CRITERIA FOR A RECOMMENDED STANDARD:

OCCUPATIONAL EXPOSURE TO 1-BROMOPROPANE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Disease Control and Prevention

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FOREWORD

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

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

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

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

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

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EXECUTIVE SUMMARY

1-Bromopropane (1-BP; CAS #106-94-5) is an organic solvent used in commercial and industrial applications, such as vapor degreasing operations and dry cleaning facilities. Peer-reviewed studies have raised concerns about the potential occupational health risks associated with exposure to 1-BP [Sclar 1999; Ichihara et al. 2002, 2004a, 2004b; Majersik et al. 2007; Raymond and Ford 2007; CDC 2008]. For this reason, the National Institute for Occupational Safety and Health (NIOSH) has conducted an analysis of the scientific information available on the human health and toxicological effects of 1-BP. This criteria document presents these results of the NIOSH assessment: (1) the salient facts on occupational exposures to 1-BP and the toxicity of 1-BP, (2) the rationale and justification for a NIOSH recommended exposure limit (REL) for 1-BP, derived with current quantitative risk assessment methodology, and (3) recommendations for eliminating or reducing workplace risks of exposure.

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

Case studies, exposure assessments, and investigations provide evidence of 1-BP exposure in the workplace and the onset of adverse neurological effects attributed to 1-BP [Sclar 1999; Ichihara et al. 2002, 2004a, 2004b; Majersik et al. 2007; Raymond and Ford 2007; CDC 2008; Blando et al. 2010; Li et al. 2010a; Samukawa et al. 2012]. NIOSH has conducted several health hazard evaluations (HHEs) intended to assess

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

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

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

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

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

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

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

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

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

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

Insufficient exposure data are available to assess the extent to which the REL of 0.3 for 1-BP is achievable in various workplaces. The hierarchy of controls (described in the next paragraph) has been applied to effectively lower airborne concentration of other organic solvents—with physiochemical properties similar to those of 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 by applying technology and the hierarchy of controls. The REL is intended to promote 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.

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

- Elimination or substitution
- Engineering controls
- Administrative and work practice controls
- Personal protective equipment (PPE)

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

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

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

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

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

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

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

ABBREVIATIONS

1-BP	1-bromopropane
2-BP	2-bromopropane
ABT	1-aminobenzotriazole
ACGIH	American Conference of Governmental Industrial Hygienists
AcPrCys	*N*-acetyl-*S*-(*n*-propyl)-L-cysteine
$AcPrCys_{cr}$	AcPrCys level adjusted for creatine
AEL	acceptable exposure limit
AIC	Akaike information criterion
AIHA	American Industrial Hygiene Association
AL	action level
ALT	alanine aminotransferase
APR	air-purifying respirator
As^{+}	arsenic
ATSDR	Agency for Toxic Substances and Disease Registry
BDNF	brain-derived neurotrophic factors
BMC	benchmark concentration
BMCL	benchmark concentration lower-bound confidence limit
BMD	benchmark dose
BMR	benchmark response
Br^{-}	bromide
BSC	Brominated Solvents Consortium
^{o}C	degrees Celsius
CA1	cornu ammonis area 1
CA DHS	California Department of Health Services
CA EPA	California Environmental Protection Agency
CAS	Chemical Abstract Service
CIB	Current Intelligence Bulletin
CAA	Clean Air Act of 1990

CERHR	Center for the Evaluation of Risks to Human Reproduction
cfm	cubic feet per minute
CFCs	chlorofluorocarbons
Cl^-	chloride
cm^2	square centimeter(s)
cm/hr	centimeter(s) per hour
cm/s	centimeter(s) per second
CNS	central nervous system
CS_2	carbon disulfide
CYP	cytochrome enzyme
CYP2E1	cytochrome P450 enzyme 2E1
CYP450	cytochrome P450 enzyme
DG	dentate gyrus
DL	distal latency
DNA	deoxyribonucleic acid
DNEL	derived no effect level
EC	European Commission
E. coli	*Escherichia coli*
ESI-MS	electrospray ionization mass spectrometry
F344	Fischer 344 rats
EPA	U.S. Environmental Protection Agency
fEPSP	field excitatory postsynaptic potential
FR	Federal Register
GABA	gamma-aminobutyric acid
$GABA_A$	GABA type A
GC	gas chromatography
GD	gestation day(s)
GESTIS	Institute of Occupational Safety and Health of the German Social Accident Insurance

GHS	Globally Harmonized System of Classification and Labeling of Chemicals
GM	geometric mean
GR	glucocorticoid receptor
GSH	glutathione
GSP	S-propyl glutathione
GSSG	glutathione disulfide, oxidized form of glutathione
GST	glutathione-S-transferase
GSTM1	glutathione-S-transferase M1
GSTT1	glutathione-S-transferase T1
HAP	hazardous air pollutant
HCFCs	hydrochlorofluorocarbons
HETAB	Hazard Evaluations and Technical Assistance Branch
HHA	health hazard alert
HHE	health hazard evaluation
HPLC	high performance liquid chromatography
HO-1	heme oxygenase-1
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life or health
Ig	immunoglobulin
(IRR)	subnotation of SK:DIR indicating the potential for a chemical to be a skin irritant following exposure of the skin
kg	kilogram(s)
L	liter(s)
L/min	liter(s) per minute
lb	pound(s)
LC	lethal concentration
LC_{LO}	lowest concentration of a chemical that caused death in humans or animals; lethal concentration low

LC_{50}	lethal concentration that causes the death of 50% (one half) of a group of test animals; median lethal concentration
LCL	lower confidence limit
LD_{LO}	lowest dose of a chemical that caused death in humans or animals; lethal dose low
LD_{50}	lethal dose that causes the death of 50% (one-half) of a group of test animals; median lethal dose
LOD	limit of detection
LOQ	limit of quantification
MA	model averaging
MBP	myelin basis protein
MCV	motor nerve conduction velocity
mEq/L	milliequivalent(s) per liter
mg	milligram(s)
mg/cm^2	milligram(s) per square centimeter
mg/kg	milligram(s) per kilogram of body weight
mg/kg-day	milligram(s) per kilogram of body weight per day
mg/dL	milligram(s) per deciliter
mg/L	milligram(s) per liter
m^3/min	cubic meter(s) per minute
ml	milliliter(s)
ML	motor latency
ml/kg	milliliter(s) per kilogram
mmol/L	millimole(s) per liter
MOA	mode of action
MRI	magnetic resonance imaging
MSDS	Material Safety Data Sheet
m/min	meter(s) per minute
MS	mass spectrometry
NADPH	nicotinamide adenine dinucleotide phosphate

ND	nondetectable
NIOSH	National Institute for Occupational Safety and Health
NJDEP	New Jersey Department of Environmental Protection
NJDHSS	New Jersey Department of Health and Senior Services
NK	natural killer (cells)
NOEL	No Observed Effect Level
NQO1	NAD(P)H:quinone oxidoreductase
NTP	National Toxicology Program
ODSs	ozone-depleting substances
OECD	Organisation for Economic Co-operation and Development
OEL	occupational exposure limit
OSH	occupational safety and health
OSHA	Occupational Safety and Health Administration
OV	organic vapor
P. aeruginosa	*Pseudomonas aeruginosa*
PAPR	powered air-purifying respirator
PBZ	personal breathing zone
PCR	polymerase chain reaction
PEL	permissible exposure limit
PERC	perchloroethylene
PID	photoionization detector
PND	postnatal day
PNS	peripheral nervous system
PPE	personal protective equipment
ppm	parts per million
PrCYS	globin S-propyl cysteine
RCRA	Resource Conservation and Recovery Act
REACH	Registration, Evaluation, Authorization, and restriction of CHemical substances
REL	recommended exposure limit

ROS	reactive oxygen species
R-Phrase	risk phrase
S9	supernatant fraction 9
SAR	supplied-air respirator
SCBA	self-contained breathing apparatus
SD	Sprague-Dawley rats
SDS	safety data sheet
SLA	spontaneous locomotor activity
S-Phrase	safety phrase
SNAP	significant new alternative policy
SRBC	sheep red blood cells
STEL	short-term exposure limit
S. typhimurium	*Salmonella typhimurium*
TCA	1,1,1-trichloroethane
TEAP	Technology and Economic Assessment Panel
TLV	threshold limit value
TWA	time-weighted average
UF	uncertainty factor
UN	United Nations
U.S.	United States
VOC	volatile organic compound
WT	wild-type
µg	microgram(s)
µg/cm^2	microgram(s) per square centimeter
µg/cm^2/hr	microgram(s) per square centimeter per hour
µg/g	microgram(s) per gram
µg/L	microgram(s) per liter
µL	microliter(s)
µmol	micromole(s)

GLOSSARY

Adenoma: an epithelial tumor of glandular origin and structure

Amenorrhea: abnormal absence or suppression of menstruation

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

Carcinoma: a malignant tumor derived from epithelial tissue

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

Diaphoresis: profuse perspiration

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

Dysphagia: difficulty in swallowing

Dysesthesia: impairment of sensitivity, especially to touch

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

Hyperreflexia: overactivity of physiological reflexes

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

Myalgia: pain in one or more muscles

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

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

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

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

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

Organic vapor cartridge: device used in respirators to remove organic vapors from the air

Paraparesis: partial paralysis affecting the lower limbs

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

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

Polyneuropathy: a noninflammatory degenerative disease of nerves, usually caused by toxicants

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

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

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

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

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

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

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

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CHAPTER 1: INTRODUCTION

1.1 PURPOSE

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

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

1.2 SCOPE

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

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

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

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

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

1.3 Background

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

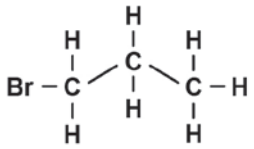
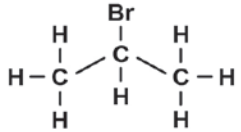
carcinogenic activity of 1-BP, due to significantly increased incidences of adenoma of the large intestine of female rats and increased incidences of alveolar/bronchiolar neoplasms in female mice.

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

1.4 Chemical and Physical Properties

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

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

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	$CH_3CH_2CH_2Br$	$(CH_3)_2CHBr$
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*)

Characteristic	1-BP	2-BP
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_{ow})	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*)

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^3, 1 mg/m^3 = 0.2 ppm	1 ppm = 5.03 mg/m^3, 1 mg/m^3 = 0.2 ppm

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

1.5 Use and Production in the United States

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

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

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

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

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

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

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

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

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

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

1.6 Worker Exposure

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

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

1.7 Occupational Exposure Limits and Health Guidelines

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

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

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

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

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

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

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

Exposure recommendation	Airborne concentration	Adverse effects (species)
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

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

***Rescinded.**

†**Recommended exposure range.**

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

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

Reference	Classification	Hazard statement
CA EPA [2008]	Reproductive/developmental toxicant	None
ECB [2010]	R11	Highly flammable
	R36/37/38	Irritant to the eyes, respiratory system, and skin
	R48/20	Harmful: Danger of serious damage to health by prolonged exposure through inhalation
	R60	May impair fertility
	R63	Possible risk of harm to the unborn child
	R67	Vapors may cause drowsiness and dizziness
	S53	Avoid exposure—obtain special instructions before use
	S45	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

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

1.8 SUMMARY

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

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.

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

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

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

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

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

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

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

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

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

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

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

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

Samukawa et al. [2012] reported a case of 1-BP-induced neurotoxicity in a 43-year-old male worker employed as a metal cleaner. The patient reported using 1-BP as a cleaning agent for 8.5-9.5 hours/day for 5-6 days/week for 18 months. Daily tasks focused on the immersion of metal parts in a wash tank (assumed to contain undisclosed 1-BP solution) for 15 seconds, in addition to their subsequent removal and wiping down with an ethanol solution. The patient also cleaned the wash tank monthly. Samukawa et al. [2012] noted that local ventilation was not used in the facility and that the patient reported wearing cloth gloves, which the authors noted, may have increased dermal exposures to 1-BP. Samukawa et al. [2012] stated that the patient did not use a protective mask prior to using1-BP as a cleaning agent. The patient did start wearing an unspecified protective mask for about 5 months before admission. Air sampling data collected via passive samplers revealed 1-BP concentrations ranging from 353-663 ppm with a mean TWA concentration of 553 ppm.

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

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

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

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

Reference	Facility type	Total number (sex)	Solvent components (%)	Reported symptoms
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*)

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.**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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^- as a biomarker of exposure	Cushion factory	30 (5 male, 25 female)	92 GM (45–200)	Urinary Br^- levels correlated with airborne 1-BP concentrations for both days of biological monitoring; urinary Br^- 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

(*Continued*)

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†
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

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

2.3 NIOSH HEALTH HAZARD EVALUATIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

TABLE 2-3 – SUMMARY OF HEALTH HAZARD EVALUATIONS

Reference	Worksite	Solvent components (%)	Reported symptoms	Assessments conducted
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

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

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

(Continued)

Reference	Worksite	Exposure assessment date	Air samples		
			Number	Type	Airborne concentration (range), ppm
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

(Continued)

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)

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

2.4 SUMMARY

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

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

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].

CHAPTER 3: DISPOSITION AND TOXICOKINETICS

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

3.1 GLUTATHIONE-DEPENDENT METABOLISM

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

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

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

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

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

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

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

Garner et al. [2006] studied the metabolism and disposition of 1-BP in F344 male rats and B6C3F1 male mice dosed by inhalation and intravenous routes. The findings demonstrated GSH-dependent metabolism of 1-BP. F344 male rats and B6C3F1 male mice were treated with radiolabelled 1-BP by inhalation (800 ppm) or 5, 20, and 100 mg/kg via intravenous injection. Exhaled breath was collected, and VOCs and CO_2 concentrations were determined. Metabolites of 1-BP were measured in urine of treated animals. Identified GSH conjugates of oxidative metabolites of 1-BP included AcPrCys, N-acetyl-3-(propylsulfinyl)alanine, N-acetyl-S-(2-hydroxypropyl)cysteine, 1-bromo-2-hydroxypropane-O-glucuronide, N-acetyl-S-(2-oxopropyl)cysteine, and N-acetyl-3-[(2-oxopropyl)sulfinyl]alanine. Treatment of rats with 1-aminobenzotriazole (ABT), a potent inhibitor of CYP450, led to excretion of a lower proportion of the administered 1-BP in urine. These animals had decreased exhaled $^{14}CO_2$ (↓80%) and increased radioactivity expired as VOC (↑52%). Urinary metabolites in ABT pretreated rats were reduced in

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

Lee et al. [2007] examined the role of GSH conjugation on 1-BP-dependent hepatic toxicity and immunotoxicity in mice. Mice were treated by gavage with 200, 500, and 1000 mg/kg 1-BP and sacrificed 12 hours post dosing. A second group of animals were dosed with 1000 mg/kg 1-BP and sacrificed at 6, 12, 24 and 48 hours post dosing. Levels of GSH and the 1-BP metabolite, GSP, in liver and measures of liver toxicity and immunotoxicity were determined. The authors reported a dose-dependent decrease of GSH in the liver and spleen of animals treated with 1-BP. Decreases of GSH were maximal at 6 and 12 hours but returned to near-control levels by 24–48 hours. Concurrent with the drop in GSH were dose- and time-dependent increases in GSP. Lee et al. [2007] concluded that 1-BP toxicity is the result of GSH depletion as a consequence of 1-BP conjugation metabolism.

Valentine et al. [2007] developed methods to measure globin S-propyl cysteine (PrCYS) in blood and AcPrCys in urine from animals and humans exposed to 1-BP. These biomarkers reflect binding of 1-BP to protein sulfhydryls of cellular proteins and ultimate GSH metabolites, respectively. In separate experiments, groups of male Wistar rats were exposed to 1-BP at 0, 50, 200, or 800 ppm by inhalation for 8 hours/day for 2 weeks or at 50 ppm, 8 hours/day, 5 days/week, for 4 weeks. Animals were sacrificed immediately after the last exposure or allowed to recover for 8 days. Levels of PrCYS and AcPrCys showed a linear dose response relative to exposure level and were measurable 8 days after exposure ended. As a second experiment, Valentine et al. [2007] measured PrCYS in blood and AcPrCys in urine of workers with occupational exposure to 1-BP. The authors found that hemoglobin PrCYS levels were higher in exposed workers than in unexposed workers and urinary levels of AcPrCys were positively correlated to workplace 1-BP exposure. Valentine et al. [2007] concluded that both PrCYS and AcPrCys were potential biomarkers for assessing worker exposure to 1-

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

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

3.2 Oxidative Metabolism via Cytochrome P450 (CYP450)

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

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

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

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

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

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

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

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

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

3.3 SUMMARY

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

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

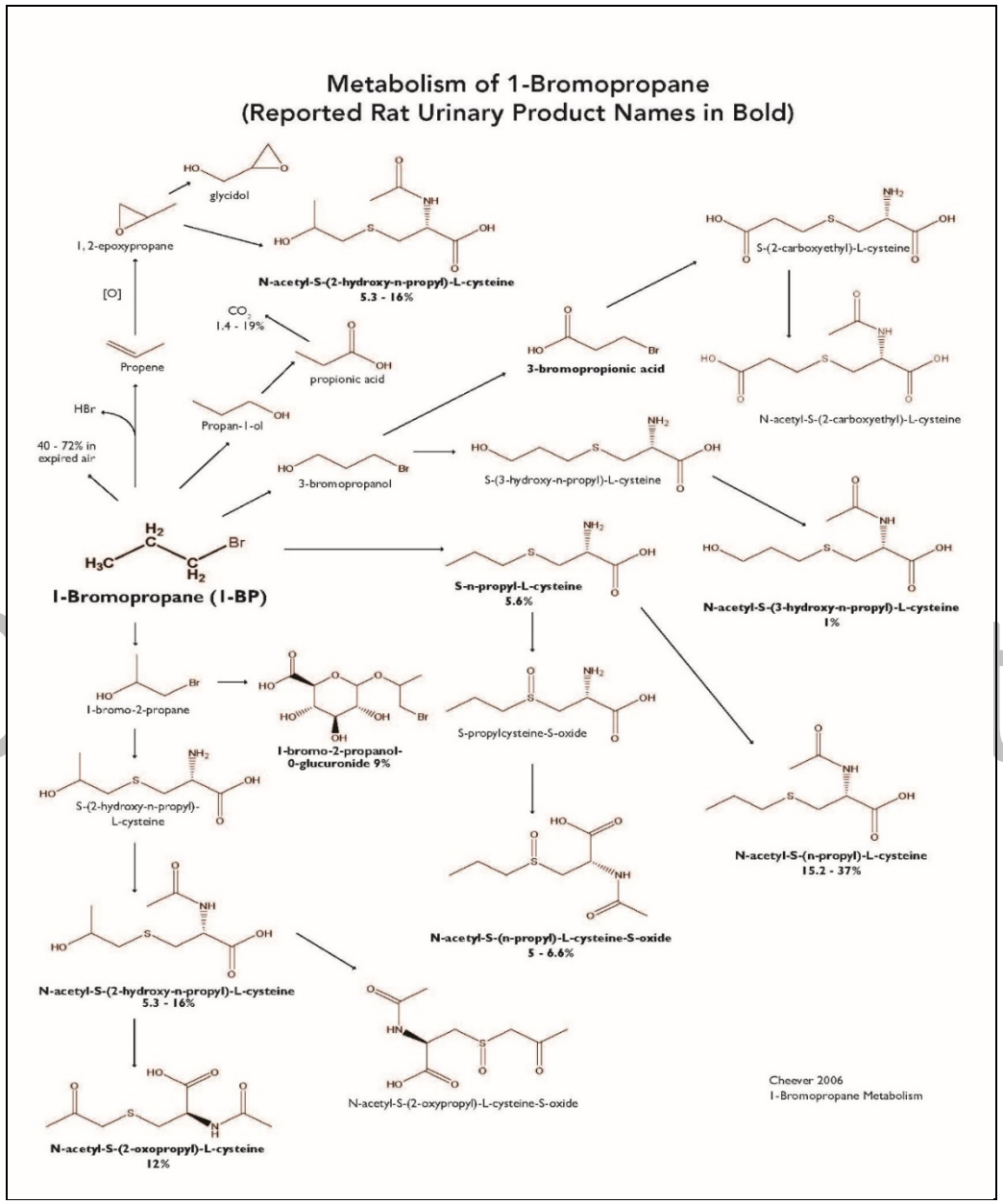


Figure 3-1 illustrates the potential metabolic pathways of 1-BP in rats. These pathways yield multiple potential metabolites. The names in bold text represents metabolites identified in rat urine [Cheever 2006].

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

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

4.1 INHALATION STUDIES

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

4.1.1 DEVELOPMENTAL AND REPRODUCTIVE EFFECTS

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

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

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

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

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

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^3) 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

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

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

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

WIL Research Laboratories [2001] conducted a two-generational toxicity study of 1-BP administered via whole-body inhalation. As part of this study, clinical observations, body weight, food consumption, and changes in the multiple organ systems were monitored; test animals were subjected to gross pathology. The F_0 generation treatment groups consisted of male and female Crl:CD (SD)IGS BR rats that were exposed to 0, 99, 252, 505, or 750 ppm 1-BP; the F_1 generation treatment groups were exposed to 0, 100, 252, or 500 ppm 1-BP. The authors noted that because of the occurrence of complete infertility of the F_0 generation, treatment animals precluded exposure of F_1 or F_2 generation animals at 750 ppm. F_0 and F_1 generation treatment groups were exposed to

1-BP for 70 days prior to mating, throughout mating, and until GD 20. After parturition, exposure to F_0 and F_1 females was reinitiated on lactation day 5 and continued until the test animals were sacrificed. Clinical observations, body weight, food consumption, and changes in the multiple organ systems were monitored; test animals were subjected to gross pathology.

WIL Research Laboratories [2001] reported that no mortalities occurred in the F_0 generation, but one male F_1 rat in the 500-ppm treatment group was sacrificed during he second week of exposure. Food consumption was not affected in any treatment group in the F_0 or F_1 generation. Parent and offspring body weights were reduced in the 500-ppm group (F_0, F_1, and F_2 generations) and 750-ppm (F_0 generation) groups. Decreased organ weights were noted, in the pituitary gland in the 500 (F_1) and 750 (F_0) ppm treatment group males and in the spleen in the F_2 male and female pups. Increased thymus weights were observed in the 250 and 500 ppm (F_1) treatment groups' males. Relative liver weights were increased in both male and female F_0 animals treated at 500 and 750 ppm; similar results were reported for the 500 ppm (F_0 and F_1) treatment groups. Microscopic centrolobular hepatocellular vacuolation and increased glycogen were observed in animals with increased liver weight. Mild pelvic mineralization occurred in the 250-ppm group F_1 females, the 500-ppm group (F_0 and F_1 males and females), and the 750-ppm group (F_0 males and females). All animals in the 750-ppm F_0 generation treatment group were identified as infertile. Fertility indices were significantly reduced in the 500-ppm F_0 generation treatment group; no significant changes in fertility indices were reported for animals treated at lower levels in the F_0 generation or any F_1 treatment group. The mean number of pups born and live litter size at time of birth were statistically decreased in the 500-ppm (F_0 and F_1) treatment groups. Postnatal survival was not affected by parental exposure to 1-BP in any treatment group (F_1 and F_2). Both decreased body weight and decreased body weight gains were noted in male and female pups born to animals treated at 500 ppm (F_1 and F_2). Gross examination of the F_0 generation revealed small testis and epididymis in male rats in the 500 and 750 ppm

treatment groups. Reduced sperm motility, morphologically normal sperm, and epididymal sperm number were observed in F_0 and F_1 generation male rats exposed to 500 and 750 ppm 1-BP. The researchers noted reduced weight in multiple organs in the male reproductive system in F_0 and F_1 generations rats exposed to 250, 500, and 750 ppm. Decreased ovary weights were reported in female rats in the highest treatment groups of the F_0 and F_1 generations; microscopic findings were observed in the ovaries in the 500-ppm (F_0 and F_1) and 750-ppm (F_0) group females.

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

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

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

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

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

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

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

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

NTP [2011] conducted a series of sub-chronic (3-month) studies to evaluate the toxicological effects of 1-BP. In one study, male and female F344/N rats were exposed

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

In the second sub-chronic study, NTP [2011] exposed male and female B6C3F1 mice to 1-BP vapor at concentrations of 0, 125, 250, or 500 ppm, 6 hours plus T90 (10 minutes)/day, 5 days/week, for 3 months (14 weeks). A significant reduction in cauda epididymis weight and decreased sperm motility were reported in the 250- and 500-ppm treatment groups. In the 500-ppm treatment group, a significant decrease in the sperm per gram cauda was also observed. In female mice in all treatment groups, there were significant alterations in the relative amount of time spent in the various stages of estrous. For example, animals in the 500-ppm treatment group spent significantly more time in extended diestrus than controls, whereas animals treated at 250-ppm spent significantly more time in extended estrus than controls.

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

Reference	Species; strain	Number per treatment (sex)	Treatment level (ppm)	Treatment regimen	Results (treatment level)
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)

(*Continued*)

Reference	Species; strain	Number per treatment (sex)	Treatment level (ppm)	Treatment regimen	Results (treatment level)
WIL Research Laboratories [2001]	Rat; Crl:CD (SD) IGS BR	(F_0) generation: 20 (male) 20 (female) (F_1) 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_0, F_1, F_2], 750 ppm [F_0]); decreased pituitary gland weight in male rats (500 [F_1], 750 [F_0]); reduced spleen weight in F_2 male and female pups; increased thymus weights in male rats (250, 500 [F_1]); increased relative liver weights both male and female (500, 750 [F_0], 500 [F_0, F_1]); microscopic centrolobular hepatocellular vacuolation and increased glycogen were observed in animals with increased liver weight; mild pelvic mineralization (250 [F_1 females]; 500 [F_0, F_1 males/females], 750 [F_0 males/females]); infertility, male and female (750 [F_0]); reduced fertility indices (500 [F_0]); decreased mean number of pups born and live litter size at time of birth (500 [F_0 and F_1]); decreased body weight and body weight gains in male and female pup (500 [F_1 and F_2]); gross examination revealed small testis and epididymis, male rats (500, 750 [F_0]); reduced sperm motility, morphologically normal sperm, and epididymal sperm number (500, 750 [F_0 and F_1]); reduced weight in male reproductive organs (250, 500, 750 [F_0 and F_1]); decreased ovary weights (500, 750 [F_0 and F_1]); microscopic findings in the ovaries (500 [F_0 and F_1], 750 [F_0])

(*Continued*)

Reference	Species; strain	Number per treatment (sex)	Treatment level (ppm)	Treatment regimen	Results (treatment level)
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)

(C*ontinued*)

Reference	Species; strain	Number per treatment (sex)	Treatment level (ppm)	Treatment regimen	Results (treatment level)
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_{90} (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_{90} (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)

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

4.1.2 Neurotoxic Effects

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

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

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

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

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

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

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

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

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

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

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

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

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

Fueta et al. [2004] focused on evaluation of behavioral abnormalities in the form of disinhibitory effects in the hippocampal CA1and the DG induced by chronic repetitive inhalation exposures to 1-BP vapor in rats, in addition to reversal of the disinhibitory effects in rats exposed for 12 weeks. Test animals were exposed to 1-BP vapor at a concentration of 0 or 700 ppm for 6 hours/day, 5 days/week, for 4, 8, or 12 weeks. Rats exposed for 12 weeks were subjected to an additional 4-week clearance period. No behavioral abnormalities were observed. Paired-pulse disinhibition was observed in both the DG and CA1 pyramidal neuron. The authors reported that the disinhibition in the DG

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

In a second study, Mohideen et al. [2011] investigated the effects of repeated exposures of 1-BP on monoamine neurons, more specifically noradrenaline and serotonin axons, in the neo-cortex region of the rat brain. Male F344 rats were exposed to 1-BP at concentrations of 0, 400, 800, and 1,000 ppm for 8 hours/day, 7 days/week, for 4 weeks. Test animals were sacrificed and the brains were harvested one day after the final exposure. Mohideen et al. [2011] reported a significant decrease in the density of noradrenergic axons in rats treated at 800 and 1000 ppm 1-BP. These effects were diffuse but more pronounced in the medial prefrontal cortex and amygdalae. No such changes in the density of serotonergic axons were observed at any treatment level. The authors theorized that the 1-BP-induced degeneration of noradrenergic axons may be associated with the altered mood states, such as depression, cognitive impairment, and sleep disturbances associated with workplace exposures to 1-BP [Mohideen et al. 2011]. In conclusion, the study demonstrated the onset of morphological changes in a dose-response manner in the brains of 1-BP-exposed rats.

Mohideen et al. [2013] continued the investigation into the neurotoxic effects of 1-BP on the CNS of male F344 rats. Test animals were exposed to 1-BP at concentrations of 0, 400, 800, and 1,000 ppm for 8 hours/day, 7 days/week, for 4 weeks. Following treatment, biochemical and histopathological examinations were conducted to ascertain the effects of 1-BP in the cerebellum and hippocampus. The analyses revealed pyknotic shrinkage of granular cells, degeneration of Purkinje cells in the cerebellum, and shrinkage of nuclei of the granular cells of test animals in the highest treatment group. Morphological changes in the form of elongation of processes in the astrocytes of rats exposed to 800 and 1,000 ppm 1-BP were also observed. The number of astrocytes per tissue volume was elevated in rats exposed to 400 ppm 1-BP. Despite the lack of evidence of demyelination, Mohideen et al. [2013] reported decreased levels of myelin basic protein and oligodendrocytes, in addition to down-regulation of mRNA and proteins associated with myelin-related genes in rats exposed to 1000 ppm. The authors theorized that these findings indicate that inhalation of 1-BP may contribute to demyelination.

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

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

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

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

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	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

(*Continued*)

Reference	Species; strain	Number per treatment group (sex)	Treatment levels (ppm)	Treatment regimen	Results (treatment)
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)

(*Continued*)

Reference	Species; strain	Number per treatment group (sex)	Treatment levels (ppm)	Treatment regimen	Results (treatment)
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)

(*Continued*)

Reference	Species; strain	Number per treatment group (sex)	Treatment levels (ppm)	Treatment regimen	Results (treatment)
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^- 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 $GABA_A$
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)

(*Continued*)

Reference	Species; strain	Number per treatment group (sex)	Treatment levels (ppm)	Treatment regimen	Results (treatment)
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)

(Continued)

Reference	Species; strain	Number per treatment group (sex)	Treatment levels (ppm)	Treatment regimen	Results (treatment)
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

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

4.1.3 Other Non-Cancer Toxicological Effects

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

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

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

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

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_{50} value of 7000 ppm.. Severe respiratory distress due to acute inflammatory response and alveolar edema occurred before the rats died. Increased lung weights were reported. The cause of death was attributed to acute inflammatory response and alveolar edema.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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_{50} 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.

(*Continued*)

Reference	Species; strain	Number per treatment group (sex)	Treatment levels (ppm)	Treatment regimen	Results (treatment)
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

(*Continued*)

Reference	Species; strain	Number per treatment group (sex)	Treatment levels (ppm)	Treatment regimen	Results (treatment)
Anderson et al. [2010]	Mice; B6C3F1 mice and F344/N rats	9 (female)	0, 125, 250, 500	6 hours plus T_{90} (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_{90} (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_{90} (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)

(*Continued*)

Reference	Species; strain	Number per treatment group (sex)	Treatment levels (ppm)	Treatment regimen	Results (treatment)
NTP [2011]	Mice; B6C3F1	5 (male); 5 (female)	0, 125, 250, 500, 1,000, 2,000	6 hours plus T_{90} (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_90 (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_{90} (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)

(Continued)

Reference	Species; strain	Number per treatment group (sex)	Treatment levels (ppm)	Treatment regimen	Results (treatment)
NTP [2011]	Rat; F344/N	10 (male); 10 (female)	0, 125, 250, 500	6 hours plus T_{90} (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_{90} (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)

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

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^2) 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_{50} 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-

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

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

4.3 SUMMARY

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

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

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

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

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

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

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

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

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

5.1 CANCER STUDIES IN EXPERIMENTAL ANIMALS

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

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

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

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

[a]Incidence (in parentheses: rate adjusted for intercurrent mortality).
[b]Statistically significant positive trend, *p*<0.05 (poly-3 test).
[c]Significantly different from control, *p*<0.05.
[d]Statistically significant negative trend, *p*<0.05 (poly-3 test).
Source: NTP [2011].

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

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

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

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

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

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

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

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

[a]Incidence (in parentheses: rate adjusted for intercurrent mortality).

[b]Statistically significant positive trend, $p<0.05$ (poly-3 test).

[c]Significantly different from control, $p<0.05$.

Source: NTP [2009].

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 (µmol)/plate (equivalent to 135–2497 µg/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 µmol. 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,

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

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

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

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

5.2.1.1b Forward mutation in eukaryotic organisms (mammalian cells)

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

5.2.1.2 DNA damage

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

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

5.2.1.3 Micronuclei Induction

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

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

5.2.1.4 Dominant Lethal Mutation

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

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

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

5.2.1.5 Genotoxic effects of 1-bromopropane metabolites

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

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

5.3 SUMMARY

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

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

Endpoint	*In vitro*	*In vivo* (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

+ = positive, ± = both positive and negative, – = negative.
NT = not tested.

CHAPTER 6: MODE OF ACTION

6.1 INTRODUCTION

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

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

6.2 NEUROTOXICITY

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

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

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

6.3 HEPATOTOXICITY

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

6.4 IMMUNOTOXICITY

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

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

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

6.7 SUMMARY

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

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

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

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

7.1 DATA SOURCES

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

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

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

Health End (sex; species)	Exposure Concentration (ppm)	Sample size	Number of tumors
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

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

*Source: NTP [2011].

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7.2 METHODS

7.2.1 Dose-response Modeling

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

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

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

7.2.2 Extrapolation to Humans

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

The NTP [2011] study of effects of 1-BP included a 2-year bioassay of $B6C3F_1$ mice. The model average BMCL for lung tumors in female $B6C3F_1$ mice was 0.64 ppm (Table 7-5). The reference body weight for a female $B6C3F_1$ mouse in a chronic study is 0.0353 kg [EPA 1988, Table 1-2]. Note that this is not simply the average body weight at the beginning or end of the study, but a representative average weight over the duration of the study. The corresponding reference inhalation rate for a female $B6C3F_1$ mouse in a chronic study is 0.06 m^3/day. The daily mg/kg inhaled dose in mice exposed to 0.64 ppm of 1-BP for a 6-hour day was estimated.

Equation 1:

0.64 ppm * 5.031 mg/m^3 per ppm * 0.06 m^3/day * 6 hour/24 hour / 0.0353 kg

= Mouse BMDL = 1.3682 mg/kg-day

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

Equation 2:

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

Human BMDL = 0.205 mg/kg-day

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

Equation 3:

0.205 mg/kg-day * 70 kg / 9.6 m3 per day * 1 ppm/5.031 mg/m3 =

Human BMCL = 0.297 ppm, rounded to 0.3 ppm[a].

The human BMCL is the human equivalent to the BMCL for lung tumors in the female $B6C3F_1$ mouse (Table 7-5).Reference body weights and inhalation rates for the animal strains used in the NTP [2011] study of 1-BP are listed in Table 7-5.

7.3 RESULTS

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

[a] 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.

TABLE 7-2 – BMC AND BMCL ESTIMATES OF PPM 1-BP ASSOCIATED WITH A 0.1% ADDED RISK OF LUNG TUMORS IN FEMALE B6C3F$_1$ MICE†

Model: BMDS [EPA 2010]	*P* value (goodness of fit)**	AIC	BMC	BMCL
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

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

†**Source: NTP [2011]**

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

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

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

Model: BMDS [EPA 20010	*P* value (goodness of fit)**	AIC	BMC	BMCL
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	3×10^{-10}
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

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

†**Source: NTP [2011]**

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

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

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TABLE 7-4 – BMC AND BMCL ESTIMATES OF PPM 1-BP ASSOCIATED WITH A 0.1% ADDED RISK OF KERATOACANTHOMAS AND 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

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

†Source: NTP [2011]

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

‡ **Model average, as described by Wheeler and Bailer [2007], based on the multistage, Weibull, and log-probit models**.
**** A higher p-value indicates a better model fit**

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7.3.1 Selection of Tumor-based BMCs and BMCLs for Extrapolation to Humans

The selection of a specific BMC or BMCL for extrapolation to humans is dependent on the biological relevance of the tumor site, adequacy of the model fit, and the biological plausibility of the model in the low-dose region. Since the experimental exposures to 1-BP were via inhalation, which is also the major route of occupational exposure, and all of the sites where tumors were observed are sites where tumors occur in humans, all of the tumor sites are regarded as biologically relevant. Therefore, the choice is between selecting the best-fitting plausible model, the most health-protective plausible model, or a weighted average of several models that are each individually plausible. A model-averaging strategy has been shown to be generally superior to either picking the best-fitting model or picking the most health-protective model [Wheeler and Bailer 2007] and was the strategy adopted here. The model average rodent BMC and BMCL estimates were extrapolated to humans on the basis of the mg/kg-day dose, scaled by body weight to the 0.75 power, as described in Section 7.3.2. The human-equivalent BMC and BMCL values for the lung, skin, and intestinal tumors are shown in Table 7.5. Based on the most sensitive of the three tumorigenic endpoints, alveolar/bronchiolar adenomas + carcinomas, 45-year lifetime occupational exposures to concentrations of 0.3–0.4 ppm of 1-BP are expected to produce approximately 1 in 1000 lifetime excess risk of lung cancer.

7.3.2 Extrapolation of Tumor-based BMCs and BMCLs to a Range of Levels of Lifetime Excess Risk

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

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^3 inhaled†	Extrapolated human BMC (ppm)‡	Extrapolated human BMCL (ppm)‡
Alveolar/bronchiolar adenoma + carcinoma	0.85	0.64	$B6C3F_1$ 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; $BW^{0.75}$= body weight to the three-fourths power; m^3 = cubic meter; ppm = parts per million; $B6C3F_1$ = F_1 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 $mg/kg^{0.75}$, as described in Section 7.2.3.

TABLE 7-6 – ESTIMATED LIFETIME ADDED RISK OF LUNG TUMORS DUE TO OCCUPATIONAL EXPOSURE TO 1-BP, BASED ON LUNG TUMORS IN FEMALE B6C3F$_1$ MICE

Lifetime added risk	Rodent BMC (ppm)	Rodent BMCL (ppm)	Reference BW (grams)*	8-hour m^3 inhaled†	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	**0.30**§
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

Abbreviations: BMC = benchmark concentration; BMCL = benchmark concentration low (95% lower confidence limit for the benchmark concentration); BW = body weight; m^3 = cubic meter; ppm = parts per million; B6C3F$_1$ = F$_1$ generation hybrid of female C57BL/6 and male C3H.
***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$^{0.75}$, as described in Section 7.2.3.
§The exposure level shown in boldface is the 95% LCL estimate of the concentration of 1-BP considered appropriate for establishment of a REL.

7.3.3 Sensitivity Analysis

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

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

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

As noted in section 7.2.2, extrapolation of carcinogenicity from animals to humans is typically assumed to scale according to (body weight)$^{0.75}$. This assumption is based on the expected cross-species scaling of the metabolism and pharmacokinetics of 1-BP. An alternative assumption for 1-BP-induced lung tumors might be that they scale across species according to the inhaled concentration of 1-BP. As shown in Table 7-2, the model average BMC and BMCL for 1-BP lung tumors in mice are 0.85 and 0.64 ppm, respectively. These results were obtained using an experimental protocol in which the mice were exposed to 1-BP for 6 hours per day, 5 days per week. Assuming that occupational exposures would involve an 8 hour per day, 5 days per week exposure, the mouse BMC and BMCL can be adjusted to an occupational exposure scenario by multiplying by 6/8. Therefore, the estimated human BMC and BMCL for a 1 in 1000 lifetime excess risk of lung cancer would be 0.6 or 0.5 ppm, respectively, when rounded to one significant figure.

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

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

7.4 DISCUSSION

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

As discussed in Appendix B, the lowest duration-adjusted BMC and BMCL values for non-cancer endpoints were observed for the dichotomous endpoints of renal pelvic mineralization in the F_0 females in the WIL Research Laboratories [2001] study and hepatic cytosolic vacuolation in the F_0 males in the WIL Research Laboratories [2001] study. These endpoints were judged to be inappropriate for extrapolation to occupational exposures. However, if hypothetical recommendations were based on these endpoints for purposes of comparison with the cancer endpoints, then the extrapolated BMCL values would be 92 ppm for renal mineralization in the F_0 females and 103 ppm for hepatic cytosolic vacuolation in the F_0 males, yielding occupational exposure levels of approximately 1.2–1.4 ppm after application of a 75-fold UF. The lowest occupationally relevant human-equivalent non-cancer BMCL for 1-BP is 144 ppm, derived from effects on sperm morphology in the F_0 generation of the WIL Research Laboratories [2001] study. Application of the 75-fold UF yields an estimated occupational exposure concentration of approximately 1.9 ppm. Similarly, the 182 ppm human-equivalent BMCL for decreased hind limb grip strength in the Ichihara [2000b] study yields an estimated occupational exposure concentration of approximately 2.4 ppm. Thus, recommendations based on the non-cancer endpoints would lead to occupational exposure concentrations

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

7.5 SUMMARY

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

CHAPTER 8: BASIS FOR THE RECOMMENDED EXPOSURE LIMIT

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

8.1 BASIS FOR THE NIOSH REL

NIOSH has proposed a REL for 1-BP of 0.3 ppm (1.5 milligrams per cubic meter of air [mg/m^3]) for an 8-hour TWA exposure, during a 40-hour workweek. This recommendation is based on the results of a quantitative assessment of cancer risks (described in Chapter 7). Data on lung tumors in female mice were selected as the basis of the REL for 1-BP because lung cancer was identified as the most sensitive health endpoint [NTP 2011]. This value is associated with a 1 in 1,000 excess risk of lung cancer over a working lifetime (see Table 7-6). The NIOSH REL represents the maximum 8-hour TWA concentration to which a worker may be exposed and is intended to reduce workers' risk of lung cancer associated with occupational exposure to 1-BP over a 45-year working lifetime. NIOSH does not consider an exposure limit set at a risk level of 1 in 1,000 to be a safe level of exposure for workers because of the residual risk of lung cancer and other health effects at the REL. Therefore, exposures should always

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

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

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

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

8.2 Analytical Feasibility of the NIOSH REL

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

8.3 Action Level

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

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.

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

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

- hazard communication and training (Chapter 9)
- exposure control (Chapter 9)
- medical monitoring and surveillance (Chapter 10)
- biological monitoring (Chapter 10)
- exposure monitoring (Chapter 11).

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

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

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

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

9.2 Elimination and Substitution

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

If elimination is not possible, substitution is the next choice of control to protect worker health, using substitution of equipment, materials, or less hazardous processes. Equipment substitution is the most common type of substitution [NIOSH 1973; Burton 2011]. It is often less costly than process substitution, and it may be easier than finding a suitable substitute material. Examples that apply to 1-BP exposure reduction include (1) the substitution of an unenclosed, manual operated degreasing unit with an enclosed, automated degreasing unit [MTAP 2011] and (2) the substitution of an organic-solvent based dry cleaning unit with a unit that relies on aqueous or "wet cleaning" systems [NIOSH 1997a,b,c; MTAP 2010].

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

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

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

9.3 Engineering Controls

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

Insufficient exposure data are available to assess the extent to which the REL of 0.3 ppm for 1-BP is achievable in various workplaces. 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 proper 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.

9.3.1 Ventilation

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

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

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

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

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

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

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

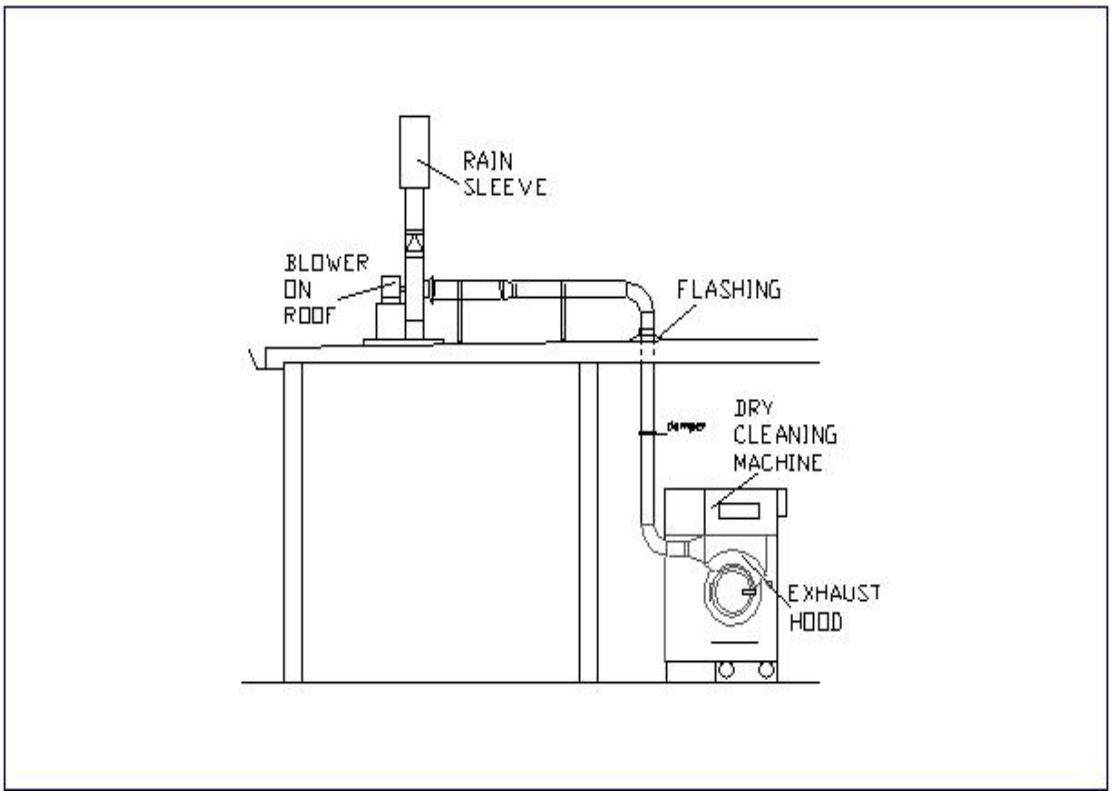
9.3.1.1 Dry Cleaning

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

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

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

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



Reference: NIOSH[1997d]

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

9.3.1.2 Vapor Degreasing

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

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

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

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

9.3.2 Isolation

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

9.3.2.1 Dry cleaning

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

9.3.2.2 Vapor Degreasing

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

9.3.3 Control of Exposure by Process

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

9.3.3.1 Dry cleaning

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

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

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

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

9.3.3.1.1 Types of Dry cleaning Machines

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

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

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

9.3.3.1.2 Important Machine Design Features

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

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

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

9.3.3.1.3 Retrofitting Machines

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

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

- Safety switches to ensure closed-door operation
- Safety interlocks for heating
- Cooling and still system failures
- Emission-free still cleaning devices
- Regenerable solvent filtration systems
- Emission-free solvent filling devices

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

9.3.3.2 Vapor Degreasing

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

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

9.3.3.2.1 Types of Vapor Degreasers

9.3.3.2.1.1 Open-top Vapor Degreasers

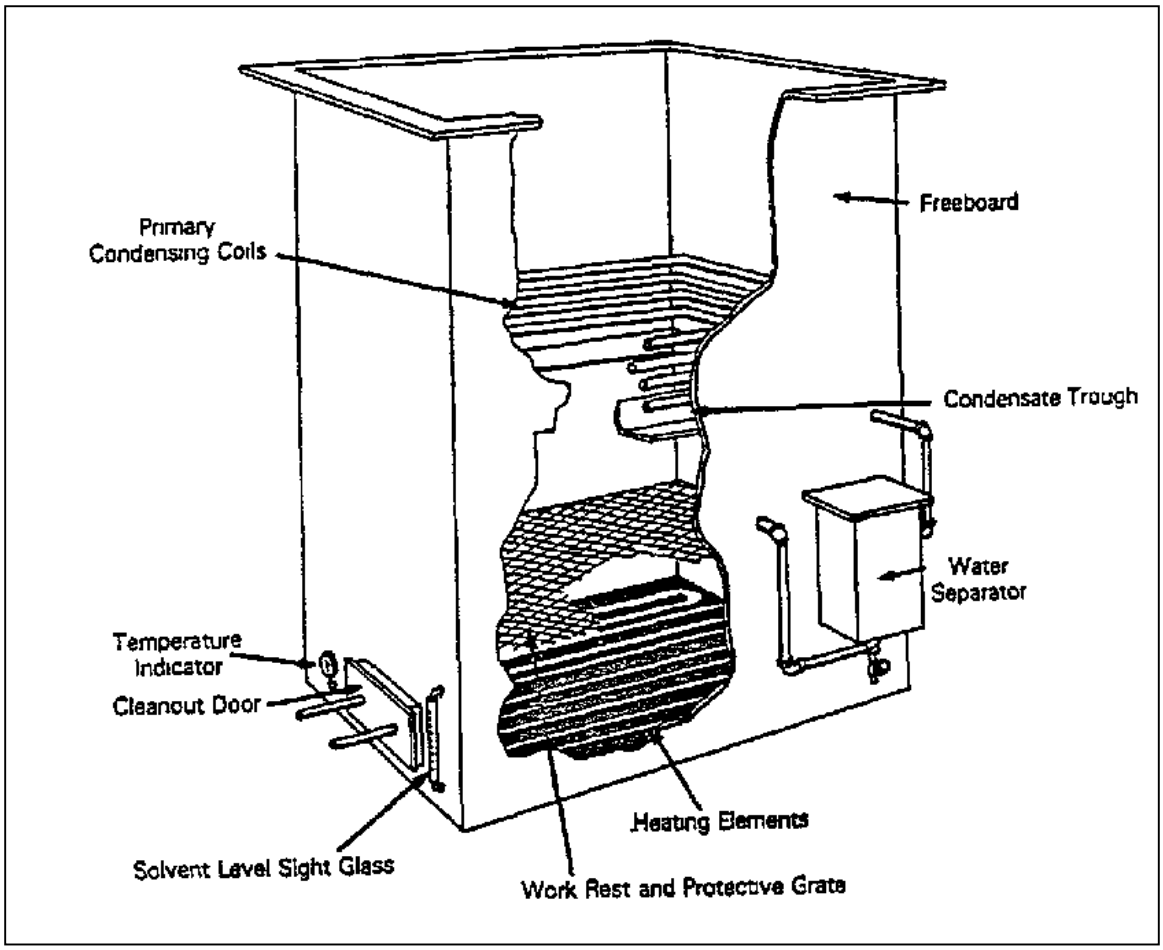
Open-top degreasers operate in batch mode. A cold metal part is lowered into the warm vapor zone either manually or mechanically to allow the solvent vapor to condense on

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

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

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

FIGURE 9-2 – OPEN-TOP DEGREASER*

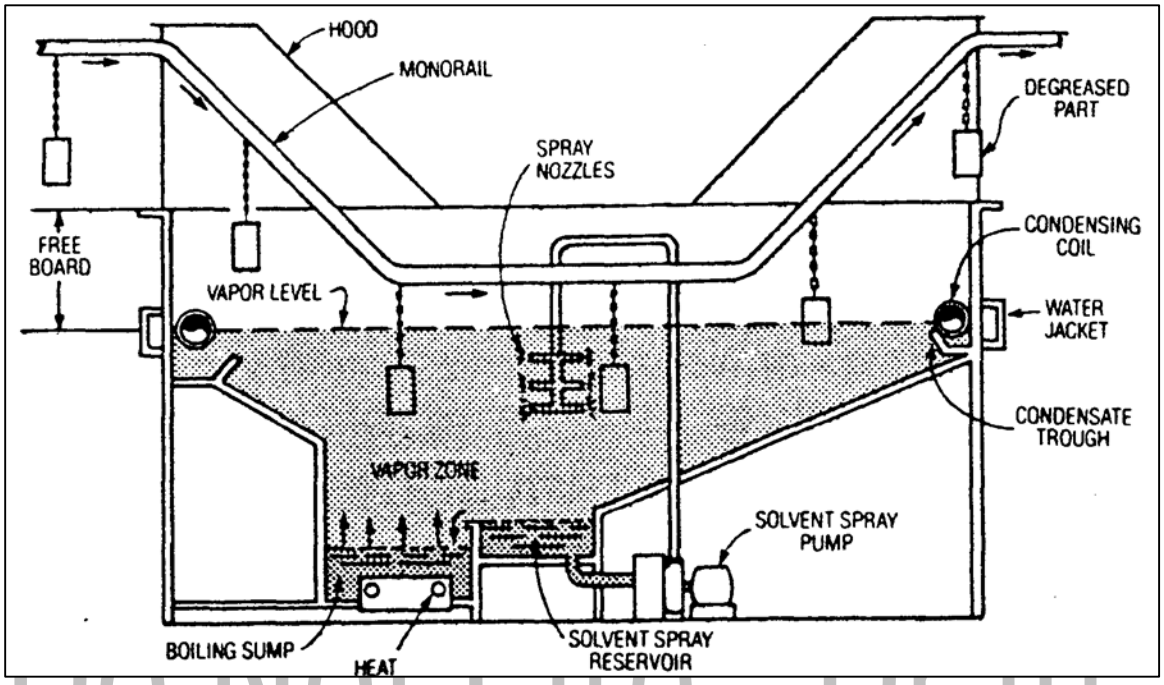


*Reference: NIOSH [2002c]

9.3.3.2.1.2 IN-LINE (CONVEYORIZED) VAPOR DEGREASER

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].

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



***Reference: Center for Emissions Control [1992]**

9.3.3.2.2 DESIGN FEATURES OF VAPOR DEGREASERS

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

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

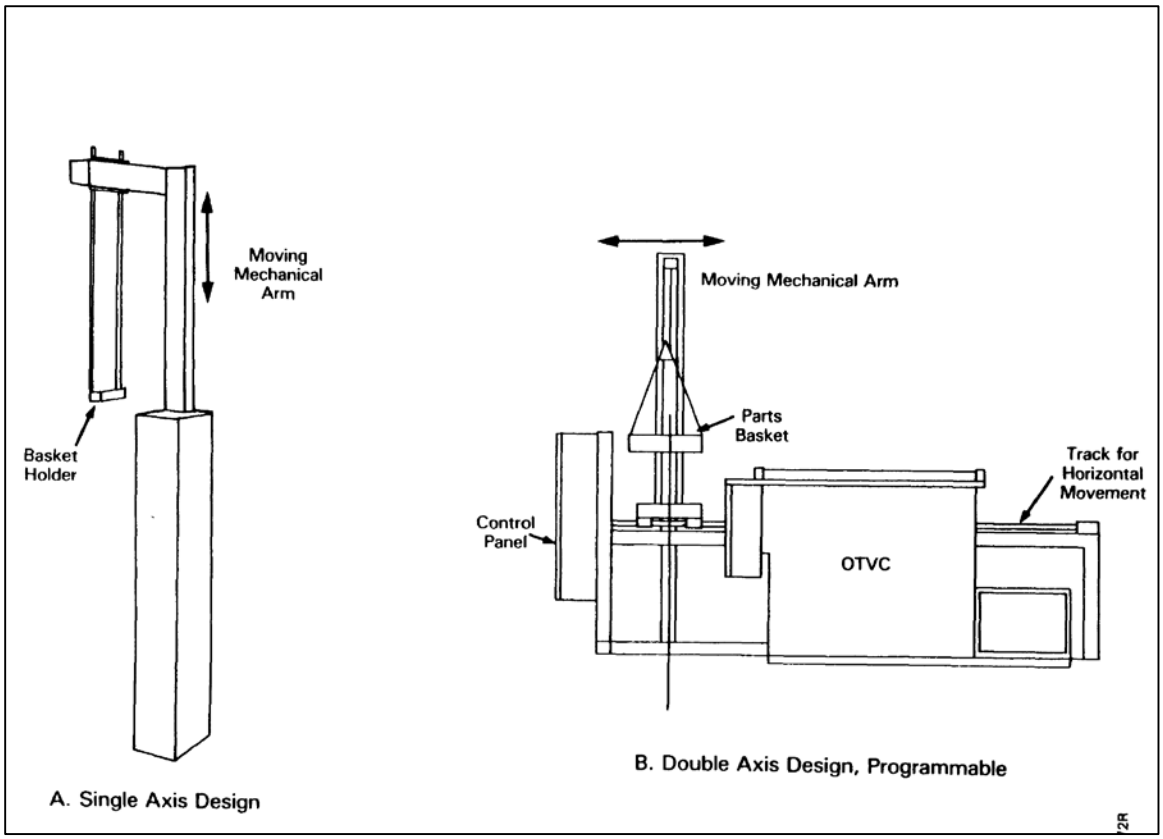
The NESHAP minimum requirement is 75%, but 100% is a control option [Center for Emissions Control 1992; EPA 1995; OSHA 1998a; MTAP 2011].

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

2011; OSHA 1998a]. Four NIOSH studies [NIOSH 2002a,b,c,d] evaluated open-top and airless vacuum vapor degreasers that used PERC as the solvent. Personal breathing zone concentrations were lower for the airless vacuum vapor degreaser (0.052 to 0.4 ppm) than for the open-top degreaser (0.9 to 17.1 ppm).

- Install a secondary condenser (a primary condenser is required on vapor cleaning machines) [MTAP 2011; EPA 1995].
- Use a carbon adsorber if lip vents are used [MTAP 2011].

FIGURE 9-4 – AUTOMATED PARTS HANDLING SYSTEM*



***Reference: EPA [1989]**

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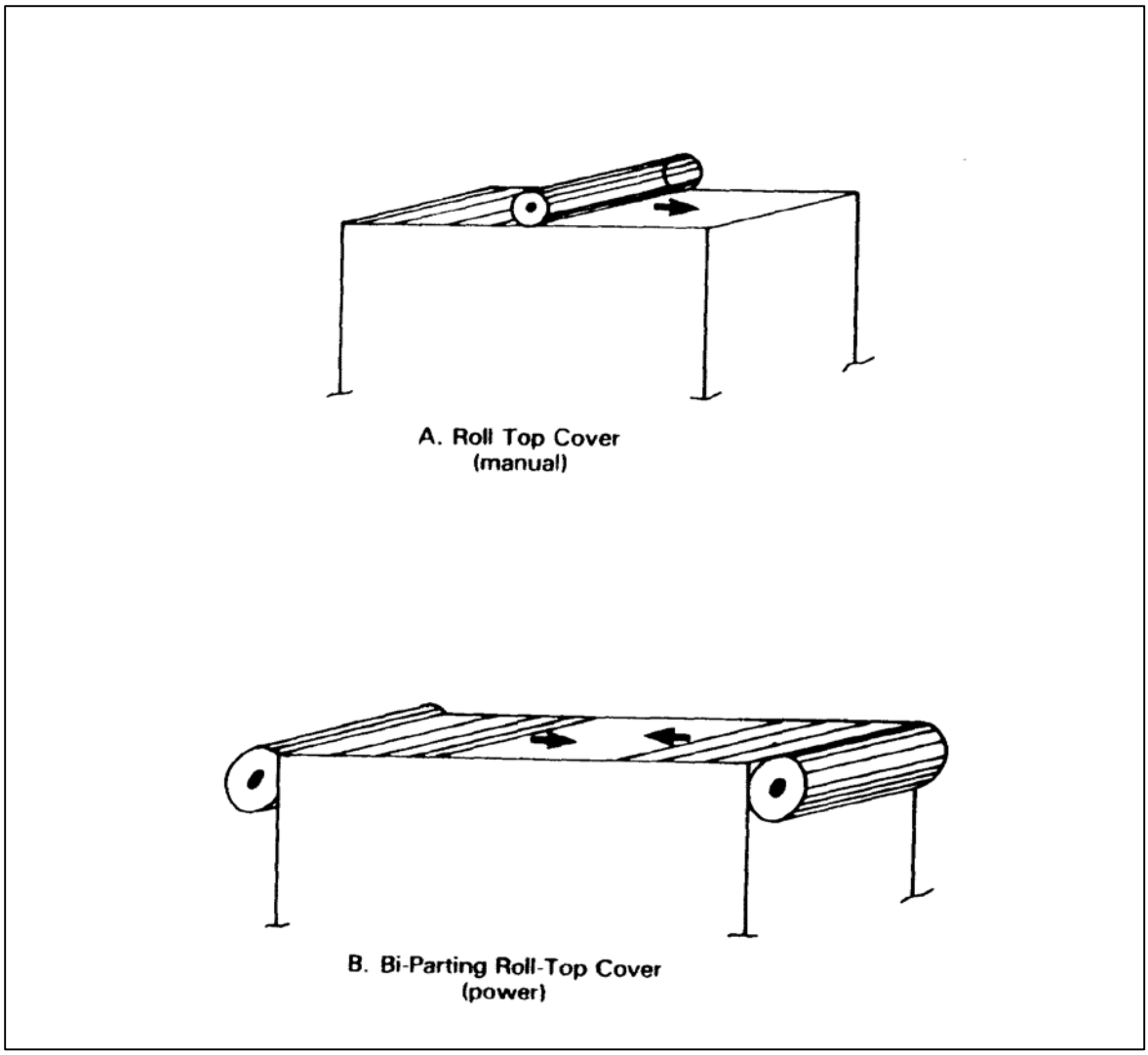
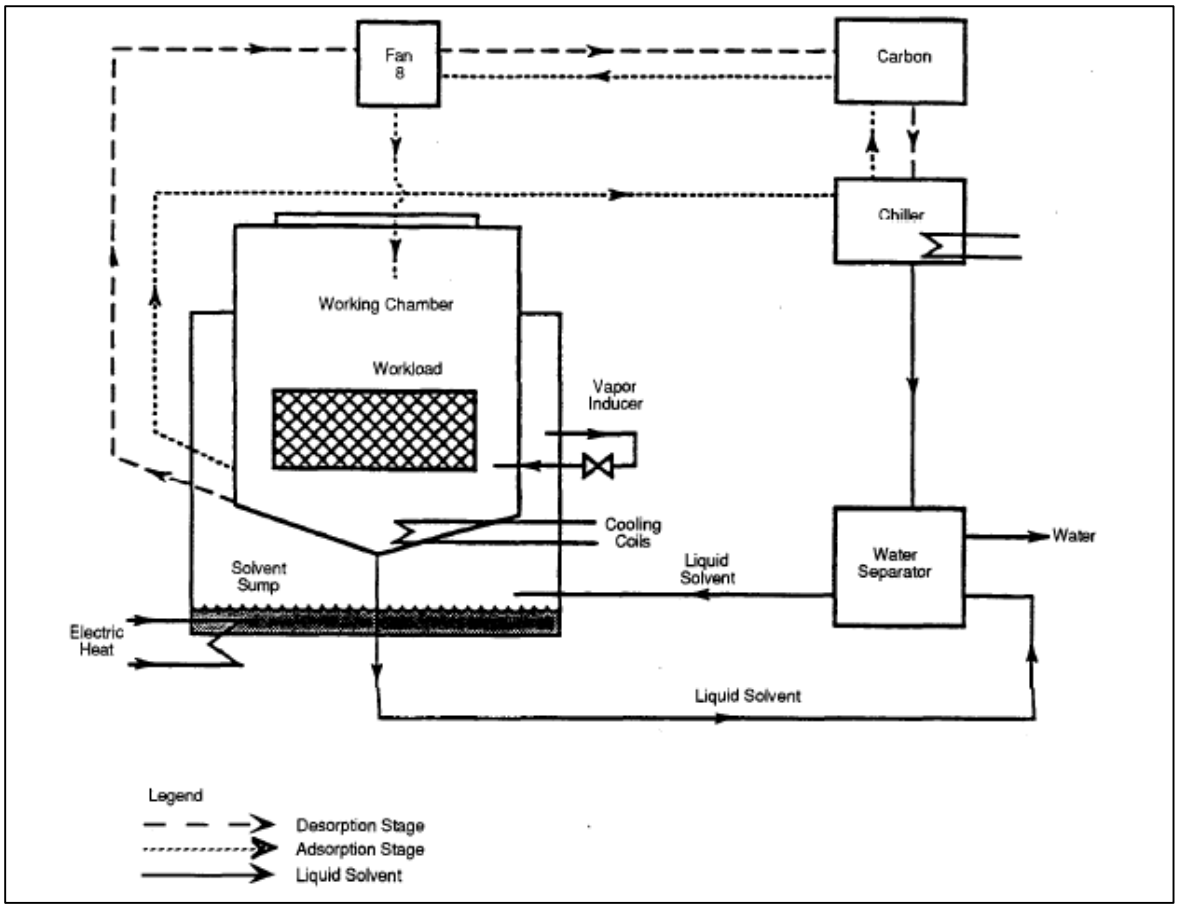
FIGURE 9-5 – OPEN-TOP VAPOR DEGREASER COVER OPTIONS*



***Reference: EPA [1989]**

FIGURE 9-6 – CLOSED-LOOP VAPOR DEGREASER*



***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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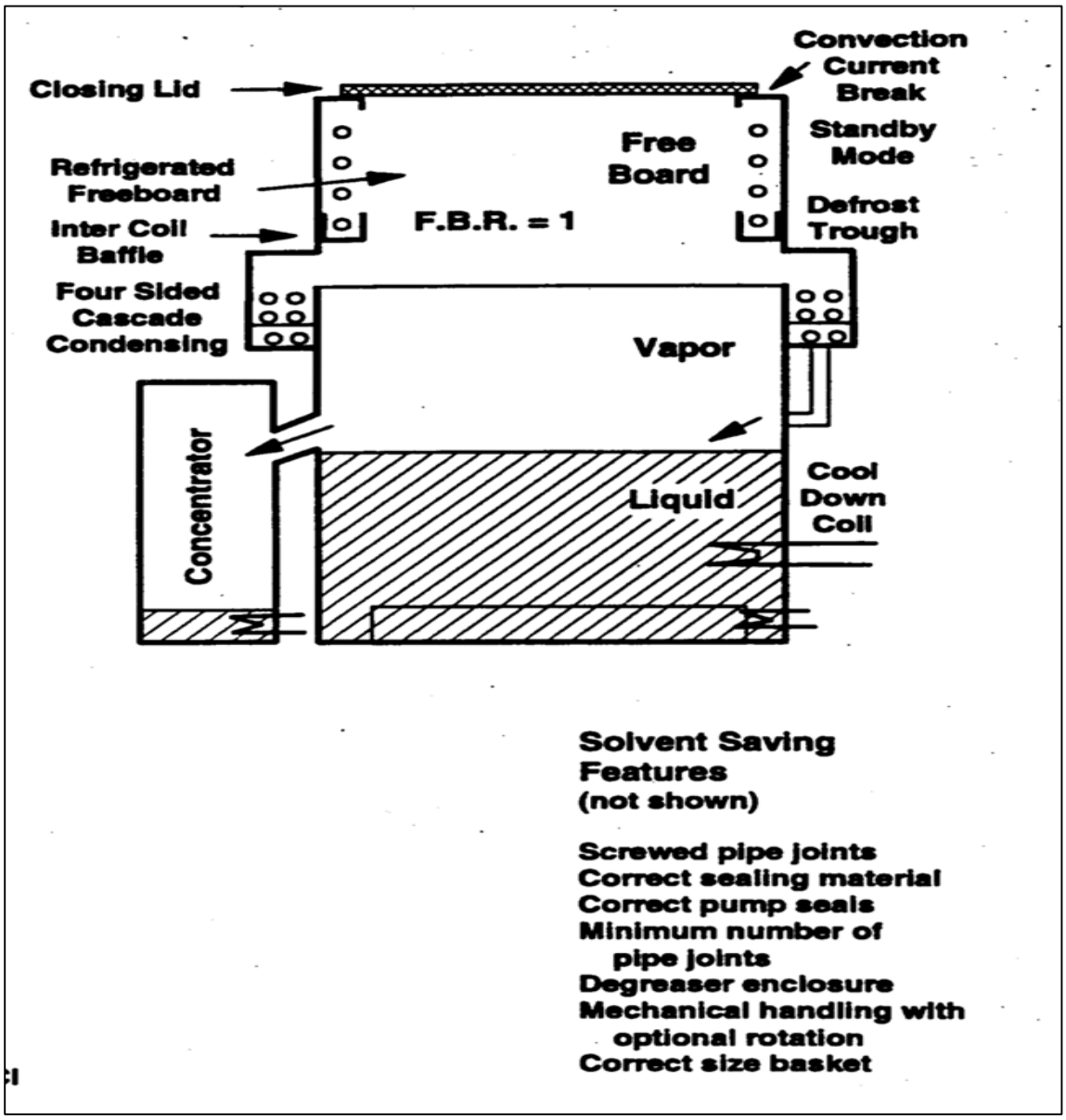
FIGURE 9-7 – VAPOR DEGREASER WITH SOLVENT REDUCTION EMISSIONS TECHNOLOGY*



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

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9.4 ADMINISTRATIVE CONTROLS AND WORK PRACTICES

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

9.4.1 GOOD HOUSEKEEPING PRACTICES AND HYGIENE PROCEDURES

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

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

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

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

9.4.2 Hazard Training and Communication

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

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

9.4.2.1 GLOBALLY HARMONIZED SYSTEM OF CLASSIFICATION AND LABELING

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

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

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

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

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

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

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

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

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

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_{50} value range: >2,500 and ≤ 20,000]	4-hour LC_{50} 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 (*Continued*)	Danger

GHS endpoint	Hazard category [Criteria]	Rationale (Species)	References	Pictogram	Hazard phrase	Signal word†
Reproductive	Category 1B [Suspected human reproductive toxicant]	Morphological abnormalities in the reproductive systems of male and female animals Sperm morphological and motility abnormalities; (*Continued*) 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) Hepatoxicity (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 (*Continued*)	Danger

GHS endpoint	Hazard category [Criteria]	Rationale (Species)	References	Pictogram	Hazard phrase	Signal word†
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

(*Continued*)

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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9.4.2.2 Labeling and Posting

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

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

9.4.2.3 Emergency Procedures

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

9.4.3 Good Work Practices: Dry cleaning

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

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

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

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

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

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

9.4.4 Good Work Practices: Vapor Degreasing

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

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

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

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

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

9.5 Personal Protective Equipment

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

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

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

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

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

9.5.1 Protective Clothing and Gloves

NIOSH recommends the use of gloves and chemical protective clothing (CPC) with maximum body coverage for all workers exposed to 1-BP. While the selection of this CPC is based on permeation properties, other selection factors such as size, dexterity, and cut and tear resistance should be considered as well. Contaminants on reusable CPC, gloves, and shoes must be removed and the items must be decontaminated with proper methods before reuse [AIHA 2005]. Further information on CPC can be obtained on the NIOSH Protective Clothing topic page: http://www.cdc.gov/niosh/topics/protclothing/. Additional information is also available in

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

9.5.2 Skin, Face, and Eye Protection

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

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

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

9.5.3 Respiratory Protection

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

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

Training in respiratory hazards should include the following:

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

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

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

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

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

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

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

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

Type of Respirator	OSHA Assigned Protection Factor*	Maximum Use Concentration for 1-BP†
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

Abbreviations: PAPR = powered, air-purifying respirator; ppm = parts per million; OV = organic vapor; SAR = supplied-air respirator; SCBA = self-contained breathing apparatus.

***APFs based on [29 CFR 1910.134 (d)(3)(i)(A)].**

†Maximum use concentrations will be lower than shown when those concentrations are equal to or exceed immediately dangerous to life and health levels.

‡The employer should have evidence provided by the respirator manufacturer that testing of these respirators demonstrates performance at a level of 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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CHAPTER 10: MEDICAL MONITORING AND BIOLOGICAL MONITORING

10.1 MEDICAL MONITORING

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

10.1.1 MEDICAL MONITORING PROGRAM DIRECTOR

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

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

10.1.2 WORKER PARTICIPATION

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

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

10.1.3 Worker Education

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

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

10.1.4 Monitoring Elements

10.1.4.1 Initial Medical Examinations

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

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

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

10.1.4.2 Periodic Medical Examinations

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

10.1.4.3 Written reports of medical findings

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

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

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

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

- A medical opinion as to whether any of the worker's medical conditions is likely to have been caused or aggravated by occupational exposures

Findings from the medical evaluations that have no bearing on the worker's ability to work with 1-BP should not be included in any reports to employers. Confidentiality of the worker's medical records should be enforced in accordance with all applicable regulations and guidelines.

10.1.5 Employer Actions

The employer should ensure that recommendations concerning restriction of a worker's exposure to 1-BP or other workplace health hazards are followed and that the REL for 1-BP is not exceeded without requiring the use of PPE. Efforts to encourage worker participation in the medical monitoring program and to report any symptoms promptly to the program director are important to the program's success. Medical evaluations performed as part of the medical monitoring program should be provided by the employer at no cost to the participating workers. Where medical removal or job reassignment is indicated, the affected worker should not suffer loss of wages, benefits, or seniority. The employer should ensure that the program director regularly collaborates with the employer's safety and health personnel (e.g., industrial hygienists) to identify and control work exposure and activities that pose a risk of adverse health effects.

Findings from the medical monitoring and surveillance program should be periodically aggregated and evaluated to identify patterns of worker health that may be linked to work activities and practices that require additional primary prevention efforts. This analysis should be performed by a qualified health-care professional or other knowledgeable person. Confidentiality of workers' medical records should be enforced in accordance with all applicable regulations and guidelines.

Employers should periodically evaluate the elements of the medical monitoring program to ensure that the program is consistent with current knowledge related to exposures and health effects associated with occupational exposure to 1-BP.

10.1.6 Record Keeping

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

10.2 Biological Monitoring

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

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

10.2.1 1-Bromopropane (1-BP)

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

10.2.2 Urinary Bromide (Br^-)

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

10.2.3 Urinary N-acetyl-S-(n-propyl)-L-cysteine (AcPrCys)

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

10.2.4 Urinary 3-Bromopropionic Acid (3-BPA)

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

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

10.2.5 SUMMARY

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

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

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

11.2 Exposure Monitoring Program Elements

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

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

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

11.2.1. Objectives of Sampling

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

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

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

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

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

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

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

11.2.2 Whom and Where to Sample

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

11.2.3 How to Sample

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

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

samples on a charcoal tube (Anasorb coconut shell charcoal, 100/50 milligram [mg] sections) at a sampling rate ranging from 0.01 to 0.2 liters of air per minute (L/min) and a recommended sample volume of 0.1 to 12 liters (L). The sample, which is stable for 30 days at 5°C, is analyzed following desorption of the specimen with 1 milliliter of carbon disulfide (CS_2), by means of a GC unit equipped with a flame ionization detector (GC-FID). For a 12-L sample, the LOD is 1 µg (0.05 ppm) 1-BP, and the limit of quantification (LOQ) is 3 µg (0.05 ppm). This method has been partially validated. It was field tested in an industrial setting as part of a NIOSH HHE, in which 1-BP was used in the application of adhesive to foam strips [NIOSH 2003b]. This method can be applied to any process in which 1-BP may be volatilized.

OSHA has developed sampling and analytical methods for 1-BP and 2-BP. The methods are partially validated and are available for information and trial use [OSHA 1999a]. Both method PV2061 for 1-BP and method PV2062 for 2-BP involve sample collection in which a known volume of air is drawn through charcoal tubes, which are then desorbed with a mixture of CS_2 and dimethylformamide (DMF) and analyzed by means of a GC-FID. The target concentration for 1-BP and 2-BP is 5 ppm. An air volume of 12 L and sampling rate at 0.1 L/min are recommended for both methods. The LOD is estimated as 0.13 µg per sample; the reliable quantification limit (RQL) for 1-BP is 0.007 ppm, and that for 2-BP is 0.004 ppm.

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

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

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

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

Because many modern analytical techniques are extremely sensitive, contamination of field samples should be carefully avoided. Samples should not be stored or shipped with bulk materials that might spill or otherwise contaminate them. The glassware or other containers used in sampling and shipping should be cleaned as recommended in the analytical method. For many sampling methods, the analytical laboratory requires submission of a specific number of blank samples with each set of samples to be analyzed; this number of samples is specific to the method. Blanks are used to mitigate the potential for unrecognized contamination due to media or sample handling [NIOSH 1994]. The two types of sample blanks are field blanks and media blanks. Field blanks are unopened new samplers or media taken to the sampling site and handled in every way like the actual samples, except that no air is drawn through them. Media blanks are simply unopened new samplers or media that are submitted to the laboratory with the samples (these blanks are not usually taken to the field). Additional blind field blanks, labeled as field samples, should be sent along with the field samples as a further check on the analysis. Another occasionally used quality control practice is to include spiked samples—samples with known amounts of 1-BP added—along with the other field samples sent to the laboratory for analysis. These spiked samples are often prepared by a separate laboratory and

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

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

11.2.4 When to Sample

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

11.2.5 How Long to Sample

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

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

11.2.6 How Many Samples to Collect

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

11.2.7 Sample Handling, Storage, and Shipment

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

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

11.3 Outcomes of Exposure Monitoring

11.3.1 Interpretation

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

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

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

11.3.2 Notification of Workers

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

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

CHAPTER 12: SURVEILLANCE AND RESEARCH NEEDS

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

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

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

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

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

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

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

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

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

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

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

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

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

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APPENDIX A: ANALYTICAL METHOD

1- and 2-BROMOPROPANE 1025

$CH_3CH_2CH_2Br$	MW: 123.00	CAS: 106-94-5	RTECS:TX4110000
$(CH_3)_2CHBr$	123.00	75-26-3	TX4111000

METHOD: 2552, ISSUE 1 **EVALUATION: PARTIAL** **Issue 1: 15 March 2003**

OSHA: None
NIOSH: None
ACGIH: None

PROPERTIES: **1-BP:** liquid; d= 1.354 g/mL @ 20 °C; BP= 71 °C; MP = -110 °C; FP= 25 °C.
2-BP: liquid; d= 1.310 g/mL @ 20 °C; BP= 59 °C; MP= -89 °C; FP= 19 °C.

NAMES & SYNONYMS: 1-Bromopropane: Propyl bromide, 1-BP.
2-Bromopropane: Isopropyl bromide, 2-BP.

SAMPLING

SAMPLER: Solid Sorbent Tube [1] (Anasorb CSC, 100/50 mg) Alternative sampler (Anasorb CMS, 150 mg/75 mg)

FLOW RATE: 0.01 to 0.2 L/min

VOL-MIN: 0.1L
-MAX: 12 L

SHIPMENT: Routine

SAMPLE STABILITY: 30 days at 5°C

BLANKS: 10% of field samples

ACCURACY

RANGE STUDIED: Not determined.

BIAS: Not determined.

OVERALL PRECISION ($\hat{S}_{rt}$): Not determined.

ACCURACY: Not determined.

MEASUREMENT

TECHNIQUE: GAS CHROMATOGRAPHY, FID

ANALYTE: 1-Bromopropane and 2-Bromopropane

DESORPTION: 1-mL CS_2 for 30 minutes with agitation.

INJECTION VOLUME: 1-µL

TEMPERATURE:
-INJECTION: 200°C
-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

CALIBRATION: Standard solutions of analytes in CS_2.

RANGE: 1-BP: 3.0 to 406.0 µg per sample [1]
2-BP: 4.5 to 393.0 µg per sample [1]

ESTIMATED LOD: 1-BP: 1.0 µg per sample [1]
2-BP: 1.0 µg per sample [1]

PRECISION ($\hat{S}_r$): 1-BP: 0.015 [1]
2-BP: 0.022 [1]

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.

NIOSH Manual of Analytical Methods (NMAM), Fourth Edition

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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-µL, 25-µL, 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 µg analyte).

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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 µL) 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 µg 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-µL 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, µg (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):

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

EVALUATION OF METHOD:

Desorption efficiency was checked for 1- and 2-bromopropane by spiking known amounts (in 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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[2] Pendergrass, SM [1998]. Analytical Report for Sequence 9015 - 1-Bromopropane, National Institue 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_0 male and female rats [WIL Research Laboratories 2001].
- F_0 sperm motility [WIL Research Laboratories 2001].
- F_0 sperm morphology [WIL Research Laboratories 2001].
- F_0 estrous cycle length [WIL Research Laboratories 2001].
- Renal pelvic mineralization in F_0 male and female rats [WIL Research Laboratories 2001].
- F_1 decreased live litter size [WIL Research Laboratories 2001].
- F_1 male fetal body weight [WIL Research Laboratories 2001].
- F_1 female fetal body weight [WIL Research Laboratories 2001].
- Decreased antral follicle counts [Yamada et al. 2003].

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

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

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

Continuously variable endpoints	Reference	Concentration	Sample size	Results	SD
F_0 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_0 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

(*Continued*)

Continuously variable endpoints	Reference	Concentration	Sample size	Results	SD
F_0 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_1 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_1 female fetal body weight	WIL Research Laboratories [2001]	ppm	Number of pups	Mean	SD
		0	23	6.9	0.59
		100	24	6.7	0.64
		250	21	6.9	0.61

(*Continue*d)

Continuously variable endpoints	Reference	Concentration	Sample size	Results	SD
F_1 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

(*Continued*)

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

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

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

Dichotomous endpoints	Study	Concentration	Sample size	Results
Hepatic vacuolation (F_0 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_0 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

(*Continued*)

Dichotomous endpoints	Study	Concentration	Sample size	Results
Renal pelvic mineralization (F_0 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_0 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

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

B.2 METHODS

B.2.1 DOSE-RESPONSE MODELING

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

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

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

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

B.2.2 Adjustment for Differences in Experimental Exposures

The BMCs and BMCLs estimated from the various studies are dependent on the specific exposure regimen employed in each study. These ranged from 6 hours/day and 5 days/week [ClinTrials BioResearch 1997b] to 8 hours/day and 7 days/week [Ichihara et al. 2000a, 2004b]. The BMCs and BMCLs were adjusted to reflect a 40-hour workweek under the assumption that they are inversely proportional to exposure duration at a given concentration. For example, the BMCs and BMCLs calculated based on the results reported in Ichihara et al. [2004a, 2004b] were multiplied by 1.4 (7*8/40) to derive adjusted BMCs appropriate to occupational exposure conditions. The adjustments applied to each BMC and BMCL are shown in Table B-4[b], for models that fit the data adequately.

B.2.3 Extrapolation to Humans

Animal-based BMC and BMCL estimates reflect the conditions used in the individual study they are derived from, including the number of hours per day and number of days per week that the animals were exposed. These animal-based estimates were then

[b] CORRECTION - Replaced Table B-3 with Table B-4.

linearly extrapolated to duration-adjusted equivalent concentrations for a 40-hour workweek.

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

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

Equation 1:

400 ppm * 5.031 mg/m^3 per ppm * 0.23 m^3/day * 8 hour/24 hour / 0.217 kg = 711 mg/kg-day

[c] 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.

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

Equation 2:

Rat BMD of 711 mg/kg-day * $(0.217 \text{ kg}/70 \text{ kg})^{0.25}$ = Human BMD = 168 mg/kg-day

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

Equation 3:

168 mg/kg-day * 70 Kg / 9.6 m^3 per day * 1 ppm/5.031 mg/m^3 = 243 ppm

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

B.2.3.1 Extrapolation of Non-cancer Endpoints

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

B.3 Results

B.3.1 Benchmark Concentration Estimates for Non-cancer Endpoints

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Benchmark concentration estimates (BMCs and BMCLs) for non-cancer endpoints are listed in Table B-4. Four of the models used to obtain the estimates shown in Table B-3 were inadequate in terms of variance structure, and they were not further considered; these were the models for F_0 estrous cycle length and F_0 sperm motility [WIL Research Laboratories 2001], decreased antral follicle counts [Yamada et al. 2003], and F_1 decreased live litter size [WIL Research Laboratories 2001].

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

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

Continuously variable endpoints					
	Study	**Model**	**Variance model**	**Model fit *P***	**Variance fit *P***
Estrous cycle length (F_0)	WIL Research Laboratories [2001]	Linear	Homogeneous	0.7699	<.0001
Sperm morphology (F_0)	WIL Research Laboratories [2001]	Polynomial	Nonconstant	0.3642	0.8531
Sperm motility (F_0)	WIL Research Laboratories [2001]	Polynomial	Nonconstant	0.3742	0.04262
Decreased live litter size (F_1)	WIL Research Laboratories [2001]	Linear	Nonconstant	0.4333	0.05343
Fetal body weight (F_1 female)	WIL Research Laboratories [2001]	Polynomial	Homogeneous	0.4636	0.3008
Fetal body weight (F_1 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
Dichotomous endpoints					
	Study	**Model**	**Variance model**	**Model fit *P***	**Variance fit *P***
Liver vacuolation (F_0 males)	WIL Research Laboratories [2001]	Log-logistic	N/A*	0.9391	N/A
Liver vacuolation (F_0 females)	WIL Research Laboratories [2001]	Log-probit	N/A	0.9879	N/A
Renal pelvic mineralization (F_0 males)	WIL Research Laboratories [2001]	Logistic	N/A	0.6294	N/A
Renal pelvic mineralization (F_0 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

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

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

Continuously variable endpoints								
[reference]	**Endpoint**	**BMC***	**BMCL***	**Animal hours/day**	**Animal days/wk**	**Duration Adjustment**	**Adjusted BMC**	**Adjusted BMCL**
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_0)	304.7	225.0	6	7	1.05	320	236
WIL Research Laboratories [2001]	Fetal body weight (F_1 female)	497.8	403.6	6	7	1.05	523	424
WIL Research Laboratories [2001]	Fetal body weight (F_1 male)	486.0	421.6	6	7	1.05	510	443
Dichotomous endpoints								
[reference]	**Endpoint**	**BMC**	**BMCL**	**Animal hours/day**	**Animal days/wk**	**Duration Adjustment**	**Adjusted BMC**	**Adjusted BMCL**
ClinTrials BioResearch [1997b]	Liver vacuolation (Male rats)	345.7	226.1	6	5	0.75	259	170
WIL Research Laboratories [2001]	Liver vacuolation (F_0 males)	187.6	143.5	6	7	1.05	197	151
WIL Research Laboratories [2001]	Liver vacuolation (F_0 Females)	415.4	322.1	6	7	1.05	436	338
WIL Research Laboratories [2001]	Renal pelvic mineralization (F_0 males)	541.3	428.3	6	7	1.05	568	450
WIL Research Laboratories [2001]	Renal pelvic mineralization (F_0 females)	185.4	135.0	6	7	1.05	195	142

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

B.3.2 Selection of Non-cancer Endpoints for Extrapolation to Humans

Two types of endpoints were modeled to generate the benchmark concentrations shown in Tables B-3 and B-4: continuously variable endpoints and dichotomous endpoints. The lowest duration-adjusted BMC and BMCL values were observed for the dichotomous endpoint of renal pelvic mineralization in the F_0 females [WIL Research Laboratories [2001]. The BMC and BMCL for hepatic cytosolic vacuolation in the F_0 males were similar [WIL Research Laboratories 2001]. The WIL Research Laboratories [2001] study was primarily a reproductive toxicity study, and exposures to the F_0 generation were limited to 10 weeks of exposure. The reproducibility of the renal and hepatic pathology observed in the WIL Research Laboratories [2001], and the long-term consequences to these organs of continued exposure to 1-BP were assessed by comparison to the results of the 13-week ClinTrials BioResearch [1997b] study, and preliminary reports of the NTP 13-week and 2-year bioassays for 1-BP [NTP 2011].

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

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

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

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

The next-lowest duration-adjusted BMC and BMCL among the continuous endpoints with adequate models were for sperm morphology in the F_0 generation of the WIL Research Laboratories [2001] study; the BMC is 320 ppm, and the BMCL is 236 ppm (Table B-4). The endpoint of decreased hind limb grip strength in the Ichihara et al. [2000b] study yielded a duration-adjusted BMC value of 400 ppm and BMCL value of 299 ppm, suggesting that neurotoxicity may occur at exposure levels similar to those that produce reproductive toxicity. The other continuous endpoints evaluated in Table B-

4 yielded larger BMC and BMCL values; therefore, recommendations for occupational exposure to 1-BP are based on the results for sperm morphology in the F_0 generation of the WIL Research Laboratories [2001] study and decreased hind limb grip strength in Ichihara et al. [2000b]. BMC and BMCL values for decreased live litter size and decreased fetal body weight for F_1 females in the WIL study were larger than the BMC and BMCL values for sperm morphology in the F_0 generation of the WIL Research Laboratories [2001] study and decreased hind limb grip strength in the Ichihara et al. [2000b] study. Extrapolation of these endpoints to humans was carried forward as a sensitivity analysis.

B.3.3 Extrapolation of Non-cancer Endpoints to Humans

Extrapolation to humans begins with the selection of a point of departure, that is, either a BMC or BMCL. Choosing a 95% lower confidence limit dose estimate, a BMCL, as the point of departure allows for the statistical variability of the benchmark concentration estimate, and it is thus more likely to be health-protective than the use of a central estimate such as a BMC. Extrapolation is therefore based on the lowest BMCL from a toxicologically relevant endpoint with an adequate dose-response model, 236 ppm, based on altered sperm morphology in the F_0 generation of the WIL Research Laboratories [2001] study.

In the case of 1-BP, the toxic effects used as a basis for risk assessment occur in sites distant from the sites of contact (respiratory tract and skin), and they thus involve the systemic uptake of 1-BP. Extrapolation from rats to humans is therefore based on an estimate of the relative mg/kg-day metabolized dose of 1-BP in humans versus rats exposed to a given concentration, with metabolism and pharmacokinetics assumed to scale across species according to body weight to the 0.75 power [O'Flaherty 1989; Travis et al. 1990]. The duration-adjusted BMC and BMCL estimates from Table B-4 were extrapolated to humans on this basis, and are shown in Table B-5.

TABLE B-5 – HUMAN-EQUIVALENT BMC AND BMCL ESTIMATES FOR 1-BP TOXICITY, EXTRAPOLATED FROM 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^3 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_0 males)	320	236	SD, male	267	0.090	195	144
WIL Research Laboratories [2001]	Decreased live litter size (F_1 female)	523	424	SD, female	204	0.073	318	258
WIL Research Laboratories [2001]	Fetal body weight (F_1 female)	510	443	SD, female	204	0.073	311	270
WIL Research Laboratories [2001]	Liver vacuolation (F_0 males)	197	151	SD, male	267	0.090	120	92
WIL Research Laboratories [2001]	Renal pelvic mineralization (F_0 females)	195	170	SD, female	204	0.073	119	103

Abbreviations: BMC = benchmark concentration; BMCL = benchmark concentration low (95% lower confidence limit for the benchmark concentration); BW = body weight; $BW^{0.75}$= body weight to the three-fourths power; m^3 = cubic meter; ppm = parts per million

***For additional information pertaining to the calculation of the values presented in Table B-3-3, see Section B.2**

†From EPA [1988], Table 1-2.; ‡From EPA [1988], Table 1-4.

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B.3.4 Application of Uncertainty Factors to Human-equivalent Concentrations Estimates for 1-BP Toxicity for Non-Cancer Endpoints

The human-equivalent BMC and BMCL estimates in Table B-5 are estimates of frankly adverse effect levels, and it must be adjusted by the application of UFs to allow for uncertainty in animal-to-human extrapolation and interindividual variability. As discussed in Methods (Section B.3.3), a total UF of 75 is appropriate for the non-cancer endpoints. Table B-6 provides the extrapolated concentrations for four endpoints, following the application of the UFs.

The lowest occupationally relevant human-equivalent BMCL for 1-BP is 144 ppm, derived from effects on sperm morphology in the F_0 generation of the WIL Research Laboratories [2001] study. Application of the 75-fold UF yields an estimated occupational exposure concentration of approximately 1.9 ppm. Similarly, the 182 ppm human-equivalent BMCL for decreased hind limb grip strength in the Ichihara et al. [2000b] study yields an estimated occupational exposure concentration of approximately 2.4 ppm.

TABLE B-6 – APPLICATION OF UNCERTAINTY FACTORS TO HUMAN-EQUIVALENT BMCL ESTIMATES FOR NON-CANCER ENDPOINTS*

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_0)	195	144	75	2.6	1.9
WIL Research Laboratories [2001]	Decreased live litter size (F_1 female)	318	258	75	4.2	3.4
WIL Research Laboratories [2001]	Fetal body weight (F_1 female)	311	270	75	4.1	3.6

Abbreviations: BMC = benchmark concentration; BMCL = benchmark concentration low (95% lower confidence limit for the benchmark concentration); ppm = parts per million; UF = uncertainty factor.

DRAFT

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B.4 DISCUSSION

One assumption made in this analysis is that recommendations for occupational exposure levels should be based on the 95% lower confidence limit estimate of a benchmark concentration, that is, a BMCL, rather than the central estimate, the BMC. The rationale for this is that the BMCL reflects the statistical variability of the data, and it is therefore more likely to be health-protective than a central estimate such as a BMC. For the endpoints selected as bases for development of occupational exposure recommendations, sperm morphology in the F_0 generation of the WIL Research Laboratories [2001] study and decreased hind limb grip strength in the Ichihara [2000b] study, the BMC estimates (shown in Table B-4) are approximately 35% higher than the corresponding BMCLs. Therefore, the recommended occupational exposure level would be correspondingly larger if recommendations were based on the BMC rather than the BMCL.

As discussed above in Section B.3.3, Extrapolation of Non-Cancer Endpoints to Humans, in this analysis the lowest duration-adjusted BMC and BMCL values were observed for the dichotomous endpoints of renal pelvic mineralization in the F_0 females in the WIL Research Laboratories [2001] study, and hepatic cytosolic vacuolation in the F_0 males in the WIL Research Laboratories [2001] study. These endpoints were judged to be inappropriate for extrapolation to occupational exposures; however, if recommendations were based on these endpoints the extrapolated BMCL values would be 92 ppm for renal pelvic mineralization and 103 ppm for hepatic cytosolic vacuolation, yielding occupational exposure levels of approximately 1.2–1.4 ppm after application of a 75-fold UF. Other non-cancer endpoints that could be adequately modeled included decreased live litter size and decreased female fetal body weight in F_1 offspring in the WIL Research Laboratories [2001] study. These endpoints yield extrapolated occupational BMCL values of 258 for live litter size and 270 ppm for female fetal body weight, which would yield occupational exposure levels of 3.4–3.6 ppm after application of a 75-fold UF.

For the non-cancer endpoints, the risk assessment assumption with the greatest numerical impact on recommended occupational exposure levels is the assumption of a 75-fold UF (after

replacing the rat-to-human pharmacokinetic factor with a body weight to the 0.75 power assumption) in extrapolating from animals to humans. Although UFs of this magnitude are widely used for nonoccupational risk assessments, it is sometimes argued that because workers must be healthy in order to work, worker populations would be unlikely to include the most susceptible individuals, and therefore a smaller UF can be applied. The use of a smaller UF would obviously increase the recommended occupational exposure level for 1-BP; however, it is difficult to rationalize a smaller UF for the endpoints of interest in this analysis. Workers experiencing reproductive toxicity would not be impacted in their ability to work, and they would be no more or less fit for work than other members of the population; therefore, it seems unlikely that workers would have any particular resistance to reproductive toxicity. Peripheral neuropathies due to occupational exposures to 1-BP have been reported (see Chapter 2–Human Studies and Exposure Assessment), so it appears that humans are vulnerable to this endpoint, and the use of a smaller UF would not represent prudent public health practice.

B.5 SUMMARY

Dose-response modeling was conducted for 1-BP using benchmark dose methods. Existing human studies do not provide adequate data for quantitative analysis; therefore, the dose-response analysis was based on animal data. The toxicologically based non-cancer BMCs and BMCLs were extrapolated to humans assuming dose-equivalency on a mg/kg^$^{0.75}$-day basis, and then a 75-fold UF was applied. The results suggest that occupational exposures to 1-BP should be limited to 8-hour TWA exposures in the range of 1.9 to 3.6 ppm, depending on the choice of endpoint and whether recommendations are based on the central estimate (BMC) or the 95% lower-bound estimate (BMCL). These results may be compared to those based on BMD modeling of tumors observed in a recent NTP chronic bioassay for 1-BP [NTP 2011]. Extrapolation of the toxicologically based BMCs and BMCLs to humans for the most sensitive endpoint—alveolar/bronchiolar adenomas + carcinomas—suggests that occupational exposures to 1-BP should be limited to 8-hour TWA exposures in the range of 0.3 to 0.4 ppm, which is approximately an order of magnitude lower than recommendations based on the non-cancer endpoints.

B.6 REFERENCES

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APPENDIX C: MODEL AVERAGING PROCEDURES FOR CANCER RISK ASSESSMENT

This appendix provides supplemental information on the model averaging (MA) procedures used in the cancer risk assessment for 1-BP described in Chapter 7.0: Quantitative Risk Assessment based on Cancer Data in Animals. Information included is 1) an overview of the NIOSH risk assessment and the use of MA procedures and 2) an example of using the MA process along with sample output.

C.1 OVERVIEW OF NIOSH RISK ASSESSMENT

NIOSH identified cancer data that provide dose-response information suitable for quantitative risk assessment for occupational exposures to 1-BP. The best available tumor data were found in the NTP bioassay [NTP 2011]. Dose-response data were identified for alveolar/bronchiolar adenoma and carcinoma in female mice, adenoma of the large intestine in female rats, and keratoacanthoma/squamous cell carcinoma of the skin in male rats.

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

Health End (sex; species)	Exposure Concentration (ppm)	Sample size	Number of tumors
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

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

*Source: NTP [2011].

The NIOSH quantitative risk assessment for 1-BP was conducted using benchmark concentration modeling. Dose-response modeling was done and benchmark concentrations were estimated with the U.S. EPA BMD software suite, version 2.12 [EPA 2010]. For tumor responses, the benchmark response was set at 0.1%, corresponding to a 1-in-1000 lifetime excess risk of cancer. The models considered were the gamma, logistic, log-logistic, multistage, probit, log-probit, quantal-linear, and Weibull models. The quantal-linear model is a subset of the multistage and Weibull models, which can assume this form if it is appropriate for a given data set, but it was included as a separate model to assess the fit of a strictly low-dose linear model. Models with chi-square goodness of fit P values of 0.10 or greater were considered to fit the data adequately. Because model-based extrapolation to a 0.1% response level is sensitive to the choice of models, the BMD results for tumor endpoints were summarized by using a model-averaging (MA) technique [Wheeler and Bailer 2007], which weights several models on the basis of the model fit. A restricted version of the model-averaging software was used to avoid supralinear models, which have low-dose properties considered biologically implausible. Confidence limits were obtained using a statistical method known as bootstrapping. The MADr-BMD software and the journal article describing the software can be obtained through the Journal of Statistical Software at http://www.jstatsoft.org/article/view/v026i05.

C.2 Example of the Application of Model Averaging

This section provides an example of the application of MA to calculate XXX using animal data. For this example, the input file for the female mouse lung tumors looks like this:

```
250 1e-8 1e-8
0 0 1 0 0 1 1 0 0
102210
2 1 0.001
0.95 5000 0
3
4
0     50    1
62.5  50    9
125.0 50    8
250.0 50    14
```

Table C-2 provides the specifications of the example input file.

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

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.

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
------------------------------------------------------------------------
```

```
----------------------------------------
'Average-Model' Benchmark Dose Estimate
----------------------------------------
Nominally Specified Confidence Level:0.950
Weighting Criterion: AIC
BMD Calculation: Added Risk
BMR: 0.001000
BMD:0.849148762733
BMDL(BCa)0.409673051027
(BMDL)Percentile:0.636052851184
Acceleration: 0.037488
Bootstrap Resamples: 5000
Random Seed: 102210
----------------------------------------

----------------------------------------
'Average-Model' Goodness of Fit Test
```

MADr-BMD provides both the individual BMD model parameters and fit statistics and the corresponding "Average Model" results.

To compare the modeling to individual BMDS models, here is a sample output of the female mouse lung tumor data for the multistage model using the EPA BMDS software suite:


```
 ======================================================================
        Multistage Model. (Version: 2.8;  Date: 02/20/2007)
        Input Data File: C:\BMDS\UNSAVED1.(d)
        Gnuplot Plotting File:  C:\BMDS\UNSAVED1.plt
                                        Mon Dec 22 13:09:24 2008
 ======================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive

   Dependent variable = COLUMN3
   Independent variable = COLUMN1
```

```
 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 4
 Total number of specified parameters = 0
 Degree of polynomial = 3


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008

                 Default Initial Parameter Values
                    Background =     0.058868
                       Beta(1) =   0.00109445
                       Beta(2) =            0
                       Beta(3) =            0

           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Beta(2)    -Beta(3)
                have been estimated at a boundary point, or have been specified
by the user,
                and do not appear in the correlation matrix )

             Background      Beta(1)

Background            1        -0.78

   Beta(1)        -0.78            1
```

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval 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.	P-value
Full model	-80.1028	4			
Fitted model	-81.4858	2	2.76596	2	0.2508
Reduced model	-87.934	1	15.6624	3	0.00133
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

```
Benchmark Dose Computation

Specified effect =          0.001

Risk Type        =      Added risk

Confidence level =           0.95

             BMD =       0.772228

            BMDL =       0.521641

            BMDU =        2.79546

Taken together, (0.521641, 2.79546) is a 90     % two-sided confidence
interval for the BMD
```

The output from the MADr-BMD software for the multistage model alone for female mouse lung tumors is provided below for comparison. One can see that the BMD's and BMDL's generated are equivalent.


```
Model          Weight    -2log(L)     AIC    BIC
-------------------------------------------------------------------------
Multistage      1.000     162.97     170.97      184.16
-------------------------------------------------------------------------

----------------------------------------
'Average-Model' Benchmark Dose Estimate
----------------------------------------
Nominally Specified Confidence Limit:0.950
Weighting Criterion: AIC
BMD Calculation: Added Risk
BMR: 0.001000
BMD: 0.772227525711
BMDL(BCa):0.473608016968
BMDL(Percentile):0.551896691322
Acceleration: 0.032744
Bootstrap Resamples: 5000
Random Seed: 123109
----------------------------------------
```

```
MODEL: Multistage, 3-degree polynomial:
----------------------------------------
Parameters  Estimate    StdErr
----------------------------------------
GAMMA:      0.033480    0.028840
BETA(1):    0.001341    0.000367
BETA(2):    0.000000    N/A
BETA(3):    0.000000    N/A
Optimization Succeeded
----------------------------------------
```