-year bioassay did not detect any significant seminal vesicle pathology. It  
15 is possible that the discrepancy between the results reported by Ichihara et al. [2000a]  
16 and the larger WIL Research Laboratories [2001] and NTP studies is due to a strain  
17 difference; Ichihara et al. [2000a] used Wistar rats, whereas SD rats were used in the  
18 WIL Research Laboratories [2001] study and F344 rats were used by the NTP. The fact  
19 that the toxicity observed in the small (n = 8-9) Ichihara study was not seen in the larger  
20 WIL Research Laboratories study and did not lead to pathological changes in the larger  
21 and much longer duration NTP 2-year study suggests that this endpoint should not be  
22 used as the basis for quantitative risk assessment without additional confirmation.

23  
24 The next-lowest duration-adjusted BMC and BMCL among the continuous endpoints  
25 with adequate models were for sperm morphology in the F<sub>0</sub> generation of the WIL  
26 Research Laboratories [2001] study; the BMC is 320 ppm, and the BMCL is 236 ppm  
27 (Table B-4). The endpoint of decreased hind limb grip strength in the Ichihara et al.  
28 [2000b] study yielded a duration-adjusted BMC value of 400 ppm and BMCL value of  
29 299 ppm, suggesting that neurotoxicity may occur at exposure levels similar to those  
30 that produce reproductive toxicity. The other continuous endpoints evaluated in Table B-

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1 4 yielded larger BMC and BMCL values; therefore, recommendations for occupational  
2 exposure to 1-BP are based on the results for sperm morphology in the F<sub>0</sub> generation of  
3 the WIL Research Laboratories [2001] study and decreased hind limb grip strength in  
4 Ichihara et al. [2000b]. BMC and BMCL values for decreased live litter size and  
5 decreased fetal body weight for F<sub>1</sub> females in the WIL study were larger than the BMC  
6 and BMCL values for sperm morphology in the F<sub>0</sub> generation of the WIL Research  
7 Laboratories [2001] study and decreased hind limb grip strength in the Ichihara et al.  
8 [2000b] study. Extrapolation of these endpoints to humans was carried forward as a  
9 sensitivity analysis.

### 11 B.3.3 EXTRAPOLATION OF NON-CANCER ENDPOINTS TO HUMANS

12 Extrapolation to humans begins with the selection of a point of departure, that is, either a  
13 BMC or BMCL. Choosing a 95% lower confidence limit dose estimate, a BMCL, as the  
14 point of departure allows for the statistical variability of the benchmark concentration  
15 estimate, and it is thus more likely to be health-protective than the use of a central  
16 estimate such as a BMC. Extrapolation is therefore based on the lowest BMCL from a  
17 toxicologically relevant endpoint with an adequate dose-response model, 236 ppm,  
18 based on altered sperm morphology in the F<sub>0</sub> generation of the WIL Research  
19 Laboratories [2001] study.

21 In the case of 1-BP, the toxic effects used as a basis for risk assessment occur in sites  
22 distant from the sites of contact (respiratory tract and skin), and they thus involve the  
23 systemic uptake of 1-BP. Extrapolation from rats to humans is therefore based on an  
24 estimate of the relative mg/kg-day metabolized dose of 1-BP in humans versus rats  
25 exposed to a given concentration, with metabolism and pharmacokinetics assumed to  
26 scale across species according to body weight to the 0.75 power [O'Flaherty 1989;  
27 Travis et al. 1990]. The duration-adjusted BMC and BMCL estimates from Table B-4  
28 were extrapolated to humans on this basis, and are shown in Table B-5.

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1 **TABLE B-5 – HUMAN-EQUIVALENT BMC AND BMCL ESTIMATES FOR 1-BP TOXICITY, EXTRAPOLATED FROM**  
 2 **BMC AND BMCL ESTIMATES FOR NON-CANCER ENDPOINTS IN RATS**

Study	Endpoint	Duration adjusted rat BMC* (ppm)	Duration adjusted rat BMCL* (ppm)	Rat strain, sex	Reference BW (grams) †	8-hour m <sup>3</sup> inhaled‡	Extrapolated human BMC (ppm)	Extrapolated human BMCL (ppm)
Ichihara et al. [2000b]	Hind limb grip strength	400	299	Wistar, male	217	0.077	243	182
WIL Research Laboratories [2001]	Sperm morphology (F <sub>0</sub> males)	320	236	SD, male	267	0.090	195	144
WIL Research Laboratories [2001]	Decreased live litter size (F <sub>1</sub> female)	523	424	SD, female	204	0.073	318	258
WIL Research Laboratories [2001]	Fetal body weight (F <sub>1</sub> female)	510	443	SD, female	204	0.073	311	270
WIL Research Laboratories [2001]	Liver vacuolation (F <sub>0</sub> males)	197	151	SD, male	267	0.090	120	92
WIL Research Laboratories [2001]	Renal pelvic mineralization (F <sub>0</sub> females)	195	170	SD, female	204	0.073	119	103

3 **Abbreviations: BMC = benchmark concentration; BMCL = benchmark concentration low (95% lower confidence limit for the benchmark**  
 4 **concentration); BW = body weight; BW<sup>0.75</sup> = body weight to the three-fourths power; m<sup>3</sup> = cubic meter; ppm = parts per million**

5 **\*For additional information pertaining to the calculation of the values presented in Table B-3-3, see Section B.2**

6 **†From EPA [1988], Table 1-2.; ‡From EPA [1988], Table 1-4.**

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1 B.3.4 APPLICATION OF UNCERTAINTY FACTORS TO HUMAN-EQUIVALENT  
2 CONCENTRATIONS ESTIMATES FOR 1-BP TOXICITY FOR NON-CANCER ENDPOINTS  
3

4 The human-equivalent BMC and BMCL estimates in Table B-5 are estimates of frankly  
5 adverse effect levels, and it must be adjusted by the application of UFs to allow for  
6 uncertainty in animal-to-human extrapolation and interindividual variability. As discussed  
7 in Methods (Section B.3.3), a total UF of 75 is appropriate for the non-cancer endpoints.  
8 Table B-6 provides the extrapolated concentrations for four endpoints, following the  
9 application of the UFs.

10

11 The lowest occupationally relevant human-equivalent BMCL for 1-BP is 144 ppm,  
12 derived from effects on sperm morphology in the F<sub>0</sub> generation of the WIL Research  
13 Laboratories [2001] study. Application of the 75-fold UF yields an estimated occupational  
14 exposure concentration of approximately 1.9 ppm. Similarly, the 182 ppm human-  
15 equivalent BMCL for decreased hind limb grip strength in the Ichihara et al. [2000b]  
16 study yields an estimated occupational exposure concentration of approximately 2.4  
17 ppm.

18

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1 **TABLE B-6 – APPLICATION OF UNCERTAINTY FACTORS TO HUMAN-EQUIVALENT BMCL ESTIMATES FOR NON-CANCER ENDPOINTS\***

2

Study	Endpoint	Extrapolated human BMC (ppm)	Extrapolated human BMCL (ppm)	UF	BMC/UF (ppm)	BMCL/UF (ppm)
Ichihara et al. [2000b]	Hind limb grip strength	243	182	75	3.2	2.4
WIL Research Laboratories [2001]	Sperm morphology (F <sub>0</sub> )	195	144	75	2.6	1.9
WIL Research Laboratories [2001]	Decreased live litter size (F <sub>1</sub> female)	318	258	75	4.2	3.4
WIL Research Laboratories [2001]	Fetal body weight (F <sub>1</sub> female)	311	270	75	4.1	3.6

3 **Abbreviations: BMC = benchmark concentration; BMCL = benchmark concentration low (95% lower confidence limit for the benchmark**  
 4 **concentration); ppm = parts per million; UF = uncertainty factor.**

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1 B.4 DISCUSSION

2 One assumption made in this analysis is that recommendations for occupational exposure  
3 levels should be based on the 95% lower confidence limit estimate of a benchmark  
4 concentration, that is, a BMCL, rather than the central estimate, the BMC. The rationale for this  
5 is that the BMCL reflects the statistical variability of the data, and it is therefore more likely to be  
6 health-protective than a central estimate such as a BMC. For the endpoints selected as bases  
7 for development of occupational exposure recommendations, sperm morphology in the F<sub>0</sub>  
8 generation of the WIL Research Laboratories [2001] study and decreased hind limb grip  
9 strength in the Ichihara [2000b] study, the BMC estimates (shown in Table B-4) are  
10 approximately 35% higher than the corresponding BMCLs. Therefore, the recommended  
11 occupational exposure level would be correspondingly larger if recommendations were based  
12 on the BMC rather than the BMCL.

13  
14 As discussed above in Section B.3.3, Extrapolation of Non-Cancer Endpoints to Humans, in this  
15 analysis the lowest duration-adjusted BMC and BMCL values were observed for the  
16 dichotomous endpoints of renal pelvic mineralization in the F<sub>0</sub> females in the WIL Research  
17 Laboratories [2001] study, and hepatic cytosolic vacuolation in the F<sub>0</sub> males in the WIL  
18 Research Laboratories [2001] study. These endpoints were judged to be inappropriate for  
19 extrapolation to occupational exposures; however, if recommendations were based on these  
20 endpoints the extrapolated BMCL values would be 92 ppm for renal pelvic mineralization and  
21 103 ppm for hepatic cytosolic vacuolation, yielding occupational exposure levels of  
22 approximately 1.2–1.4 ppm after application of a 75-fold UF. Other non-cancer endpoints that  
23 could be adequately modeled included decreased live litter size and decreased female fetal  
24 body weight in F<sub>1</sub> offspring in the WIL Research Laboratories [2001] study. These endpoints  
25 yield extrapolated occupational BMCL values of 258 for live litter size and 270 ppm for female  
26 fetal body weight, which would yield occupational exposure levels of 3.4–3.6 ppm after  
27 application of a 75-fold UF.

28  
29 For the non-cancer endpoints, the risk assessment assumption with the greatest numerical  
30 impact on recommended occupational exposure levels is the assumption of a 75-fold UF (after

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1 replacing the rat-to-human pharmacokinetic factor with a body weight to the 0.75 power  
2 assumption) in extrapolating from animals to humans. Although UFs of this magnitude are  
3 widely used for nonoccupational risk assessments, it is sometimes argued that because workers  
4 must be healthy in order to work, worker populations would be unlikely to include the most  
5 susceptible individuals, and therefore a smaller UF can be applied. The use of a smaller UF  
6 would obviously increase the recommended occupational exposure level for 1-BP; however, it is  
7 difficult to rationalize a smaller UF for the endpoints of interest in this analysis. Workers  
8 experiencing reproductive toxicity would not be impacted in their ability to work, and they would  
9 be no more or less fit for work than other members of the population; therefore, it seems unlikely  
10 that workers would have any particular resistance to reproductive toxicity. Peripheral  
11 neuropathies due to occupational exposures to 1-BP have been reported (see Chapter 2–  
12 Human Studies and Exposure Assessment), so it appears that humans are vulnerable to this  
13 endpoint, and the use of a smaller UF would not represent prudent public health practice.

#### 14 B.5 SUMMARY

15 Dose-response modeling was conducted for 1-BP using benchmark dose methods. Existing  
16 human studies do not provide adequate data for quantitative analysis; therefore, the dose-  
17 response analysis was based on animal data. The toxicologically based non-cancer BMCs and  
18 BMCLs were extrapolated to humans assuming dose-equivalency on a  $\text{mg/kg}^{0.75}$ -day basis,  
19 and then a 75-fold UF was applied. The results suggest that occupational exposures to 1-BP  
20 should be limited to 8-hour TWA exposures in the range of 1.9 to 3.6 ppm, depending on the  
21 choice of endpoint and whether recommendations are based on the central estimate (BMC) or  
22 the 95% lower-bound estimate (BMCL). These results may be compared to those based on  
23 BMD modeling of tumors observed in a recent NTP chronic bioassay for 1-BP [NTP 2011].  
24 Extrapolation of the toxicologically based BMCs and BMCLs to humans for the most sensitive  
25 endpoint—alveolar/bronchiolar adenomas + carcinomas—suggests that occupational exposures  
26 to 1-BP should be limited to 8-hour TWA exposures in the range of 0.3 to 0.4 ppm, which is  
27 approximately an order of magnitude lower than recommendations based on the non-cancer  
28 endpoints.

29  
30

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1 **APPENDIX C: MODEL AVERAGING PROCEDURES FOR CANCER RISK**

2 **ASSESSMENT**

3 This appendix provides supplemental information on the model averaging (MA) procedures used  
4 in the cancer risk assessment for 1-BP described in Chapter 7.0: Quantitative Risk Assessment  
5 based on Cancer Data in Animals. Information included is 1) an overview of the NIOSH risk  
6 assessment and the use of MA procedures and 2) an example of using the MA process along  
7 with sample output.

8 **C.1 OVERVIEW OF NIOSH RISK ASSESSMENT**

9 NIOSH identified cancer data that provide dose-response information suitable for quantitative  
10 risk assessment for occupational exposures to 1-BP. The best available tumor data were found  
11 in the NTP bioassay [NTP 2011]. Dose-response data were identified for alveolar/bronchiolar  
12 adenoma and carcinoma in female mice, adenoma of the large intestine in female rats, and  
13 keratoacanthoma/squamous cell carcinoma of the skin in male rats.

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1 **TABLE C-1 - SUMMARY OF 1-BP INHALATION DATA FROM NTP 2-YEAR BIOASSAY\* THAT PROVIDE DOSE-RESPONSE INFORMATION**  
 2 **SUITABLE FOR BENCHMARK CONCENTRATION ESTIMATION: DICHOTOMOUS ENDPOINTS**

<b>Health End (sex; species)</b>	<b>Exposure Concentration (ppm)</b>	<b>Sample size</b>	<b>Number of tumors</b>
Pulmonary adenomas + carcinomas (female; B6C3F1 mice)	0	50	1
	62.5	50	9
	125	50	8
	250	50	14
Large intestine adenomas (female; F344 rats)	0	50	0
	125	50	1
	250	50	2
	500	50	5
Dermal keratoacanthoma + squamous cell carcinoma (male; F344 rats)	ppm	Number of rats	No. of tumors
	0	50	1
	125	50	4
	250	50	6
	500	50	8

3 **Abbreviations: ppm = parts per million; SD = standard deviation.**

4 \*Source: NTP [2011].

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1 The NIOSH quantitative risk assessment for 1-BP was conducted using benchmark  
2 concentration modeling. Dose-response modeling was done and benchmark concentrations  
3 were estimated with the U.S. EPA BMD software suite, version 2.12 [EPA 2010]. For tumor  
4 responses, the benchmark response was set at 0.1%, corresponding to a 1-in-1000 lifetime  
5 excess risk of cancer. The models considered were the gamma, logistic, log-logistic, multistage,  
6 probit, log-probit, quantal-linear, and Weibull models. The quantal-linear model is a subset of  
7 the multistage and Weibull models, which can assume this form if it is appropriate for a given  
8 data set, but it was included as a separate model to assess the fit of a strictly low-dose linear  
9 model. Models with chi-square goodness of fit P values of 0.10 or greater were considered to fit  
10 the data adequately. Because model-based extrapolation to a 0.1% response level is sensitive  
11 to the choice of models, the BMD results for tumor endpoints were summarized by using a  
12 model-averaging (MA) technique [Wheeler and Bailer 2007], which weights several models on  
13 the basis of the model fit. A restricted version of the model-averaging software was used to  
14 avoid supralinear models, which have low-dose properties considered biologically implausible.  
15 Confidence limits were obtained using a statistical method known as bootstrapping. The MADr-  
16 BMD software and the journal article describing the software can be obtained through the  
17 Journal of Statistical Software at <http://www.jstatsoft.org/article/view/v026i05>.

## 18 C.2 EXAMPLE OF THE APPLICATION OF MODEL AVERAGING

19 This section provides an example of the application of MA to calculate XXX using animal data.  
20 For this example, the input file for the female mouse lung tumors looks like this:

```
21 250 1e-8 1e-8  
22 0 0 1 0 0 1 1 0 0  
23 102210  
24 2 1 0.001  
25 0.95 5000 0  
26 3  
27 4  
28 0 50 1  
29 62.5 50 9  
30 125.0 50 8  
31 250.0 50 14
```

32  
33 Table C-2 provides the specifications of the example input file.

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1  
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3

**TABLE C-2 SPECIFICATIONS OF THE EXAMPLE INPUT FILES**

250 1e-8 1e-8	Maximum number of iterations, relative convergence, general convergence
0 0 1 0 0 1 1 0 0	MA specifications: 1 = model included, 0 = model not included  Model order: quantal-linear, quantal-quadratic, multistage, logistic, probit, Weibull, log-probit, log-logistic, gamma
122809	Random Seed (specifying 0 implies current clock time will be used)
2 1 0.1	Averaging criterion (1 = BIC, 2 = AIC, 3 = KIC, 4 = BICB, 5 = AICB, 6 = KICB)  Risk type (1 = added risk, 2 = extra risk)  BMR (in percent)
0.95 5000 0	Type I error rate, Number of bootstrap resamples, output bootstrap resamples (0 = no, 1 = yes)
3	Degree of multistage polynomial
4	Number of data lines
0 50 1 62.5 50 9 125.0 50 8 250.0 50 14	Data specification:  Dose, number of experimental units, number of observed responses

4  
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So, in the case of the female mouse lung tumors, the three BMD models averaged were the multistage, Weibull and log-probit models. The degree of the multistage polynomial was specified as 3. These models adequately cover the model space and provide an average model that adequately characterizes the dose-response data. The 95% confidence limits were constructed using 5000 bootstrap resamples. The sample outputs of this analysis are included in Section C-3.

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### C.3 SAMPLE OUTPUT FOR EXAMPLE

MABMD VERSION 1.0

Wed Mar 02 15:29:27 2011

This program's results are given "as is", without warranty, either expressed or implied by the National Institute for Occupational Safety and Health.

#### INPUT DATA

Dose	Count	Observed
0.000000	50	1
62.500000	50	9
125.000000	50	8
250.000000	50	14

#### Model Fit Statistics

Model	Weight	-2log(L)	AIC	BIC
Multistage	0.245	162.97	170.97	184.16
Weibull	0.665	162.97	68.97	178.87
Log-Probit	0.091	166.96	172.96	182.85

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```
1 -----  
2 'Average-Model' Benchmark Dose Estimate  
3 -----  
4 Nominally Specified Confidence Level:0.950  
5 Weighting Criterion: AIC  
6 BMD Calculation: Added Risk  
7 BMR: 0.001000  
8 BMD:0.849148762733  
9 BMDL(BCa)0.409673051027  
10 (BMDL)Percentile:0.636052851184  
11 Acceleration: 0.037488  
12 Bootstrap Resamples: 5000  
13 Random Seed: 102210  
14 -----
```

```
15 -----  
16 -----  
17 'Average-Model' Goodness of Fit Test  
18
```

19 MADr-BMD provides both the individual BMD model parameters and fit statistics and the corresponding “Average  
20 Model” results.

21 To compare the modeling to individual BMDS models, here is a sample output of the female mouse lung tumor data  
22 for the multistage model using the EPA BMDS software suite:

```
23  
24 =====  
25     Multistage Model. (Version: 2.8; Date: 02/20/2007)  
26     Input Data File: C:\BMDS\UNSAVED1.(d)  
27     Gnuplot Plotting File: C:\BMDS\UNSAVED1.plt  
28                               Mon Dec 22 13:09:24 2008  
29 =====
```

30  
31 BMDS MODEL RUN

```
32 ~~~~~  
33  
34     The form of the probability function is:
```

```
35  
36     P[response] = background + (1-background)*[1-EXP(  
37         -beta1*dose^1-beta2*dose^2-beta3*dose^3)]  
38
```

39 The parameter betas are restricted to be positive

40  
41 Dependent variable = COLUMN3

42 Independent variable = COLUMN1

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1  
2 Total number of observations = 4  
3 Total number of records with missing values = 0  
4 Total number of parameters in model = 4  
5 Total number of specified parameters = 0  
6 Degree of polynomial = 3  
7  
8  
9 Maximum number of iterations = 250  
10 Relative Function Convergence has been set to: 1e-008  
11 Parameter Convergence has been set to: 1e-008

12  
13 Default Initial Parameter Values

14 Background = 0.058868  
15 Beta(1) = 0.00109445  
16 Beta(2) = 0  
17 Beta(3) = 0

18  
19 Asymptotic Correlation Matrix of Parameter Estimates

20  
21 ( \*\*\* The model parameter(s) -Beta(2) -Beta(3)  
22 have been estimated at a boundary point, or have been specified  
23 by the user,  
24 and do not appear in the correlation matrix )

25  
26 Background Beta(1)  
27  
28 Background 1 -0.78  
29  
30 Beta(1) -0.78 1  
31  
32  
33  
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Parameter Estimates

95.0% Wald Confidence

Interval

Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
Background	0.0334801	*	*	*
Beta(1)	0.00134051	*	*	*
Beta(2)	0	*	*	*
Beta(3)	0	*	*	*

\* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.
Full model	-80.1028	4		
Fitted model	-81.4858	2	2.76596	2
Reduced model	-87.934	1	15.6624	3

P-value: 0.2508 (for Fitted model), 0.00133 (for Reduced model)

AIC: 166.972

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0335	1.674	1	50	-0.530
62.5000	0.1112	5.558	9	50	1.549
125.0000	0.1826	9.130	8	50	-0.413
250.0000	0.3087	15.435	14	50	-0.439

Chi^2 = 3.04      d.f. = 2      P-value = 0.2184

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1 Benchmark Dose Computation  
2  
3 Specified effect = 0.001  
4  
5 Risk Type = Added risk  
6  
7 Confidence level = 0.95  
8  
9 **BMD = 0.772228**  
10  
11 **BMDL = 0.521641**  
12  
13 BMDU = 2.79546  
14

15 Taken together, (0.521641, 2.79546) is a 90 % two-sided confidence  
16 interval for the BMD

---

17  
18 The output from the MADr-BMD software for the multistage model alone for female mouse lung tumors is provided  
19 below for comparison. One can see that the BMD's and BMDL's generated are equivalent.

20

21 Model	Weight	-2log(L)	AIC	BIC
22 -----				
23 Multistage	1.000	162.97	170.97	184.16
24 -----				

25  
26 -----  
27 'Average-Model' Benchmark Dose Estimate  
28 -----  
29 Nominally Specified Confidence Limit:0.950  
30 Weighting Criterion: AIC  
31 BMD Calculation: Added Risk  
32 BMR: 0.001000  
33 **BMD: 0.772227525711**  
34 BMDL(BCa):0.473608016968  
35 **BMDL(Percentile):0.551896691322**  
36 Acceleration: 0.032744  
37 Bootstrap Resamples: 5000  
38 Random Seed: 123109  
39 -----

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```
1  MODEL: Multistage, 3-degree polynomial:
2  -----
3  Parameters  Estimate      StdErr
4  -----
5  GAMMA:      0.033480      0.028840
6  BETA(1):    0.001341      0.000367
7  BETA(2):    0.000000      N/A
8  BETA(3):    0.000000      N/A
9  Optimization Succeeded
10 -----
```

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