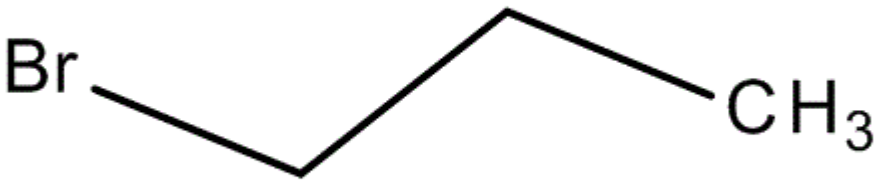
United States
Environmental Protection Agency

EPA Document# 740-R1-5001
February 2016
Office of Chemical Safety and
Pollution Prevention

TSCA Work Plan Chemical Risk Assessment
PEER REVIEW DRAFT

1-Bromopropane:
(*n*-Propyl Bromide)
Spray Adhesives, Dry Cleaning, and Degreasing Uses

CASRN: 106-94-5



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This report was developed by the United States Environmental Protection Agency (EPA), Office of Chemical Safety and Pollution Prevention (OCSPP), Office of Pollution Prevention and Toxics (OPPT). The 2015 Work Plan Risk Assessment for 1-Brompropane (also called *n*-propyl bromide or 1-BP) was prepared based on existing data. Mention of trade names does not constitute endorsement by EPA.

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Acknowledgements

Portions of this document were prepared for EPA/OPPT by Abt Associates, the Eastern Research Group (ERG), Inc., SRC, and Versar.

Special thanks to ATSDR for permission to use Section 3.4 Toxicokinetics – 3.4.1 through 3.4.4 from the January 2015 draft Toxicological Profile of 1-BP for Appendix J.

Special thanks to Margaret Sheppard for consultation on previous SNAP assessment.

Special thanks to NIOSH for consultation on NIOSH assessment and inspection activities and model averaging approach for cancer dose response.

Special thanks to OSHA staff who provided consultation and informal comment during development of this document.

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Please visit the EPA/OPPT's Work Plan Chemicals web page for additional information on the 1-BP's peer review process (http://www.epa.gov/assessing-and-managing-chemicals-under-tsca/assessments-tsca-work-plan-chemicals) and the public docket (Docket: EPA-HQ-OPPT-2015-0084) .

ABBREVIATIONS

AC	Acute concentration
ACH	Air changes per hour
ADC	Average daily concentration
ADR	Acute dose rate
ADR_{pot}	Potential acute dose rate
AEGL	Acute exposure guideline level
AER	Air exchange rate
ACGIH	American Conference of Government Industrial Hygienists
Apx	Appendix
AT	Averaging time
Atm	Atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BAF	Bioaccumulation factor
BCF	Bioconcentration factor
BL	Baseline
BMCL	Benchmark concentration, lower confidence limit(s)
BMD	Benchmark dose
BMDL	Benchmark dose, lower confidence limit(s)
BMR	Benchmark response level
BLS	Bureau of Labor Statistics
BOD	Biochemical oxygen demand
BOP	3-bromo-1-hydroxypropanone
BW	Body weight
C	Contaminant concentration
C_{air}	Air concentration
°C	Degree Celsius
C_{FF}	Average far field concentration
C_{FFTWA}	Time weighted average far field concentration
CNF	Average near field concentration
CNF_{TWA}	Time weighted average near field concentration
Cp_{pot}	Modeled peak concentration
CASRN	Chemical Abstracts Service Registry Number
CBI	Confidential business information
CCD	Chemical Control Division
CCRIS	Chemical Carcinogenesis Research Information System
CDR	Chemical Data Reporting
CEM	Consumer exposure module
CESSD	Chemistry, Economics, and Sustainable Strategies Division
CI	Confidence interval
cm	Centimeter(s)
cm^3	Cubic meter(s)

CNS	Central nervous system
CO_2	Carbon dioxide
CYP	Cytochrome P450
DEv	Duration of an event
DIY	Do-it-yourself
DNA	Deoxyribonucleic acid
EC	Engineering controls
ECA	Enforceable consent agreement
ED	Exposure duration
EF	Exposure frequency
E-FAST2	Exposure and Fate Assessment Screening Tool version 2
EFH	Exposure Factors Handbook
EMIC	Environmental Mutagens Information Center
EPA	Environmental Protection Agency
ERG	Eastern Research Group, Inc.
EU	European Union
EvapTime	Evaporation time
FF	Far field
FQ	Frequency of product use
FSA	Free surface area
ft	Foot/feet
ft^2	Square foot/feet
ft^3	Cubic foot/feet
g	Gram(s)
g/cm^3	Grams per cubic centimeters
g/L	Grams per liter
G	Average generation rate
GM	Geometric mean
GSD	Geometric standard deviation
GD	Gestational day
GENE-TOX	Genetic Toxicology Data Bank
GSH	Glutathione (reduced)
H_{NF}	Near field height
HAPs	Hazardous air pollutants
HCV	Human cancer value
HEC	Human equivalent concentration
HHE	Human Health Evaluation
hr	Hour(s)
HSDB	Hazardous Substances Data Bank
HSIA	Halogenated Solvents Industry Alliance
IA	Indoor air
IARC	International Agency for Research on Cancer
IMIS	Integrated Management Information System
InhR	Inhalation rate

IRIS	Integrated Risk Information System
IUR	Inhalation unit risk
k	Emission rate
K_{ow}	Octanol: water partition coefficient
kg	Kilogram(s)
K_{oc}	Soil organic carbon-water partitioning coefficient
L	Liter(s)
lb	Pound(s)
L_{NF}	Near field length
LADC	Lifetime average daily concentration
LADD	Lifetime average daily dose
LEV	Local exhaust ventilation
LT	Lifetime
LOAEL	Lowest-observed-adverse-effect level
MA	Model-averaging
m	Meter(s)
m^2	Square meter(s)
m^3	Cubic meter(s)
MCCEM	Multi-Chamber Concentration and Exposure Model
$\mu g/m^3$	Microgram(s) per cubic meter
mg	Milligram(s)
mg/kg-bw	Milligram(s) per kilogram body weight
mg/L	Milligram(s) per liter
mg/m^3	Milligram(s) per cubic meter
mg/mL	Milligram(s) per milliliter
min	Minute(s)
MITI	Ministry of International Trade and Industry
Mlbs	Million of pounds
mm Hg	Millimeters of mercury
MOE	Margin of exposure
MOE_{acute}	Margin of exposure for acute exposures
$MOE_{chronic}$	Margin of exposure for chronic exposures
MOU	Memorandum of understanding
MW	Molecular weight
NAICS	North American Industry Classification System
NAPL	Nonaqueous phase liquid
NAS	National Academies of Science
NCEA	National Center for Environmental Assessment
NCI	National Cancer Institute
NEI	National Emissions Inventory
NESHAP	National Emissions Standards for Hazardous Air Pollutants
NF	Near field
NF/FF	Near field/far field
NHANES	National Health and Nutrition Examination Survey

NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NIST	National Institute of Standards and Technology
nm	Nanometer(s)
NOAEL	No-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHSC	National Occupational Health and Safety Commission
NJDEP	New Jersey Department of Environmental Protection
NPS	Nonpoint source
NTP	National Toxicology Program
OAR	Office of Air and Radiation
OCSPP	Office of Chemical Safety and Pollution Prevention
OECD	Organization for Economic Co-operation and Development
OPPT	Office of Pollution Prevention and Toxics
OR	Odds ratio
OSHA	Occupational Safety and Health Administration
OSWER	Office of Solid Waste and Emergency Response
OW	Office of Water
oz	Ounce(s)
PERC	Perchloroethylene
PEL	Permissible exposure limit
PA	Personal air
PBZ	Personal breathing zone
PID	Photoionization detector
PND	Postnatal day
POD	Point of departure
ppb	Parts per billion
ppm	Parts per million
PS	Point Source
PVC	Polyvinyl chloride
Q_{FF}	Far field ventilation rate
QNF	Near field ventilation rate
QA	Quality assurance
QC	Quality control
RAD	Risk Assessment Division
RCRA	Resource Conservation and Recovery Act
REACH	Registration Evaluation Authorization and Restriction
RfC	Reference concentration
RfD	Reference dose
RR	Rate ratio
RTECS	Registry of Toxic Effects of Chemical Substances
s	Second(s)
SAB	Science Advisory Board

SARA	Superfund Amendments and Reauthorization Act
SCG	Scientific Consulting Group, Inc.
SD	Standard deviation
SDS	Safety data sheet(s)
SNAP	Significant New Alternative Policy for ozone depleting substances
SVHC	Substance of Very High Concern
t	Time
TCA	Trichloroacetic acid
TCE	Trichloroethylene
TOXLINE	Toxicology Literature Online
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TSCATS	Toxic Substance Control Act Test Submission database
TWA	Time-weighted average
UF	Uncertainty factor
UF_S	Subchronic to chronic uncertainty factor
UF_A	Interspecies uncertainty factor
UF_H	Intraspecies uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_D	Database uncertainty factor
US EPA	United States Environmental Protection Agency
V_{FF}	Far field volume
v_{NF}	Indoor wind speed
V_{NF}	Near field volume
VOC	Volatile organic compound
VP	Vapor pressure
WWTP	Waste Water Treatment Plant
WNF	Near field width
WY	Working years
Yr (s)	Year(s)

EXECUTIVE SUMMARY

As a part of EPA's comprehensive approach to enhance the Agency's existing chemicals management, in March 2012, EPA identified a work plan of chemicals for further assessment under the Toxic Substances Control Act (TSCA).[1] The Agency is performing risk assessments for chemicals in the work plan. If an assessment identifies unacceptable risks to humans or the environment, EPA will pursue risk management. EPA/OPPT assessed 1-Bromopropane (1-BP), also referred to as *n*-propyl bromide (TSCA inventory name), as part of this work plan.

1-BP is a solvent that exhibits high volatility, low flammability, and no explosivity. It has low persistence and low bioaccumulation potential in the environment. 1-BP is produced or imported in the US in large quantities and is a high production volume chemical (over 15 million lb in 2011). It has a variety of TSCA uses including numerous solvent applications in degreasing, spray adhesives, and dry cleaning. In the past, 1-BP was used as a solvent for fats, waxes, or resins and as an intermediate in pharmaceutical, insecticide, quaternary ammonium compound, flavor, and fragrance synthesis (NTP, 2013).

Focus of this Risk Assessment

EPA/OPPT identified 1-BP for further evaluation in the TSCA work plan based on high hazard concerns due to its toxicity profile, and high exposure concerns due to its use in consumer products. During scoping and problem formulation, EPA/OPPT considered all known TSCA uses for 1-BP and focused on those which involve products with high 1-BP content, and those which are emissive, exhibiting high potential for worker and/or consumer exposure. Occupational uses of concern identified for 1-BP include its use in spray adhesives, dry cleaning (including spot cleaning), and degreasing (vapor, cold cleaning, and aerosol). Consumer uses of concern identified for 1-BP include those that involve aerosol spray adhesives, aerosol spot removers, and aerosol cleaning and degreasing products – many of which were identified to contain 60-100% 1-BP.

Based on the physical-chemical properties and use scenarios described in this assessment, EPA/OPPT expects inhalation to be the primary exposure route of concern for 1-BP. Because of limited toxicological data and the lack of toxicokinetic information needed to develop physiologically-based pharmacokinetic models for route-to-route extrapolations, EPA/OPPT did not evaluate dermal exposures.

EPA/OPPT reviewed the evidence for 1-BP toxicity and selected liver toxicity, kidney toxicity, reproductive/developmental toxicity, neurotoxicity, and cancer as the most robust, sensitive and consistent adverse human health effects for risk characterization. EPA/OPPT applied benchmark dose (BMD) modeling and when modeling results were adequate, generated points of departure (PODs) for the selected endpoints.

[1] http://www.epa.gov/assessing-and-managing-chemicals-under-tsca/assessments-tsca-work-plan-chemicals

EPA/OPPT did not include a quantitative evaluation of environmental effects in this risk assessment because 1-BP exhibits a low hazard potential for ecological receptors and a low persistence and bioaccumulation potential if released into aquatic or terrestrial environments.

Risk Assessment Approach

EPA/OPPT evaluated acute and chronic inhalation exposures to workers and occupational non-users in association with 1-BP use in spray adhesives, dry cleaning (including use in spot cleaning), and degreasing (vapor, cold cleaning, and aerosol). EPA/OPPT also evaluated acute exposures to consumers in association with 1-BP use in aerosol spray adhesives, aerosol spot removers, and aerosol cleaners and degreasers. Acute exposures were defined as those occurring within a single day; whereas chronic exposures were defined as exposures comprising 10% or more of a lifetime (U.S. EPA, 2011). Repeated exposures (e.g., five consecutive days or more) are anticipated during chronic exposure.

For the occupational exposure assessment, EPA/OPPT used monitoring data from literature sources where available, and a modeling approach to estimate potential inhalation exposures. For the consumer exposure assessment, EPA/OPPT relied on models incorporating information on generalized consumer use patterns, and the physical-chemical properties of 1-BP to estimate potential inhalation exposures.

The evaluation of non-cancer risks associated with acute exposures was based on developmental toxicity (WIL Research, 2001), which is representative of a sensitive subpopulation (i.e., adult women of child-bearing age and their offspring). EPA/OPPT consulted EPA's Guidelines for Developmental Toxicity Risk Assessment when making the decision to use a developmental endpoint (i.e., decreased live litter size) as the basis of the dose-response analysis for acute exposures. Other non-cancer endpoints from acute toxicity studies were not used to derive a POD for acute exposures because the doses that caused other types of acute toxicity or lethality were higher than those that negatively impacted development.

Although developmental studies typically involve multiple exposures, they are considered relevant for evaluating single exposures because some developmental effects (e.g., fetal resorptions and mortality), may result from a single exposure during a critical period of development (Davis et al., 2009; Van Raaij et al., 2003; U.S. EPA, 1991). This is consistent with EPA's Guidelines for Reproductive Toxicity Risk Assessment which state that repeated exposure is not a necessary prerequisite for the manifestation of developmental toxicity. Consequently, EPA/OPPT concluded that developmental endpoints are applicable when assessing acute exposures, where it is assumed that the risk of their occurrence depends on the timing and magnitude of exposure. This is based on the presumption and EPA's policy that a single exposure during a critical window of development may produce adverse developmental effects (U.S. EPA, 1996, 1991).

The risk assessment for chronic exposures was based on a range of adverse outcomes with neurotoxicity (Honma et al., 2003), determined to be the most sensitive human health domain for chronic non-cancer effects. Non-cancer and cancer risk estimates for chronic exposures were only

derived for occupational scenarios since the consumer exposure scenarios were not considered to be chronic in nature.

1-BP is carcinogenic in laboratory animals. The weight-of-evidence analysis for the cancer endpoint is sufficient to support a probable mutagenic mode of action for 1-BP carcinogenesis. EPA/OPPT derived an inhalation unit risk (IUR) of 3 x 10^{-3} per ppm (7 x 10^{-7}per µg/m^3) based on lung tumors in female mice. The IUR adapted from the definition in U.S. EPA (2011) is the estimated upper bound added lifetime cancer risk resulting from occupational exposure scenarios (i.e., 8 hours per day, 5 days per week) to an airborne agent at 1 µg/m^3. For chronic scenarios, cancer risk estimates were calculated by multiplying the inhalation unit risk value derived from cancer bioassay data (NTP, 2011) by occupational scenario-specific exposure estimates.

Risks for adverse developmental effects following acute inhalation exposure and adverse neurological effects following chronic inhalation exposure were identified for the 1-BP uses considered under the scope of this assessment. Cancer risks associated with chronic worker inhalation exposure in adults were also identified. EPA/OPPT did not use the IUR to estimate added cancer risks for acute exposures because the relationship between cancer induction in humans and a single short-term exposure to 1-BP has not been firmly established in the scientific literature.

Uncertainties of this Risk Assessment

There are a number of uncertainties associated with the monitoring and modeling approaches used to assess 1-BP exposures. For example, the sites used to collect exposure monitoring data were not selected randomly, and the data reported therein may not be representative of all exposure scenarios. Further, of necessity, exposure modeling approaches employed knowledge-based assumptions that may not apply to all use scenarios. Because site-specific differences in use practices and engineering controls exist, but are largely unknown, this represents another source of variability that EPA/OPPT could not quantify in the assessment. Consumer exposures were estimated based on modeling approaches due to the lack of monitoring information that could be used to assess consumer products. In addition, the inability to include dermal exposures results in potential underestimation of overall exposure and risk.

Human Populations Considered in this Assessment

EPA/OPPT assessed risks for acute and chronic exposure scenarios in workers and occupational non-users for 1-BP use as a spray adhesive, during dry cleaning (including spot cleaning), and during degreasing operations (vapor, cold cleaning, and aerosol). EPA/OPPT assumed that workers (those directly handling 1-BP at the facility) and occupational non-users (workers at the facility not directly involved with the 1-BP use; for example, cashiers at a dry cleaner) would be individuals of both sexes (≥ 16 and older, including pregnant workers) based upon occupational work permits, although exposures to younger workers in occupational settings cannot be ruled out. An objective of the monitored and modeled inhalation data was to provide separate exposure level estimates for workers and occupational non-users.

EPA/OPPT also examined risks for acute exposure scenarios for consumer uses. EPA/OPPT assumed that consumers would be individuals (≥ 16 and older; both sexes including women of

childbearing age) that intermittently use 1-BP in aerosol spray adhesives, aerosol spot cleaners, and aerosol degreasers/cleaners, although exposures to younger non-users may be possible in residential settings. Non-users may be individuals of any age group (e.g., children, adults, and elderly) who are nearby during product application.

Main Conclusions of this Risk Assessment

Most acute exposure scenarios for occupational and consumer uses presented risks based on concerns for adverse developmental effects that may occur as a result of a single exposure to 1-BP during a critical window of susceptibility. Particularly, inhalation risks were identified for all occupational and consumer acute exposure scenarios, with only a few MOE values above the benchmark MOE of 100 (acceptable risk range). These included the 50^{th} percentile estimates for dry cleaning (modeling post-EC worker and pre-EC occupational non-user), vapor degreasing (monitoring post-EC occupational non-user), and cold cleaning (modeling post–EC occupational non-user); and for the 95^{th} percentile estimates for vapor degreasing (monitoring and modeling post-EC occupational non-user) and cold cleaning (modeling post-EC occupational non-user).

There is a concern for a range of adverse human health effects due to chronic inhalation exposures resulting from 1-BP use in spray adhesive, dry cleaning, and degreasing applications. Cancer and neurological effects represent the greatest human health concern for chronic exposure, with the highest risks expected for the spray adhesive occupational exposure scenario. In general, risks were observed across all uses in workers and occupational non-users. High-end (95^{th} percentile/pre-EC) exposures (considered to represent exposure levels at the baseline exposure condition) showed risks to workers and occupational non-users for all health effects and all use scenarios evaluated. Risks for adverse neurological and developmental effects were apparent regardless of the type of 1-BP exposure (50^{th} percentile/central tendency or 95^{th} percentile/high-end) pre-EC for all the uses evaluated. Occupational non-users showed risks for adverse neurological and developmental effects with high-end exposures (95^{th} percentile) regardless of the availability of engineering controls for most use scenarios.

Cancer risks were determined as added lifetime cancer risks, meaning the probability that an individual will develop cancer as a result of occupational exposure over a normal lifetime of 70 years. Added lifetime cancer risk estimates from 1-BP exposure were compared to benchmark cancer risk levels of 10^{-6}, 10^{-5} and 10^{-4} (i.e., 1 in 10,000, 1 in 100,000 and 1 in 1,000,000). All of the spray adhesive exposure scenarios evaluated using monitoring data exceeded the benchmark cancer risk levels by multiple orders of magnitude and were near or above the cancer risk of 10^{-2} (1 in 100). This analysis showed higher estimated cancer incidences for occupational exposures associated with commercial use of 1-BP in spray adhesives, vapor degreasing, cold cleaning, dry cleaning and aerosol degreasing in descending order. A greater cancer risk was observed with the spray adhesive and degreasing (vapor, cold cleaning) occupational exposure scenarios, with the highest risks resulting from direct use of 1-BP containing spray adhesive and degreasing formulations in the absence of engineering controls (e.g., local exhaust ventilation) in the workplace.

EPA/OPPT estimated the population size for workers and occupational non-users at risk as:

- *Spray Adhesives:* 1,503 to 11,952
- *Dry Cleaning and/or Spot Cleaning at Dry Cleaning:* 1,088
- *Vapor Degreasing:* 4,712 to 23,558
- *Aerosol Degreasing:* 2,466 to 12,329

At this time, there is not sufficient information to develop estimates of the number of workers and occupational non-users potentially exposed to 1-BP during cold-cleaning; however, the use of 1-BP in this sector is expected to be minimal.

Also, at this time, there is not sufficient information to develop estimates of the populations for consumers and non-users exposed to 1-BP during the use of aerosol spray adhesives, aerosol spot removers, and aerosol cleaners and degreasers.

In summary, the risk assessment showed the following risk findings:

There Are Non-Cancer Risks Identified for Consumers as a Result of Acute Exposure to 1-BP from Use in Spray Adhesives, Spot Removers, and Degreasers.

A concern for adverse developmental effects was identified for all acute consumer exposure scenarios (i.e., MOEs were below the benchmark MOE of 100), with 1-BP use in aerosol spray cleaners and degreasers showing the greatest risk. Risks for most acute consumer scenarios were 1-2 orders of magnitude below the benchmark MOE.

There Are Non-Cancer Risks Identified for Workers as a Result of Acute Exposure to 1-BP from Occupational Use in Spray Adhesives, Dry Cleaning, and Degreasing Operations.

A concern for non-cancer risks (including risks to workers and occupational non-users) was identified for all but three acute occupational exposure scenarios (i.e., MOEs were below the benchmark MOE of 100), with 1-BP use in spray adhesives showing the greatest risk. Risks for most acute occupational scenarios were 1-2 orders of magnitude below the benchmark MOE.

There are Non-Cancer Risks Identified for Workers as a Result of Chronic Exposure to 1-BP from Occupational Use as a Spray Adhesive, Dry Cleaning (including as a spot cleaner), and Degreasing Operations (vapor, cold cleaning, and aerosol)

A concern for non-cancer risks (including risks to workers and occupational non-users) was identified for all chronic occupational exposure scenarios evaluated based on a range of adverse human health effects. In general, higher risks were indicated for adverse neurological effects in association with 1-BP use in spray adhesives.

All chronic occupational exposure scenarios presented risks for adverse neurological or developmental effects in the absence of engineering controls (pre-EC).

In many instances, occupational non-users with chronic high-end exposures (95^{th} percentile) showed risks for adverse neurological effects regardless of the availability of engineering controls.

Risks for non-cancer effects following chronic occupational exposure (without engineering controls) were 2-3 orders of magnitude below the benchmark MOE.

There are Added Cancer Risks Identified for Workers as a Result of Chronic Exposure to 1-BP from Occupational Use as a Spray Adhesive, Dry Cleaning (including as a spot cleaner), and Degreasing Operations (vapor, cold cleaning, and aerosol)

Added cancer risks were identified for workers and occupational non-users who may be exposed as a result of 1-BP use in spray adhesive, dry cleaning (including spot cleaning), and degreasing operations (vapor, cold cleaning, and aerosol).

Cancer risk estimates exceeded 1 in 1,000 (exceeding all of the cancer risk benchmarks) for all occupational use scenarios evaluated (workers and occupational non-users) based on monitoring and modeling estimates (regardless of the use of engineering controls), with relatively few exceptions. 1-BP use in spray adhesives presented the greatest cancer risk concern.

1 BACKGROUND AND SCOPE

1.1 INTRODUCTION

As a part of EPA's comprehensive approach to enhance the Agency's existing chemicals management, in March 2012 EPA/OPPT identified a work plan of chemicals for further assessment under the Toxic Substances Control Act (TSCA)[2]. EPA/OPPT is assessing chemicals in this work plan and if an assessment identifies unacceptable risks to humans or the environment, EPA/OPPT will pursue risk reduction options. After gathering input from stakeholders, EPA/OPPT developed criteria used for identifying chemicals for further assessment[3]. The criteria focused on chemicals that meet one or more of the following: (1) potential concern to children's health (for example, because of reproductive or developmental effects); (2) neurotoxic effects; (3) persistent, bioaccumulative and toxic (PBT); (3) probable or known carcinogen; (4) use in children's products; or (5) detected in biomonitoring programs. Using this methodology, EPA/OPPT developed a TSCA Work Plan of chemicals as candidates for risk assessment in the next several years. In the prioritization process, 1-Bromopropane or *n*-propyl bromide (1-BP; Chemical Abstracts Service Registry Number [CASRN] 106-94-5) was identified for assessment based on high human health hazard and exposure concerns based on its use profile and physical chemical properties.

The target audience for this risk assessment is primarily EPA/OPPT risk managers; however, it may also be of interest to the broader risk assessment community as well as US stakeholders that are interested in issues related to 1-BP, especially when used in spray adhesive, dry cleaning (including spot cleaning) or degreasing (vapor, cold cleaning and aerosol) uses. The information

[2] http://www.epa.gov/oppt/existingchemicals/

[3] http://www2.epa.gov/sites/production/files/2014-03/documents/work_plan_methods_document_web_final.pdf

presented in the risk assessment may be of assistance to other Federal, State and Local agencies as well as members of the general public who are interested in the risks associated with 1-BP use.

The initial step in EPA/OPPT's risk assessment development process includes scoping and problem formulation, which is distinct from the prioritization criteria used to add a chemical to the work plan. During scoping and problem formulation EPA/OPPT reviews currently available data and information, including but not limited to, assessments conducted by others (*e.g.*, authorities in other countries), published or readily available reports and published scientific literature. During scoping and problem formulation, a robust review may result in refinement – either addition/ expansion or removal/contraction – of specific hazard or exposure concerns previously identified in the work plan methodology.

1.2 USES AND PRODUCTION VOLUME

According to data collected in EPA's 2012 Chemical Data Reporting (CDR) Rule, 15.4 million pounds of 1-BP were produced or imported in the US in 2011 (U.S. EPA, 2012c). Albemarle Corporation, Dow Chemical Company, ICL, Special Materials Company, and one company claiming CBI status currently manufacture or import 1-BP in the US (Appendix A), (Appendix B).

1-BP is a high production volume chemical used in numerous solvent applications including spray adhesive, dry cleaning, and degreasing uses (vapor, cold cleaning, and aerosol). In the past, 1-BP was used as a solvent for fats, waxes, or resins and as an intermediate in pharmaceutical, insecticide, quaternary ammonium compound, flavor, and fragrance synthesis (NTP, 2013). See Appendix B for more details.

The largest use of 1-BP (six to eight million pounds per year) is as a vapor degreaser for cleaning optics, electronics, plastics, and metals (NCDOL, 2013; NTP, 2013; U.S. EPA, 2007c). Industry estimates indicate 500 to 2,500 businesses currently use 1-BP for vapor degreasing, a process by which soiled components are cleaned using vaporized solvents. 1-BP is also used in cold cleaning, which is similar to vapor degreasing, except that cold cleaning does not require the solvent to be heated to its boiling point in order to clean a given component. Vapor degreasing and cold cleaning scenarios may include a range of open-top or closed systems, conveyorized/enclosed/inline systems, spray wands, containers, and wipes.

The second largest use of 1-BP (five to seven million pounds per year) is as an adhesive, primarily for foam cushion manufacturing and (less often) for laminates (NTP, 2013; HSIA, 2012; U.S. EPA, 2007c). EPA estimates 100 to 280 foam manufacturers (one-third of all such manufacturers) use 1-BP as an adhesive. Use of 1-BP as an industrial adhesive is expected to decline over time due to health and safety concerns.

1-BP is occasionally used in dry cleaning, both in machine cleaning and as a component of spot cleaners used to remove stains before and after machine cleaning. EPA has included dry cleaning in this risk assessment because 1-BP is a drop-in replacement for regulated chlorinated solvents currently used in dry cleaning (TURI, 2012). Perchloroethylene (perc) remains the solvent of choice for textiles (dry cleaning), but its market share is decreasing as dry cleaners continue to transition to alternative solvents. 1-BP can be used as a substitute for the dominant solvent used

in dry cleaning machines (perc) and the heavily-used solvent (trichloroethylene) used in spot cleaners.

EPA found a variety of consumer products containing 1-BP based on their current safety data sheets (SDS; see Table 2-). These products include aerosol spray solvents used in spray adhesives (5 products), spot removers (4 products), degreasers and cleaners (11 products), coin cleaning (1 product), paintable mold release (1 product), automotive refrigerant flush (1 product), and lubricants (1 product). Although EPA does not believe 1-BP is the solvent predominantly used in these specific product markets, this could not be confirmed with sales data.

1.3 ASSESSMENT AND REGULATORY HISTORY

Under the Clean Air Act (CAA), EPA evaluated 1-BP as a substitute for ozone-depleting substances (ODS) through the Significant New Alternatives Policy (SNAP) program. In the 2003 Notice of Proposed Rulemaking, EPA proposed to allow use of 1-BP as a carrier solvent in adhesives; as an aerosol solvent; and as a solvent in cleaning equipment for metals, electronics, and precision cleaning, subject to a limit of no more than 0.05% isopropyl bromide (2-bromopropane) by weight (U.S. EPA, 2003). In 2007, EPA issued a final rule where EPA determined that 1-BP is an acceptable substitute for ozone-depleting substances (i.e., methyl chloroform and chlorofluorocarbon (CFC)-113); for metals cleaning, electronics cleaning and precision cleaning (U.S. EPA, 2007c). At the same time, EPA proposed a new rule to list 1-BP as an acceptable substitute in the coatings end use (subject to use restrictions) and to list 1-BP as an unacceptable substitute in adhesives or aerosol solvents (U.S. EPA, 2007b). EPA has not finalized this proposal to date.

1-BP is regulated as a volatile organic compound under Clean Air Act regulations (see 40 CFR 51.100(s)) addressing the development of State Implementation Plans to attain and maintain the National Ambient Air Quality Standards. In 2015, EPA announced the receipt of a complete petition requesting that EPA add 1-BP to the list of hazardous air pollutants (HAP) under section 112(b)(1) of the CAA (U.S. EPA, 2015b). EPA proposed to add 1-BP to the Toxics Release Inventory (TRI) subject to reporting under section 313 of the Emergency Planning and Community Right-to-Know Act (EPCRA) and section 6607 of the Pollution Prevention Act (PPA) (U.S. EPA, 2015a). Both of these actions are still pending.

In July 2013, the Occupational Safety and Health Administration (OSHA) and the National Institute for Occupational Safety and Health (NIOSH) issued a hazard alert to urge employers that use 1-BP to take appropriate steps to protect workers from exposure (OSHA, 2013). OSHA has not issued a Permissible Exposure Limit (PEL) for 1-BP. The American Conference of Governmental Industrial Hygienists (ACGIH) has adopted a Threshold Limit Value (TLV) of 0.1 ppm as an 8-hour TWA (ACGIH, 2014).

The National Toxicology Program (NTP) evaluated the toxicity of 1-BP in a technical report (NTP, 2011), and identified 1-BP as 'reasonably anticipated to be a human carcinogen' in the thirteenth report on carcinogens in 2014 (NTP, 2014).

In 2004, California's Office of Environmental Health Hazard Assessment listed 1-BP for developmental and male and female reproductive toxicity under Proposition 65 (OEHHA, 2004). California has proposed a 5 ppm (25 mg/m^3) time-weighted average PEL along with a skin notation for 1-BP (CDIR, 2009b). A number of other U.S. states have taken action to address 1-BP hazard and risk concerns. This information is available in Appendix C.

In 2006, under the Canadian Environmental Protection Act (CEPA) (Health Canada, 2006), 1-BP was prioritized and categorized as an additional substance for consideration due to its developmental and reproductive toxicity. The Notice with respect to certain inanimate substances (chemicals) on the Domestic Substances List was published in the Canada Gazette in October 2009 to collect information on its manufacture and import (Environment Canada, 2009). As a result of this notice, 1-BP was reported as a chemical manufactured and/or imported in Canada during 2008 (Environment Canada, 2013).

In August 2012, the European Chemicals Agency (ECHA), at the request of the European Commission (EC), presented a proposal on the identification of 1-BP as a Substance of Very High Concern (SVHC) under Registration, Evaluation, Authorization, and Restriction (REACH) due to its reproductive toxicity (ECHA, 2012a, c, d). In September 2012, a dossier was circulated to Member States and was made available for comment on the ECHA website (ECHA, 2012b). The dossier, which classified 1-BP as toxic for reproduction category 1B, was referred to the Member State Committee and was adopted in November 2012 (ECHA, 2012b). At the same time, the Member State Committee agreed on the identification of 1-BP as a SVHC (ECHA, 2012a). In December 2012, 1-BP was listed on the Candidate list as a SVHC (ECHA, 2012a).

Due to its reproductive toxicity, 1-BP is registered as a Class I Designated Chemical Substance subject to reporting requirements under the Pollutant Release and Transfer Register Law in Japan (METI, 2009). It was listed both as a Hazardous Air Pollutant under the Japanese Air Pollution Control Law in 2009 (NITE, 2014b), and "General Chemical Substance", with lower risks expected for human health and the environment, through the 2013 screening assessment (NITE, 2014a).

The Organisation for Economic Co-operation and Development (OECD) lists 1-BP as a High Production Volume (HPV) chemical (OECD, 2015).

1.4 SCOPE OF THE ASSESSMENT

Most of 1-BP (approximately 47%) is used as a vapor degreaser to clean optics, electronics, plastics, and metals. Roughly 30-45% of the total production volume is used in spray adhesives. Use in the dry cleaning sector is less clearly defined. Perchloroethylene remains the solvent of choice for textiles dry cleaning but its market share is decreasing as dry cleaners continue to transition to alternative solvents; 1-BP is also used as a solvent in aerosol spot cleaners, spray adhesive and degreasing products.

Reports of adverse neurologic effects in 1-BP exposed workers and carcinogenic, developmental, and reproductive effects following 1-BP exposure in rodents (NTP, 2013) prompted the Agency to evaluate risks associated with its occupational and consumer uses.

The following occupational and consumer uses were selected due to their high exposure potential:

1. Occupational use in spray adhesives (workers and occupational non-users)
2. Occupational use in dry cleaning machines (workers and occupational non-users)
3. Occupational use in spot cleaning during dry cleaning (workers and occupational non-users)
4. Occupational use in vapor degreasing (workers and occupational non-users). Vapor Degreasing was assessed as a broad category of use. At this point, EPA/OPPT has not developed assessments by the specific type of degreasing such as open-top, closed and in-line.
5. Occupational use in cold cleaning degreasing (workers and occupational non-users)
6. Occupational use in aerosol degreasing (workers and occupational non-users)
7. Consumer use in aerosol spray adhesives (consumer users and non-users),
8. Consumer use in aerosol spot removers (consumer users and non-users), and
9. Consumer use in aerosol cleaners and degreasers (including engine degreasing, brake cleaning and electronics cleaning scenarios for consumer users and non-users)

Readily available information on the physicochemical properties of 1-BP support inhalation as the primary route of exposure, and information regarding its toxicity supports human health concerns. Risk estimates based on cancer and non-cancer endpoints were developed for the identified occupational (acute and chronic) and consumer (acute) use scenarios. Dermal exposures are possible; however, limited toxicological data are available for this route of exposure, and no toxicokinetic information is available to develop physiologically-based pharmacokinetic models for route-to-route extrapolations. Therefore, dermal exposure estimates, and route to route extrapolations are not included in this assessment. Upon consideration of physical chemical properties, environmental fate, persistence and bioconcentration factors derived for 1-BP, it was determined that a quantitative assessment of environmental risks would not be included under the scope of this risk assessment.

In summary, the 1-BP assessment addresses the following questions:

1. Do risks of concern exist (i.e., acute and chronic non-cancer and cancer) for workers and occupational non-users during occupational use of 1-BP in spray adhesives?

2. Do risks of concern exist (i.e., acute and chronic non-cancer and cancer) for workers and occupational non-users during occupational use of 1-BP in dry cleaning machines?

3. Do risks of concern exist (i.e., acute and chronic non-cancer and cancer) for workers and occupational non-users during occupational use of 1-BP for spot cleaning during dry cleaning?

4. Do risks of concern exist (i.e., acute and chronic non-cancer and cancer) for workers and occupational non-users during occupational use of 1-BP in vapor degreasing?

5. Do risks of concern exist (i.e., acute and chronic non-cancer and cancer) for workers and occupational non-users during occupational use of 1-BP in cold cleaning degreasing?

6. Do risks of concern exist (i.e., acute and chronic non-cancer and cancer) for workers and occupational non-users during occupational use of 1-BP in aerosol degreasing?

7. Do risks of concern exist (i.e., acute) for consumer users and non-users where 1-BP is used in consumer products (i.e., aerosol spray adhesives, aerosol spot removers and aerosol cleaners and degreasers)?

1.5 PROBLEM FORMULATION

During problem formulation, EPA/OPPT identified the exposure pathways, receptors and health endpoints that would be included in this risk assessment. To make this determination, physical chemical properties and environmental fate were evaluated within the context of selected scenarios: occupational uses (spray adhesive; dry cleaning, (includes spot cleaning); degreasing (includes vapor, cold, and aerosol cleaning) and consumer uses (spray adhesives, spot removers and aerosol degreasers/cleaners).

During problem formulation, it was determined that a quantitative assessment of environmental risks associated with 1-BP releases would not be included in this assessment. EPA/OPPT reviewed and summarized available published studies on ecotoxicity (U.S. EPA, 2012d, 1999) to understand the potential effects of 1-BP releases on ecological receptors, including toxicity to fish, invertebrates, plants and birds. Based on this review, EPA/OPPT concluded that the acute hazard of 1-BP to aquatic organisms is low based on available data. The hazard of 1-BP is expected to be low for chronic aquatic organisms, sediment, and terrestrial organisms based on physical and chemical properties of 1-BP and that data were not available to assess risk to sediment dwelling or terrestrial organisms. Thus, environmental risks were not evaluated further in this assessment. Appendix D contains a summary of the aquatic toxicity studies considered during the initial environmental hazard evaluation for 1-BP.

1.5.1 Physical and Chemical Properties

1-BP is a colorless liquid with a sweet hydrocarbon odor. It is a brominated hydrocarbon that is slightly soluble in water. 1-BP is a volatile organic compound (VOC) that exhibits high volatility, a low boiling point, low flammability and no explosivity. Figure 1-1 presents the chemical structure and Table 1-1 summarizes the physical chemical properties of 1-BP.

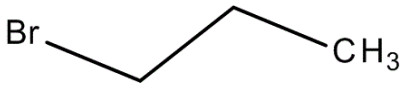


Figure 1-1 Chemical Structure of 1-Bromopropane

Table 1-1 Physical and Chemical Properties of 1-BP

Molecular formula	C_3H_7Br
Molecular weight	122.99
Physical form	Colorless liquid; sweet hydrocarbon odor
Melting point	-110 °C
Boiling point	71 °C at 760 mmHg
Density	1.353 g/cm^3 at 20 °C
Vapor pressure	146.26 mmHg (19.5 kPa) at 20 °C
Vapor Density	4.25 (Patty, 1963)
Log K_{ow}	2.10 (Hansch, 1995)
Water solubility	2.450 g/L at 20 °C (Yalkowsky et al., 2010)
Flash point	22 °C

Source: The Merck Index (2013)

1.5.2 Environmental Fate

This section summarizes current knowledge of the transport, persistence, bioconcentration and bioaccumulation of 1-BP in the environment, including biological and abiotic reactions and environmental distribution. Fate characteristics are summarized in Table 1-2.

Table 1-2 Environmental Fate Characteristics of 1-BP

Property	Value
CASRN	106-94-5
Photodegradation half-life	9 to 12 days (estimated, 1.5×10^6 hydroxyl radicals per cm^3 for a 12-hour day)
Hydrolysis half-life	26 days at pH 7 and 25°C
Biodegradation	70% after 28 days (readily biodegradable, OECD 301C) 19.2% after 28 days (not readily biodegradable, OECD 301D) (See Appendix E for study details)
Bioaccumulation	BAF = 12 (estimated)
Log K_{oc}	1.6 (estimated)
Fugacity (Level III Model) Air (%) Water (%) Soil (%) Sediment (%)	 44.1 45.7 10.1 < 0.1

1-BP is a volatile liquid with high vapor pressure, moderate water solubility, and high mobility in soil. It is expected to exhibit low adsorption to soils and thus can migrate rapidly through soil to groundwater. 1-BP is slowly degraded by sunlight and reactants when released to the atmosphere (half-life 9-12 days). Based on this estimated half-life in air, long range transport via the atmosphere is possible (see Appendix E). Volatilization and microbial degradation influence the fate of 1-BP when released to water, sediment, or soil. Biotic and abiotic degradation rates ranging from days to months have been reported.

The manufacturing, processing, and use of 1-BP can result in releases to air, water, sediment, and soil. However, since 1-BP does not currently have Toxics Release Inventory reporting data, and is not listed as a Hazardous Air Pollutant (HAP), data on the environmental releases of 1-BP to air (fugitive source air releases via ambient air monitoring data), landfills or surface water are not available.

1.5.3 Persistence and Bioconcentration

Biotic and abiotic degradation studies have not shown this substance to be persistent (overall environmental half-life of less than two months). No measured bioconcentration studies for 1-BP are available. An estimated bioaccumulation factor of 12 suggests that bioconcentration and bioaccumulation in aquatic organisms are low (bioconcentration/bioaccumulation factor of less than 1000).

1.5.4 Conceptual Model

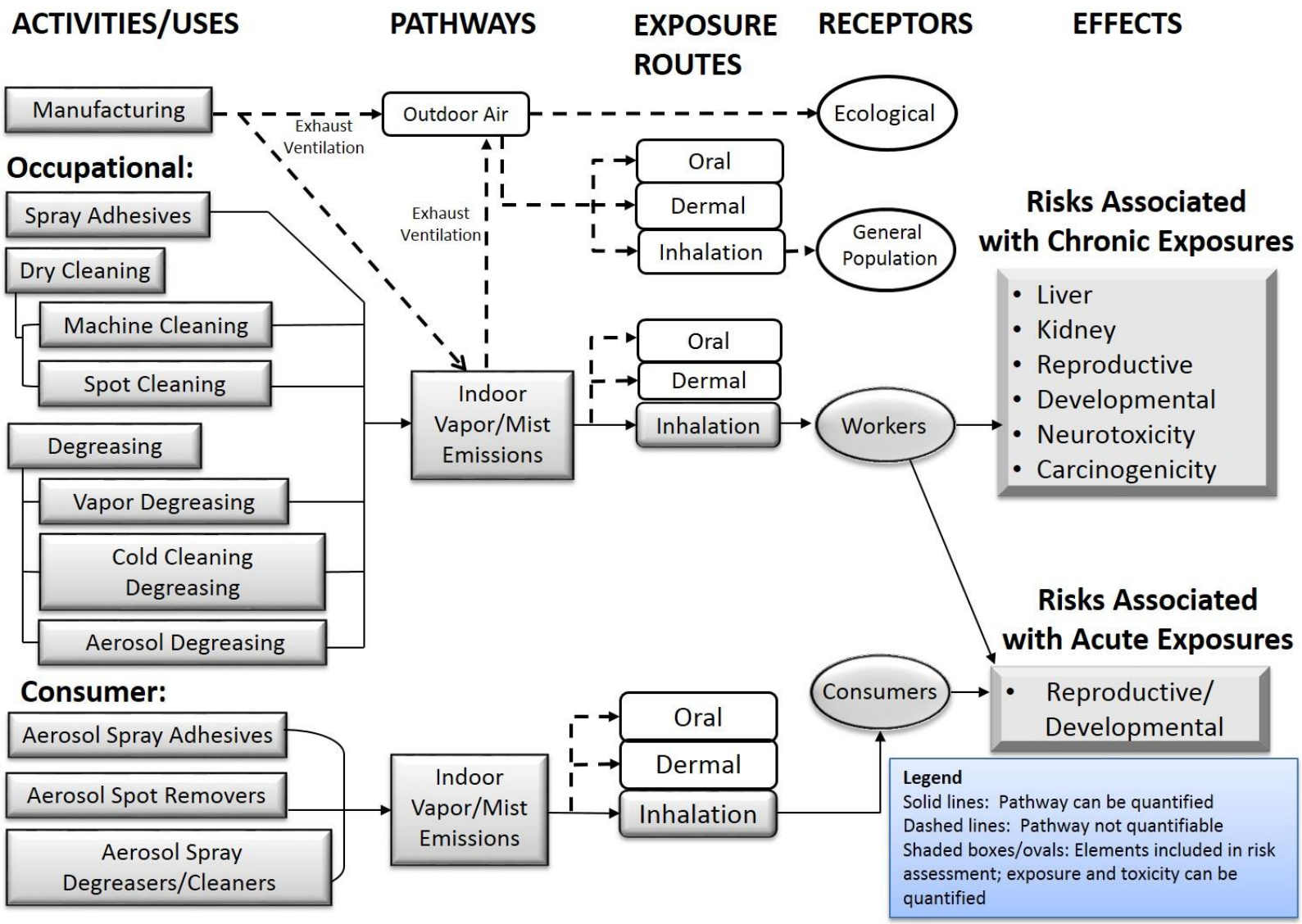


Figure 1-2 Schematic of Human and Environmental Exposure Pathways for 1-BP

1.5.4.1 Exposure Pathways

The conceptual model above (Figure 1-2) illustrates the 1-BP uses and pathways that may result in exposure (e.g., occupational, consumer, general population, or environmental). Shaded areas indicate the exposure pathways included in this risk assessment; unshaded areas are not included in this assessment. EPA/OPPT considered all TSCA uses and focused on uses of products that have high 1-BP content and which present high potential for exposures to workers and consumers.

Occupational exposure assessment: Risks to workers and occupational non-users in association with 1-BP use in spray adhesives, dry cleaning (including use as a spot cleaner), and degreasing (vapor, cold, and aerosol cleaning) based on acute and chronic inhalation exposures.

Consumer exposure assessment: Risks to consumers and non-users from use of 1-BP-based aerosol spray adhesives, aerosol spot removers, and aerosol cleaners and degreasers (including engine degreasing, brake cleaning, and electronics cleaning), based on acute inhalation exposures.

Pathways Excluded from the Risk Assessment

EPA/OPPT excluded the following exposure pathways from this assessment as indicated (via dashed lines) in the conceptual model:

General population exposure: The manufacturing, processing, and use of 1-BP can result in releases to air, water, sediment, and soil; however, general population exposures that may result from environmental releases of 1-BP were excluded from this assessment because no reliable exposure data for calculating general population risks are available. As 1-BP is not on the Toxics Release Inventory (TRI) database or the National Emissions Inventory (NEI), quantitative data on the environmental releases of 1-BP to air (fugitive or point source air releases via ambient measured/monitoring data), landfills, or surface water are not available. EPA/OPPT is aware of a petition by the New York State Department of Environmental Conservation (NYSDEC) and the Halogenated Solvent Industry Alliance (HSIA) to list 1-BP (n-propyl bromide) as a hazardous air pollutant (HAP) under Section 122 of the Clean Air Act. EPA/OPPT is coordinating with the Office of Air and Radiation, Office of Air Quality Planning and Standards to review information submitted to the docket regarding the potential human health impacts on communities within the vicinity of facilities that emit 1-BP.

Occupational and consumer population exposure by the oral and dermal route: Based on the physical-chemical properties of 1-BP (e.g., volatility) and the emissive nature of uses identified for this assessment, EPA/OPPT expects inhalation to be the predominant route of consumer/ occupational exposure to 1-BP. Data from an in-vitro dermal penetration study (Frasch et al., 2011) indicate that 1-BP has the potential for substantial dermal penetration depending on the type and duration of exposure. Un-occluded (e.g., splash) exposures may not lead to significant systemic uptake, whereas submersion or occluded exposures may contribute to greater dermal uptake (Frasch, 2014). Despite the potential for uptake, dermal uptake is likely to be orders of magnitude lower than uptake by inhalation because 1-BP will evaporate quickly if it comes in contact with the skin.

Ecological Receptors Exposure: Because 1-BP exhibits a low ecological hazard profile and low persistence and bioaccumulation potential if released into aquatic or terrestrial environments, a quantitative assessment of environmental risks was not included in this assessment. Appendix D contains a summary of the aquatic toxicity studies considered during the evaluation of the ecological hazard potential for 1-BP.

1.5.4.2 Health Effects and Human Receptors

EPA/OPPT reviewed available toxicological data, including the published and unpublished literature and assessments completed by other organizations (NTP, 2013, 2011; U.S. EPA, 2007b, c) to support hazard characterization. Based on this review, EPA/OPPT narrowed the hazard assessment to a suite of effects (e.g., liver toxicity, kidney toxicity, reproductive/developmental toxicity, neurotoxicity, and cancer) that are sensitive, robust, and biologically relevant to humans.

1-BP was initially prioritized for work plan assessment based on high concern for reproductive toxicity; however, EPA/OPPT's more detailed dose-response analysis revealed that use of the developmental toxicity endpoints for point of departure derivation would be protective of reproductive effects and those that may adversely impact the most sensitive subpopulations, including women of child bearing age and the developing fetus.

1.5.5 Analysis Plan

For each of the exposure pathways included in the assessment (Figure 1-2), EPA/OPPT quantified occupational exposures based on a combination of monitoring data and modeled exposure concentrations. Inhalation exposures were assessed for both workers and occupational non-users. EPA/OPPT estimated consumer exposure based on consumer behavioral patterns and modeled exposure concentrations.

For hazard characterization and dose-response analysis, EPA/OPPT reviewed available data and selected studies that, taken as a whole, demonstrated the most robust, sensitive and consistent effects for use in the risk assessment. EPA/OPPT used benchmark dose (BMD) modeling where practicable and when model results were adequate, they were used to generate the point of departure (POD) for acute and chronic exposure scenarios. EPA/OPPT quantified risk based on the Margin of Exposure (MOE), which is the ratio between the exposure (50^{th} and 95^{th} percentiles) and the POD. The endpoint specific MOEs were compared to endpoint specific benchmark MOEs to determine if the relevant exposure scenarios exhibit unacceptable risks. EPA/OPPT calculated acute or chronic MOEs (MOE_{acute} or $MOE_{chronic}$) separately based on the appropriate POD and estimated exposure. MOEs below the benchmark MOEs are considered to be indicative of unacceptable risks.

For chronic occupational scenarios considering cancer risk estimation, scenario-specific exposure estimates were multiplied by the cancer slope factor derived from the dose-response of bioassay data to obtain the cancer inhalation unit risk value.

2 HUMAN EXPOSURE ASSESSMENT

2.1 OCCUPATIONAL EXPOSURES

Workplace exposures have been assessed for the following occupational uses of 1-BP in:

1. Spray Adhesives
2. Dry Cleaning – dry cleaning facility has converted their PERC dry cleaning machine system to 1-BP and also uses 1-BP in spot cleaning
3. Spot Cleaning at Dry Cleaners – dry cleaning facility uses 1-BP based spot cleaner formulations but has not converted their dry cleaning machine system to 1-BP
4. Vapor Degreasing – vapor degreasing was assessed as a broad category of use of 1-BP. At this point, EPA/OPPT has not yet developed more specific assessments by the type of vapor degreasing operation such as open-top, closed and in-line.
5. Cold Cleaning Degreasing
6. Aerosol Degreasing

2.1.1 Approach and Methodology

The objectives of the occupational exposure assessment for each of the uses in the scope were to:

1. Describe the process and worker activities with a potential for inhalation exposure.

2. Estimate the number of workers potentially exposed.

3. Assess inhalation exposure based on monitoring data. This involved:
    a. Conducting a literature search to obtain available monitoring data.
    b. Where possible, breaking down the data into exposures for workers and occupational non-user categories and pre- or post-engineering controls (EC). The pre-EC is considered the baseline exposure condition. The post-EC could be measures such as local exhaust ventilation or equipment substitution which reduce the 1-BP exposure concentrations in the workplace. Workers are those directly involved in handling the 1-BP, for example, sprayers for the 1-BP spray adhesive use, and occupational non-users are workers at the facility who are not directly involved, for example, cashiers and clerks, but still have a potential for exposure to 1-BP. Pre-EC estimates are considered to represent exposure levels at the baseline exposure condition with Post-EC representing exposure levels after improvements in engineering controls or equipment substitution were made.
    c. Calculating central tendency (50^{th}) and high-end (95^{th}) percentile exposures in ppm as 8-hr Time-Weighted Averages (TWAs).

4. Assess inhalation exposure based on modeling for all uses except spray adhesives. For some of the 1-BP uses, monitoring data was limited. Modeling allowed for assessment of exposures to workers and non-occupational users for both pre- and post-engineering

control conditions. Modeling also allows for use of different values for key parameters to see the effect they have on the exposure and risk estimates. The modeling approaches for this assessment included:

a. Using a near-field/far-field modeling approach to estimate 1-BP air concentrations in the workplace. The near-field concentrations are assumed to represent potential exposures to workers and the far-field concentrations represent potential exposure to occupational non-users.
b. Dry cleaning modeling as a special case using a multi-zone modeling approach which considered emissions from three separate sources within the dry cleaning facility: spot cleaning; loading and unloading the dry cleaning machines; and finishing steps. The other modeling scenarios considered 1-BP being emitted from one source.
c. Conducting a targeted literature search to identify chemical and industry specific information to calculate the 1-BP vapor generation rates. The majority of model parameters were assumed to be the same across all use scenarios.
d. Using a Monte Carlo simulation to capture variability in the model input parameters. The number of iterations was selected as 1 million.
e. Presenting central tendency (50^{th}) percentile and high-end (95^{th}) percentile modeling results in ppm as 8-hr TWAs.
f. Presenting a second set of 50^{th} and 95^{th} percentile estimates with an additional assumption of engineering control effectiveness (90% or 98%) to assess inhalation exposures pre- and post- engineering controls (EC). These control effectiveness are "what-if" values where engineering control (e.g. local exhaust ventilation) is effectively implemented (90%) or when equipment is substituted (98%) to reduce exposure.

5. Convert monitoring and modeling exposures estimates in ppm (as 8-hr TWAs) to the values to be used in the risk assessment. The 8-hr TWAs were used as the estimates of Acute Concentration (AC). These values (50^{th} and 95^{th} percentile ACs) were also converted to estimates of Average Daily Concentration (ADC) and Lifetime Average Daily Concentration (LADC). The AC, ADC and LADC values were then used in the risk assessment to evaluate acute and chronic health risks as further described in Section 4 of this document.

In assessing exposure using monitoring data, EPA/OPPT analyzed and used 8-hour TWA personal breathing zone (PBZ) data obtained from published literature. Short-term and partial-shift exposure monitoring data that cannot be translated into 8-hr TWA values and area samples are not used for the exposure assessment because they are not representative of 1-BP exposure throughout the work day. Several sources describe the data as "full-shift TWA" but do not specify the duration of the shift. In these cases, EPA/OPPT assumed the work shift lasted eight hours and that the data are equivalent to 8-hr TWA values.

The assessments of each of the identified uses are presented below in Sections 2.1.2 through 2.1.7. The following appendices provide further details and examples.

Appendix F – Approach for Estimating Number of Workers
Appendix G – Approach Used to Collect Monitoring Data and Information on Model Parameters
Appendix H – Equations for Calculating Acute and Chronic (Non-Cancer and Cancer) Exposures
Appendix I – Example of Monitoring Data Analysis for the Spray Adhesive Use
Appendix J – Occupational Exposure Modeling (Near-field/Far-field) Approach
Appendix K – Occupational Exposure Modeling Parameters

2.1.2 Spray Adhesives

2.1.2.1 Process and Worker Activity Descriptions

1-BP is used in spray adhesives for foam cushion manufacturing (e.g., the furniture industry). Figure 2-1 illustrates a typical process of using spray adhesives for foam cushion manufacturing. During foam cushion manufacturing, spray guns are used to spray-apply an adhesive onto flexible foam surfaces. Adhesive spraying typically occurs either on an open top workbench with side panels that may have some local ventilation, or in an open workspace with general room ventilation. After the adhesive is applied, workers assemble the cushions by hand-pressing together pieces of cut flexible foam (NIOSH, 2003, 2002b).

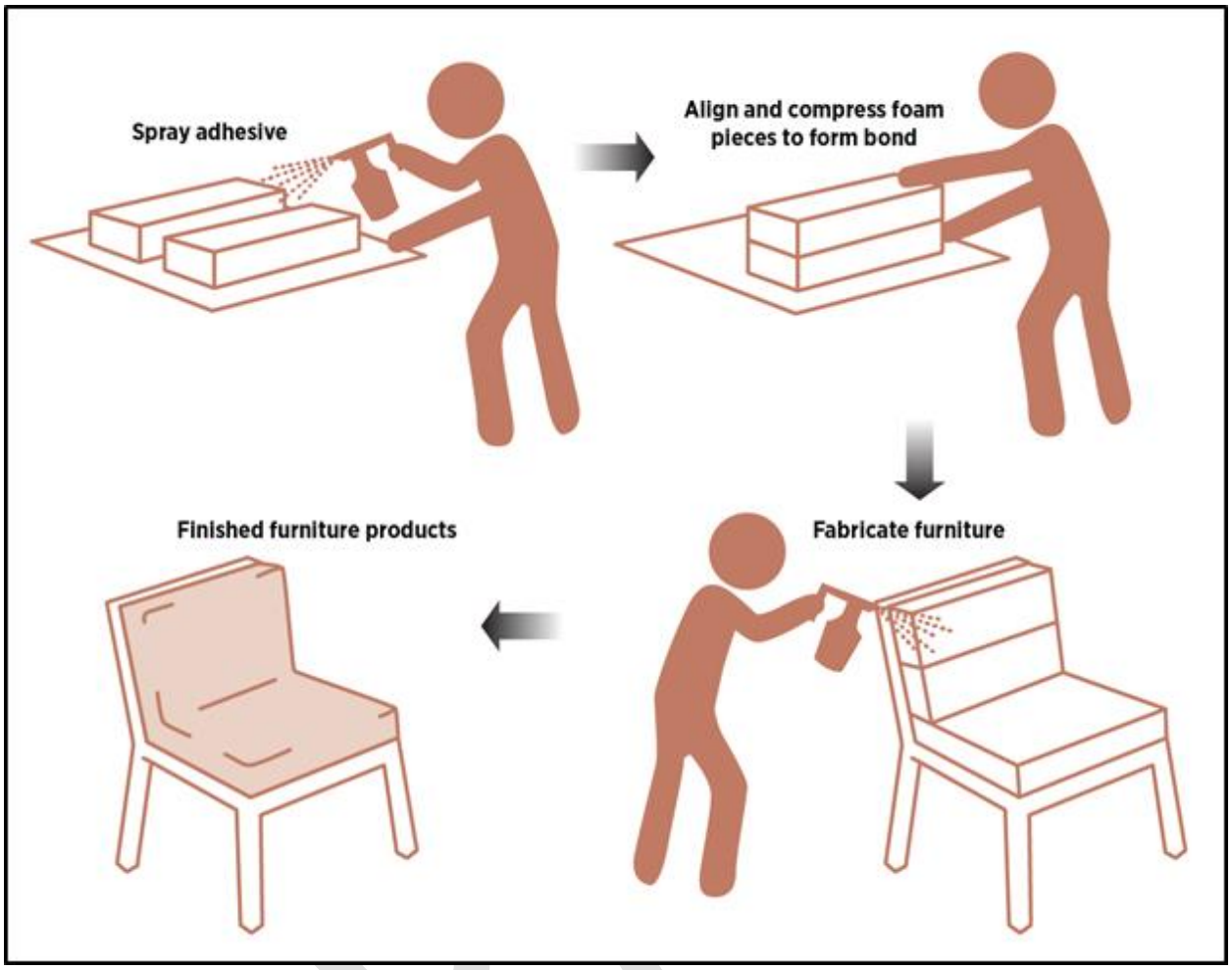


Figure 2-1 Overview of Use of Spray Adhesive in the Furniture Industry

2.1.2.2 Estimate of Number of Workers Potentially Exposed

EPA/OPPT estimated the number of workers potentially exposed to 1-BP in spray adhesives using Bureau of Labor Statistics' Occupational Employment Statistics (OES) data (2015) and U.S. Census' Statistics of US Businesses (SUSB) (2012). The method for estimating number of workers is detailed in Appendix F. The worker estimates were derived using industry- and occupation-specific employment data from these sources. The industry sectors and occupations that EPA/OPPT determined to be relevant to spray adhesive use are presented in Appendix F.

The number of businesses in this use sector of 1-BP is estimated to be between 100 and 280 (U.S. EPA, 2007b). Based on a total of 2,386 establishments in the industry sectors shown in Appendix F, the 1-BP market penetration is 4.2 percent to 11.7 percent. Alternatively, an article published in The New York Times estimated that one third (33 percent) of the foam cushion industry switched from 1,1,1-trichloroethane (TCA) to 1-BP based adhesives when 1-BP was introduced in the 1990s (NY Times, as cited in (U.S. EPA, 2013c)). Table 2-1 presents the estimated number of workers and occupational non-users using the low-end market penetration of 4.2 percent and the high-end market penetration of 33 percent. The total number of potentially exposed workers and occupational non-users ranges from 1,503 to 11,952. Note the high-end estimate is based

information on past 1-BP market, and may not be representative of the current foam cushion industry. It is possible that some companies have switched to a different chemical due to reports of worker health issues. The New York Times article also stated that two large chemical manufacturers have since stopped selling 1-BP (NY Times, as cited in (U.S. EPA, 2013c)).

Table 2-1 Estimated Number of Workers Potentially Exposed to 1-BP in Spray Adhesive Use in Foam Cushion Manufacturing

Exposed Workers	Exposed Occupational Non-Users	Total Exposed	Estimated Number of Establishments	Workers per Site	Occupational Non-Users per Site
Low-end					
551	952	1,503	100	6	10
High-end					
4,384	7,568	11,952	795	6	10

Note: Number of workers and occupational non-users per site are calculated by dividing the exposed number of workers or occupational non-users by the number of establishments. Values are rounded to the nearest integer.

2.1.2.3 Assessment of Inhalation Exposure Based on Monitoring Data

1-BP exposure monitoring data were identified in several literature studies, including journal articles, NIOSH Human Health Evaluations (HHEs), and OSHA Integrated Management Information System (IMIS). NIOSH HHEs are conducted at the request of employees, employers, or union officials and help inform on potential hazards present at the workplace. OSHA IMIS data are workplace monitoring data from OSHA inspections. These inspections can be random or targeted, or can be the result of a worker complaint.

Among these sources, three NIOSH studies provide the most comprehensive information on worker exposure to 1-BP from spray adhesives in foam cushion manufacturing. Two of the three HHEs also compare exposure pre- and post-engineering controls (EC). A summary of these HHEs follows:

- From March 1998 to April 2001, NIOSH investigated a facility in Mooresville, North Carolina to assess 1-BP exposures during manufacturing of foam seat cushions (NIOSH, 2002a). The company had four departments: Saw, Assembly, Sew, and Covers. Workers in Assembly and Covers departments worked directly with the adhesive; however, workers in all four departments were exposed. The spray adhesive used at this facility contained between 60 and 80 percent 1-BP. NIOSH conducted an initial exposure assessment in 1998, and observed that the ventilation exhaust filters were clogged with adhesive. In 2001, NIOSH conducted a follow-up exposure assessment after the facility made improvements to its ventilation system.
- From November 2000 to August 2001, NIOSH investigated workplace exposures to 1-BP during manufacturing of foam seat cushions at another cushion company in North Carolina (NIOSH, 2002b). This facility uses a spray adhesive containing 55 percent 1-BP. NIOSH conducted an initial exposure assessment in 2000, and recommended that the facility reduce worker exposure by enclosing the spray stations to create “spray booths”.

Subsequently, in 2001, NIOSH conducted a follow-up assessment after spray station enclosures were installed.

- From April 1999 to May 2001, NIOSH investigated another cushion company in North Carolina (NIOSH, 2003). In this study, NIOSH conducted two separate exposure assessments. In the initial assessment, NIOSH measured 1-BP inhalation exposures to workers in and near the adhesive spray operation areas. In the second assessment, NIOSH measured additional 1-BP inhalation exposures at the facility. There were no changes to the facility's ventilation system (i.e. engineering controls) between the first and second assessment.

Table 2-2 summarizes the 1-BP exposures in pre-EC and post-EC scenarios for each worker job category. EPA/OPPT defined three job categories for 1-BP spray adhesive use:

- Sprayers: Workers who perform manual spraying of 1-BP adhesive as a regular part of his or her job;
- Non-sprayers: Workers who are not "sprayers", but either handle the 1-BP adhesive or spend the majority of their shift working in an area where spraying occurs. For example, the NIOSH (2002a) study indicated spraying occurs in the Assembly and Covers departments. EPA/OPPT assumes workers in these departments who do not perform spraying still work in the vicinity of spraying operations and may be regularly exposed to 1-BP; and
- Occupational non-users: Workers who do not regularly perform work in an area of the facility where spraying occurs. For example, EPA/OPPT assumes workers in the Saw and Sew departments of the 2002 NIOSH study (NIOSH, 2002a) are "occupational non-users".

Pre-EC exposure scenarios suggest that all workers at foam cushion manufacturing facilities that use 1-BP spray adhesives have substantial exposure to 1-BP. Sprayers have the highest levels of exposure because they work directly with the 1-BP adhesive. However, non-sprayers and occupational non-users may be exposed. Exposure levels for occupational non-users vary widely depending on their specific work activity pattern, individual facility configuration, and proximity to the 1-BP adhesive. For example, workers in the Saw and Sew departments in the NIOSH (2002a) study classified as "occupational non-users" are exposed at levels above 100 ppm 8-hr TWA. The high exposure levels are caused by their proximity to spraying operations in other departments, even though no adhesive is used in the Saw and Sew departments (NIOSH, 2002a). Post-EC exposure scenarios suggest that engineering controls, if well designed, maintained, and operated, can reduce worker exposures by an order of magnitude. However, engineering controls alone do not reduce exposures for sprayers and non-sprayers to levels below 0.1 ppm, the time-weighted average threshold limit value (TLV) recommended by the American Conference of Governmental Industrial Hygienists (ACGIH).

Additional 1-BP worker exposure monitoring data have been identified in other literature studies such as Hanley et al. (2009; 2006), Ichihara et al. (2002), and Majersik et al. (2007). However, these studies are not used in EPA/OPPT's analysis because they either do not provide individual data points or lack specific information on worker job descriptions to adequately categorize the exposure results.

Table 2-2 Summary of 1-BP Inhalation Exposures (AC, ADC and LADC) for Spray Adhesive Use Based on Monitoring Data

Category	Acute and Chronic, Non-Cancer Exposures (8-Hour TWAs in ppm) $AC_{1\text{-BP, 8-hr TWA}}$ and $ADC_{1\text{-BP, 8-hr TWA}}$		Chronic, Cancer Exposures (ppm) $LADC_{1\text{-BP, 8-hr TWA}}$		
	95th Percentile	50th Percentile	95th Percentile	50th Percentile	Data Points
Sprayers					
Pre EC	253	131	145	75.1	85
Post EC[a]	41.9	17.8	23.9	10.2	49
Non-sprayers[b]					
Pre EC	211	127	120	72.7	31
Post EC[a]	28.8	18.0	16.5	10.3	9
Occupational non-users[c]					
Pre EC	129	3.00	73.5	1.71	39
Post EC[a]	5.48	2.00	3.13	1.14	17

Note: AC = Acute Concentration; ADC = Average Daily Concentration and LADC = Lifetime Average Daily Concentration. Equations and parameters for calculation of the AC, ADC, and LADC are described in Appendix H;
Sources: (OSHA, 2013; NIOSH, 2003, 2002a, b)
[a] EC = Engineering Controls. Pre-EC = Initial NIOSH visit; Post EC = Follow-up NIOSH visit engineering controls implemented: Enclosing spray tables to create "spray booths" and/or improve ventilation.
[b] Non-Sprayer refers to those employees who are not sprayers, but either handle the adhesive or spend the majority of their shift working in an area where spraying occurs.
[c] Occupational non-user refers to those employees who do not regularly work in a department/area where spraying occurs (e.g., employees in Saw and Sew departments).

2.1.2.4 Estimate of Inhalation Exposure Based on Modeling

A near-field/far-field modeling approach was not developed for the use of 1-BP as spray adhesive. EPA/OPPT determined the monitoring was adequate and of acceptable quality.

2.1.3 Dry Cleaning

2.1.3.1 Process and Worker Activity Descriptions

1-BP is a solvent used in dry cleaning machines. 1-BP formulations such as DrySolv® are often marketed as "drop-in" replacements for perchloroethylene (PERC), which indicates they can be used in third generation or higher PERC equipment (TURI, 2012). Third generation equipment, introduced in the late 1970s and early 1980s, are non-vented, dry-to-dry machines with refrigerated condensers. These machines are essentially closed systems, and are only open to the atmosphere when the machine door is opened. In third generation machines, heated drying air is recirculated back to the drying drum through a vapor recovery system (CDC, 1997).

Fourth generation dry cleaning equipment are essentially third-generation machines with added secondary vapor control. These machines "rely on both a refrigerated condenser and carbon adsorbent to reduce the PERC concentration at the cylinder outlet below 300 ppm at the end of the dry cycle", and are more effective at recovering solvent vapors. Fifth generation equipment have the same features as fourth generation machines, but 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 (CDC, 1997).

Dry cleaners who opt to use 1-BP can either convert existing PERC machines or purchase a new dry cleaning machine specifically designed for 1-BP. To convert existing PERC machines to use 1-BP, machine settings and components must be changed to prevent machine overheating and solvent leaks (Blando et al., 2010). 1-BP is known to damage rubber gaskets and seals. It can also degrade cast aluminum, which is sometimes used on equipment doors and other dry cleaning machine components. In addition, 1-BP is not compatible with polyurethane and silicone (TURI, 2012).

Figure 2-2 provides an overview of the dry cleaning process. Worker exposure monitoring studies for 1-BP at dry cleaning facilities suggest workers are exposed when 1) adding makeup solvent, typically by manually dumping it through the front hatch, 2) opening the machine door during the wash cycle, and 3) removing loads from the machines (Blando et al., 2010).

Engineering controls such as local exhaust ventilation (LEV) located at or near the machine door can reduce worker exposure during machine loading, machine unloading, and maintenance activities (NCDOL, 2013). However, there are currently no regulatory requirements for installing such controls to reduce 1-BP emissions and associated worker exposures at dry cleaning facilities.

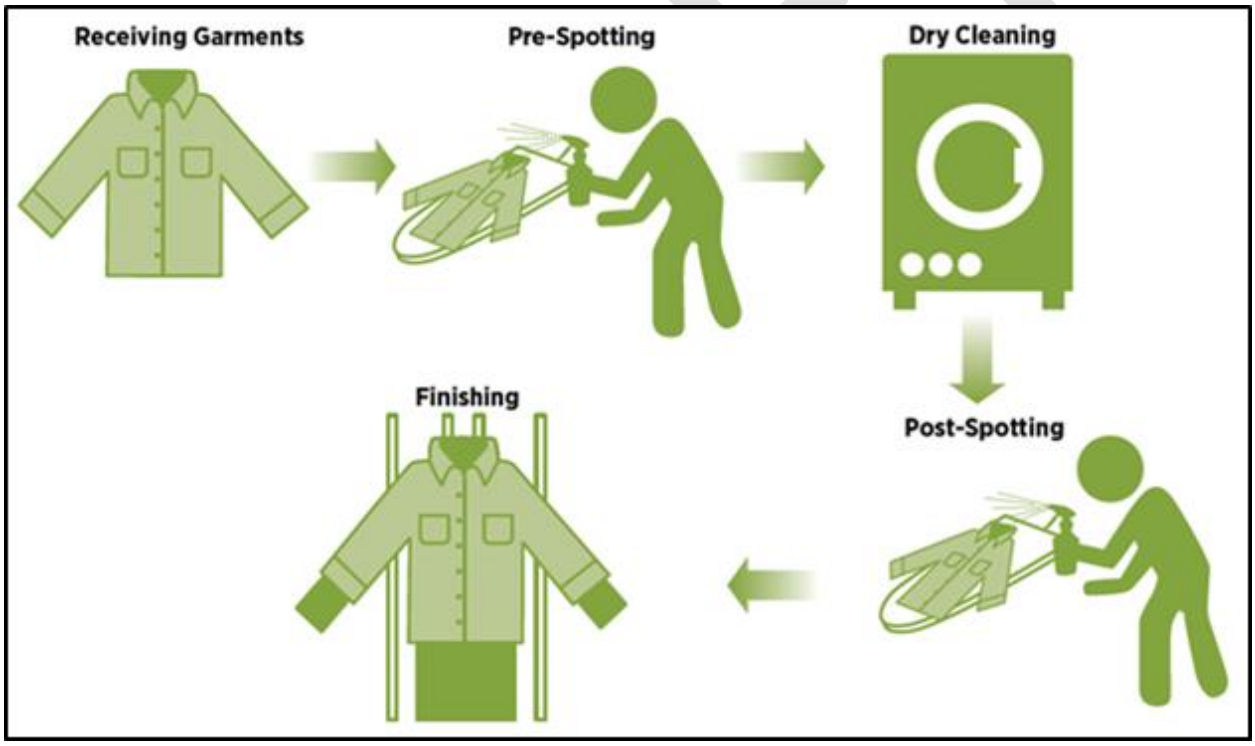


Figure 2-2 Overview of Dry Cleaning

2.1.3.2 Estimate of Number of Workers Potentially Exposed

EPA/OPPT estimated the number of workers and occupational non-users potentially exposed to 1-BP at dry cleaners using Bureau of Labor Statistics' OES data (2015) and the U.S. Census' SUSB (2012). The method for estimating number of workers is detailed in Appendix F. These estimates were derived using industry- and occupation-specific employment data from the BLS and U.S.

Census. The industry sectors and occupations that EPA/OPPT determined to be relevant to dry cleaning use are presented in Appendix F.

There are 22,359 dry cleaning establishments in the United States under NAICS 812320 (U.S. Census Bureau, 2012). Among these establishments, only a small subset use 1-BP as a dry cleaning solvent. In 2009, the Drycleaning and Laundry Institute (DLI) estimated only about 50 dry cleaning systems used DrySolv® (U.S. EPA, 2013c). A more recent survey conducted by AmericanDrycleaner.com in 2012 indicated that 1.1% of respondents used DrySolv, but did not specify the number of respondents participating in the survey (Beggs, 2012, as cited in (U.S. EPA, 2013c). EPA/OPPT conservatively assumed a 1-BP market penetration of 1.1 percent. Using this factor, EPA/OPPT estimated that approximately 246 dry cleaning establishments and 1,088 workers and occupational non-users are exposed to 1-BP (Table 2-3).

Table 2-3 Estimated Number of Workers Potentially Exposed to 1-BP in Dry Cleaning Shops

Exposed Workers	Exposed Occupational non-users	Total Exposed	Estimated Number of Establishments	Workers per Site	Occupational non-users per Site
821	267	1,088	246	3	1

Note: Number of workers and occupational non-users per site are calculated by dividing the exposed number of workers or occupational non-users by the number of establishments. Values are rounded to the nearest integer.

2.1.3.3 Assessment of Inhalation Exposure Based on Monitoring Data

Table 2-4 presents an analysis of the 8-hr TWA Personal Breathing Zone (PBZ) monitoring data from literature. The data were obtained from two literature studies of dry cleaning shops in New Jersey. The studies noted significant variability in 1-BP exposure among different dry cleaning shops, different job titles, and in some cases on different days when the exposure monitoring was conducted. The exposure data were also impacted by the willingness of individual shops to participate in exposure monitoring. Note the study (NIOSH, 2010) contains additional partial-shift exposure data that are not summarized here. For those data, an 8-hr TWA value was not obtained because owners of the shop requested that NIOSH remove the sampling equipment once they had finished running the dry cleaning machines (NIOSH, 2010).

The facilities studied had general building ventilation, ceiling-mounted or wall-mounted fans, but lacked controls specifically designed to reduce exposure to the dry cleaning solvent. Therefore, EPA/OPPT did not identify any monitoring data to be representative of a post-EC scenario.

EPA/OPPT defined workers as dry cleaning machine operators. For workers, the 95th and 50th percentile exposures are 50.2 and 29.4 ppm 8-hr TWA, respectively. The exposure level is impacted by the number of loads cleaned, the number of solvent cooking cycles used, and whether any "make-up" solvent was added in that particular shop and on that particular day when the monitoring was conducted (Blando et al., 2010). These activities can result in a larger release of solvent vapors into the work environment, contributing to higher worker exposure to 1-BP. The studies also noted that work load and work practices varied greatly among the shops (NIOSH, 2010). Further, NIOSH (NIOSH, 2010) noted that the highest 1-BP concentration in air was found when a facility with a converted PERC machine cooked the solvent, a practice that "had

been performed widely for PERC but is no longer recommended by the manufacturers for 1-BP operation" (NIOSH, 2010).

EPA/OPPT defined occupational non-users as employees who work in the dry cleaning shops but do not operate the machine. For occupational non-users, the 95th and 50th percentile exposures are 20.6 and 12.1 ppm 8-hr TWA, respectively. The data suggest that 1-BP exposure for cashiers, clerks, and other employees at the shop can still be significant.

Table 2-4 Summary of 1-BP Inhalation Exposures (AC, ADC and LADC) at Dry Cleaning Facilities Based on Monitoring Data

Category	Acute and Chronic, Non-Cancer Exposures (8-Hour TWAs in ppm) $AC_{1\text{-BP, 8-hr TWA}}$ and $ADC_{1\text{-BP, 8-hr TWA}}$		Chronic, Cancer Exposures (ppm) $LADC_{1\text{-BP, 8-hr TWA}}$		Data Points
	95th Percentile	50th Percentile	95th Percentile	50th Percentile	
Workers [a]					
Pre EC[c]	50.2	29.4	28.7	16.8	11
Occupational non-users [b]					
Pre EC[c]	20.6	12.1	11.8	6.89	5

Sources: (Blando et al., 2010; NIOSH, 2010).
AC = Acute Concentration; ADC = Average Daily Concentration and LADC = Lifetime Average Daily Concentration. Equations and parameters for calculation of the AC, ADC, and LADC are described in Appendix H
[a] Worker refers to dry cleaning machine operators.
[b] Occupational non-user refers to cashiers and clerks.
[a] Pre-EC = Pre-Engineering Controls. All data assumed to be representative of a Pre-EC scenario

2.1.3.4 Assessment of Inhalation Exposure Based on Modeling

Because there are multiple activities with potential 1-BP exposure at a dry cleaner, a multi-zone modeling approach is used to account for 1-BP vapor generation from multiple sources. Figure 2-3 illustrates this multi-zone approach, which considers the following three worker activities:

- **Spot cleaning of stains on both dirty and clean garments:** On receiving a garment, dry cleaners inspect for stains or spots they can remove as much of as possible before cleaning the garment in a dry cleaning machine. Spot cleaning may also occur after dry cleaning if the stains or spots were not adequately removed. Spot cleaning occurs on a spotting board and can involve the use of a spotting agent containing various solvents, such as 1-BP. Workers are exposed to 1-BP when applying it via squeeze bottles, hand-held spray bottles, or even from spray guns connected to pressurized tanks. Once applied, the worker may come into further contact with the 1-BP if using a brush, spatula, pressurized air or steam, or their fingers to scrape or flush away the stain (Young, 2012; NIOSH, 1997). For modeling, EPA/OPPT assumed the near-field is a rectangular volume covering the body of a worker.
- **Unloading garments from dry cleaning machines:** At the end of each dry cleaning cycle, dry cleaning workers manually open the machine door to retrieve cleaned garments. During this activity, workers are exposed to 1-BP vapors remaining in the dry cleaning

machine cylinder. For modeling, EPA/OPPT assumed that the near-field consists of a hemispherical area surrounding the machine door, and that the entire cylinder volume of air containing 1-BP exchanges with the workplace air, resulting in a "spike" in 1-BP concentration in the near-field, C_D, during each unloading event. This concentration is directly proportional to the amount of residual 1-BP in the cylinder when the door is opened. The near-field concentration then decays with time until the next unloading event occurs.

- **Finishing and pressing:** The cleaned garments taken out of the cylinder after each dry clean cycle contain residual solvents and are not completely dried (von Grote et al., 2003). The residual solvents are continuously emitted into the workplace during pressing and finishing, where workers manually place the cleaned garments on the pressing machine to be steamed and ironed. EPA/OPPT assumed any residual solvent is entirely evaporated during pressing, resulting in an increase in the near-field 1-BP concentration during this activity. Workers are exposed to 1-BP vapors while standing in vicinity of the press machine. Because this activity is typically performed while standing, EPA/OPPT assumed the near-field to be a rectangular volume covering the upper body of the worker.

As the figure shows, 1-BP vapor is generated in each of the three near-fields, resulting in worker exposures at concentrations C_S, C_D, and C_F. The volume of each zone is denoted by V_S, V_D, and V_F. The ventilation rate for the near-field zone (Q_S, Q_D, Q_F) determines how quickly 1-BP dissipates into the far-field (i.e., the facility space surrounding the near-fields), resulting in occupational non-user exposures to 1-BP at a concentration C_{FF}. V_{FF} denotes the volume of the far-field space into which the 1-BP dissipates out of the near-field. The ventilation rate for the surroundings, denoted by Q_{FF}, determines how quickly 1-BP dissipates out of the surrounding space and into the outside air.

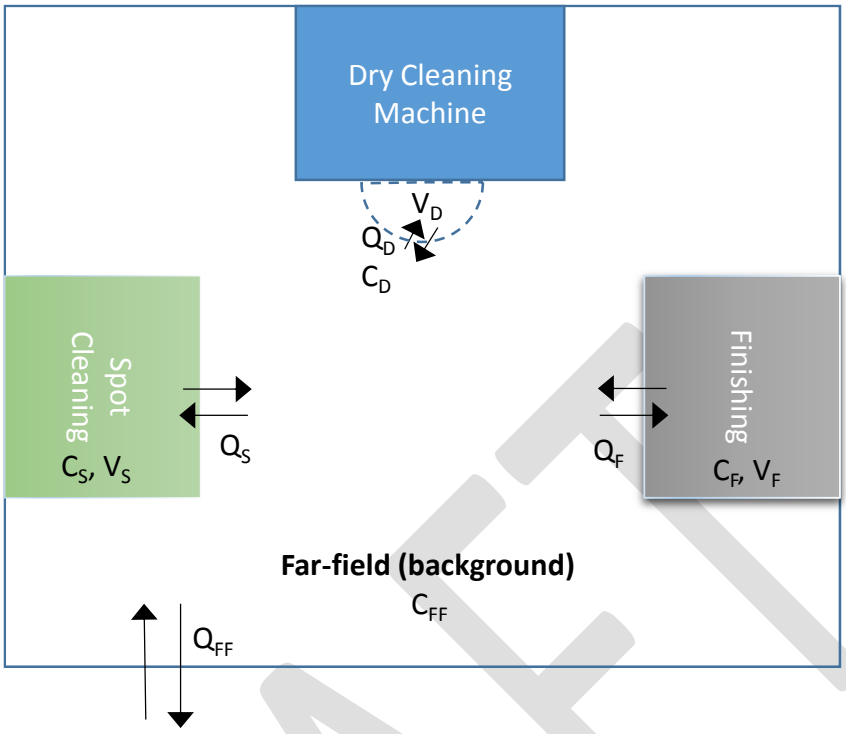


Figure 2-3 Illustration of the Multi-Zone Model

The dry cleaning industry is characterized by a large number of small businesses, many are family-owned and operated. In addition, many dry cleaning facilities are open longer than eight hours per day. As such, EPA/OPPT assumed small dry cleaners operate up to 12 hours a day and up to 6 days a week. In addition, EPA/OPPT assumed each facility has a single converted third generation or fourth generation machine in modeling 1-BP exposure. This assumption is based on a 2000 HSIA survey that very few PERC machines were fifth generation at the time (ERG, 2005). It should also be noted that all three New Jersey dry cleaners evaluated in the Blando et al. (2010) study used converted third generation machines.

Appendix J summarizes the modeling equations. Appendix K summarizes the environmental parameters for the multi-zone model. The far-field volume, air exchange rate, and near-field indoor wind speed are identical to those used in the 1-BP Spot Cleaning Model (see Section 2.1.4.4). These values were selected using engineering judgment and literature data that EPA/OPPT believed to be representative of a typical dry cleaner.

EPA/OPPT assessed three types of workers within the modeled dry cleaning facility: 1) a worker who performs spot cleaning; 2) a worker who unloads the dry cleaning machine and finishes and presses the garments; and 3) an occupational non-user. Each worker type is described in further detail below. EPA/OPPT assumed each worker activity is performed over two eight-hours shifts. The two shifts cover the full 12-hour operating day with a four-hour overlap in the middle of the day when both shifts are present at the facility.

EPA/OPPT assumed spot cleaning occurs for eight hours (see Section 2.1.4.4) in the middle of the 12-hour work day (from hour 2 through hour 10). The first-shift worker spot cleans garments from hour 2 through hour 8, while the second-shift worker spot cleans garments from hour 8 to hour 10. The first-shift worker is exposed at the far-field concentration for two hours, and then at the spot cleaning near-field concentration for six hours. The second-shift worker is exposed at the far-field concentration for four hours, at the spot cleaning near-field concentration for two hours, and then again at the far-field concentration for two hours. Spot cleaning can occur throughout the day for both dry cleaned loads and for laundered loads, because many dry cleaning facilities also perform laundering.

During each shift, EPA/OPPT assumed a separate worker unloads the dry cleaning machine, and finishes and presses the garments. After each load, EPA/OPPT assumed this worker spends five minutes unloading the machine, during which he or she is exposed at the machine near-field concentration. After unloading, the worker spends five minutes in the finishing near-field to prepare the garments. Then, the worker spends another 20 minutes finishing and pressing the cleaned garments. During this 20-minute period of finishing and pressing, the residual 1-BP solvent is off-gassed into the finishing near-field. The amount of residual 1-BP solvent is estimated using measured data presented in (von Grote et al., 2003) for a non-vented, dry-to-dry machine (i.e., 3rd generation). These unloading and finishing activities are assumed to occur at regular intervals throughout the twelve-hour day. The frequency of unloading and finishing depends on the number of loads dry cleaned each day, which varies from one to 14, where 14 was the maximum number of loads observed in the (NIOSH, 2010) and (2010) studies. When this worker is not unloading the dry cleaning machine or finishing and pressing garments, the worker is exposed at the far-field concentration. During the 4-hr overlap period, EPA/OPPT assumed the first-shift worker performs the work activity if a given load can be completed prior to the end of the first shift (i.e. hour 8). EPA/OPPT defined a load as being "completed" if it is completely unloaded, finished, and pressed. If a load cannot be completed by the end of the first shift, it is assigned to the second-shift worker.

EPA/OPPT assumed one occupational non-user is present during the first shift, and another is present during the second shift, such that each occupational non-user is exposed at the far-field concentration for eight hours a day. The occupational non-user could be the cashier, tailor, or launderer, who works at the facility but does not perform dry cleaning activities.

Table 2-5 presents the Monte Carlo results with the Latin hypercube sampling method and 5,000 iterations. For each iteration, the average exposure for each work category is calculated across the two shifts. Statistics of the average-shift exposures (95th and 50th percentiles) are then calculated at the end of the simulation after all iterations have completed. For the dry cleaning worker who performs unloading and finishing, the average shift 95th and 50th percentile exposures are 60.7 ppm and 7.35 ppm 8-hr TWA, respectively (Table 2-5). For spot cleaning worker, the average shift 95th and 50th percentile exposures are 6.93 ppm and 1.83 ppm 8-hr TWA, respectively. For occupational non-users, the average shift 95th and 50th percentile exposures are 4.84 ppm and 0.931 ppm 8-hr TWA. The model values cover a wider distribution of exposure levels when compared to the monitoring data. This is likely due to the wide range of

model input parameter values covering a higher number of possible exposure scenarios. However, the modeled occupational non-user exposures are lower than actual monitoring results presented in Section 2.1.3.3. The model assumes the occupational non-user spends their time entirely in the far-field. In reality, it is possible that these employees will occasionally perform activities in the near-field, thereby having a higher level of exposure.

The AC, ADC, and LADC calculations are included in Appendix H. These calculations are integrated into the Monte Carlo simulation, such that the exposure frequency matches the model input values for each iteration. The exposure frequency varies from 250 to 312 days per year.

Note there are additional activities with potential 1-BP exposure at dry cleaners that are not included in this multi-zone model. For example, workers could be exposed to 1-BP emitted due to equipment leaks, when re-filling 1-BP solvent into dry cleaning machines, when interrupting a dry cleaning cycle, or when performing maintenance activities (e.g., cleaning lint and button traps, raking out the still, changing solvent filter, and handling solvent waste) (OSHA, 2005). However, there is a lack of information on these activities in the literature, and the frequency of these activities is not well understood. The likelihood of equipment leaks is dependent on whether the PERC machines are properly converted and maintained. The frequency of solvent re-filling depends on a specific dry cleaner's workload and solvent consumption rate, which is also affected by the presence of leaks. Based on observations reported by (NIOSH, 2010) and (Blando et al., 2010), solvent charging is not performed every day. EPA/OPPT was unable to develop a modeling approach for these exposure activities due to the lack of available information.

Table 2-5 Statistical Summary of 1-BP Dry Cleaning Exposures for Workers and Occupational Non-users based on Modeling

Category	Acute and Chronic, Non-Cancer Exposures (Average Shift 8-Hour TWAs in ppm) $AC_{1\text{-BP, 12-hr TWA}}$ and $ADC_{1\text{-BP, 12-hr TWA}}$		Chronic, Cancer Exposures (ppm) $LADC_{1\text{-BP, 12-hr TWA}}$	
	95th Percentile	50th Percentile	95th Percentile	50th Percentile
Workers: Machine Unloading and Finishing (Near-Field)				
Pre EC	60.7	7.35	34.7	4.20
Post EC	6.07	0.735	3.47	0.420
Workers: Spot Cleaning (Near-Field)				
Pre EC	6.93	1.83	3.96	1.04
Post EC	0.693	0.183	0.396	0.104
Occupational non-users (Far-Field)				
Pre EC	4.84	0.931	2.76	0.532
Post EC	0.484	0.0931	0.276	0.0532

AC = Acute Concentration; ADC = Average Daily Concentration and LADC = Lifetime Average Daily Concentration. Equations and parameters for calculation of the AC, ADC, and LADC are described in Appendix H.
Pre-EC: refers to modeling where no reduction due to engineering controls was assumed.
Post-EC: refers to modeling where engineering controls with an assumed 90% efficiency were implemented.

2.1.4 Spot Cleaning at Dry Cleaners

2.1.4.1 Process and Worker Activity Descriptions

On receiving a garment, dry cleaners inspect for stains or spots they can remove as much of as possible before cleaning the garment in a dry cleaning machine. As Figure 2-4 shows, spot cleaning occurs on a spotting board and can involve the use of a spotting agent containing various solvents, such as 1-BP. The spotting agent can be applied from squeeze bottles, hand-held spray bottles, or even from spray guns connected to pressurized tanks. Once applied, the dry cleaner may come into further contact with the 1-BP if using a brush, spatula, pressurized air or steam, or their fingers to scrape or flush away the stain (Young, 2012; NIOSH, 1997).

Figure 2-4 Overview of Use of Spot Cleaning at Dry Cleaners

EPA/OPPT assesses a separate spot cleaning at dry cleaners scenario to account for dry cleaners that may use 1-BP-based spot cleaner formulations but not convert their PERC dry cleaning machine system to 1-BP. Therefore, this scenario represents dry cleaners where spot cleaning is the only source of 1-BP exposure.

2.1.4.2 Estimate of Number of Workers Potentially Exposed

See Section 2.1.3.2 for the estimated number of workers and occupational non-users at dry cleaning shops. Workers at these shops often perform multiple activities; as such, a single worker who spot treats the garments using 1-BP may also load and unload the dry cleaning machines.

2.1.4.3 Assessment of Inhalation Exposure Based on Monitoring Data

Table 2-6 presents 8-hr TWA PBZ monitoring data from OSHA IMIS for a David's Bridal, Inc. facility. The facility is a bridal store (not a dry cleaners) where alterations, steaming, pressing and spot cleaning are performed. The facility used approximately one gallon of Albatross per month, a formulation containing 40 to 70 percent 1-BP. Workers spray-applied the solvent formulation to stained portions of the dresses via a 16-oz handheld Arrow Textile spray gun. The workers operated approximately 8 to 10 feet apart from each other and did not wear any personal protective equipment. Each worker may clean up to 8 dresses per day. The study did not mention the use of any engineering controls at the facility to mitigate worker exposure.

Actual exposure for the two workers were 1.8 and 1.2 ppm 8-hr TWA. EPA/OPPT presented the data as a range because only two data points are available from this source. It should be noted

that these exposure levels may not be representative of spot cleaning exposure at dry cleaning facilities, where a larger work load is likely handled.

Table 2-6 Summary of Inhalation Exposure Data for Spot Cleaning

Category	Acute and Chronic, Non-Cancer Exposures (8-Hour TWAs in ppm) $AC_{1\text{-BP, 8-hr TWA}}$ and $ADC_{1\text{-BP, 8-hr TWA}}$		Chronic, Cancer Exposures (ppm) $LADC_{1\text{-BP, 8-hr TWA}}$		Data Points
	High-end	Low-end	High-end	Low-end	
Workers					
Pre EC[a]	1.80	1.20	1.03	0.686	2

Source: (OSHA, 2013).
AC = Acute Concentration; ADC = Average Daily Concentration and LADC = Lifetime Average Daily Concentration. Equations and parameters for calculation of the AC, ADC, and LADC are described in Appendix H.
[a] Pre-EC = Pre-Engineering Controls. Data assumed to be representative of a Pre-EC scenario

2.1.4.4 Assessment of Inhalation Exposure Based on Modeling

A more detailed description of the modeling approach is provided in Appendix J. Figure 2-5 illustrates the near-field/far-field modeling approach that EPA/OPPT applied to spot cleaning facilities. As the figure shows, chemical vapors evaporate into the near-field (at evaporation rate G), resulting in near-field exposures to workers at a concentration C_{NF}. The concentration is directly proportional to the amount of spot cleaner applied by the worker, who is standing in the near-field-zone (i.e., the working zone). The volume of this zone is denoted by V_{NF}. The ventilation rate for the near-field zone (Q_{NF}) determines how quickly the chemical of interest dissipates into the far-field (i.e., the facility space surrounding the near-field), resulting in occupational non-user exposures at a concentration C_{FF}. V_{FF} denotes the volume of the far-field space into which the chemical of interest dissipates out of the near-field. The ventilation rate for the surroundings, denoted by Q_{FF}, determines how quickly the chemical dissipates out of the surrounding space and into the outdoor air.

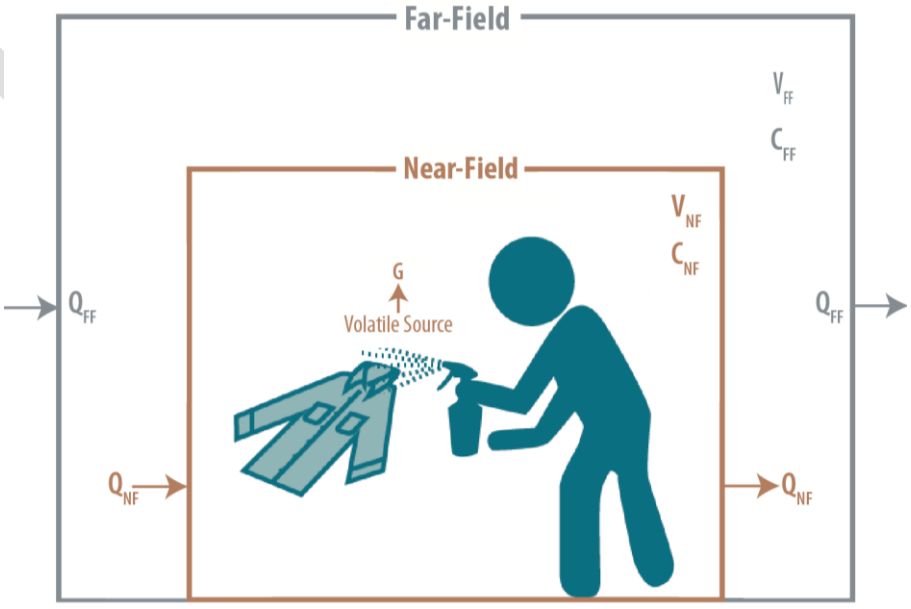


Figure 2-5 Schematic of the Near-Field/Far-Field Model for Spot Cleaning

It should be noted that although 1-BP has been marketed for use as a spot cleaner, the prevalence of this use is not known at this time.

To determine the 1-BP use rate, EPA/OPPT conducted a targeted literature search to identify information on the typical amount of spotting agents used at dry cleaners. The Massachusetts Department of Environmental Protection (MADEP) provided a comparative analysis of several dry cleaner case studies using various PERC alternatives. This document estimates a dry cleaner using 1-BP spends $60 per month on spotting agents. This particular facility dry cleans 100 pieces of garments per day. MADEP noted that the facility size can vary greatly among individual dry cleaners (MassDEP, 2013). Blando et al. (2009) estimated that 1-BP solvent products cost $45 per gallon. Based on this information, EPA/OPPT calculated a spot cleaner use rate of 1.33 gallons per month, or 16 gallons per year. The Safety Data Sheet for DrySolv, a common 1-BP formulation, indicates the product contains greater than 87 percent 1-BP by weight (Enviro Tech International, 2013). The model input parameters are documented in Appendix K.

EPA/OPPT performed Monte Carlo simulations, applying one million iterations and the Latin hypercube sampling method. Table 2-7 presents a statistical summary of the exposure modeling results for the pre-EC and post-EC scenarios. For pre-EC, the 50th percentile near-field exposure is 2.57 ppm 8-hr TWA, with a 95th percentile of 9.44 ppm 8-hr TWA. These results are generally comparable to the monitoring data. With engineering controls, model exposure is reduced to 0.257 and 0.944 ppm 8-hr TWA, respectively. Engineering control (e.g., LEV) is assumed to be 90 percent effective as a "what-if" engineering assumption.

For occupational non-users (far-field), model exposure has a 50th percentile value of 0.888 ppm and a 95th percentile value of 3.79 ppm 8-hr TWA. With engineering controls, the exposure is reduced to 0.0888 and 0.379 ppm 8-hr TWA, respectively.

Estimates of Acute Concentration (AC), Average Daily Concentrations (ADC) and Lifetime Average Daily Concentration (LADC) for use in assessing risk were made using the approach and equations described in Appendix H.

Table 2-7 Statistical Summary of 1-BP 8-hr TWA Exposures (AC, ADC and LADC) for Use of Spot Cleaning at Dry Cleaners Based on Modeling

	Acute and Chronic, Non-Cancer Exposures (8-Hour TWAs in ppm) $AC_{1\text{-BP, 8-hr TWA}}$ and $ADC_{1\text{-BP, 8-hr TWA}}$		**Chronic, Cancer Exposures (ppm) $LADC_{1\text{-BP, 8-hr TWA}}$**	
Category	95th Percentile	50th Percentile	95th Percentile	50th Percentile
Workers (Near-Field)				
Pre EC	9.44	2.57	5.39	1.47
Post EC	0.944	0.257	0.539	0.147
Occupational non-users (Far-Field)				
Pre EC	3.79	0.888	2.16	0.507
Post EC	0.379	0.0888	0.216	0.0507

Note: AC = Acute Concentration; ADC = Average Daily Concentration and LADC = Lifetime Average Daily Concentration. Equations and parameters for calculation of the AC, ADC, and LADC are described in Appendix H; EC – Engineering controls
Pre-EC: refers to modeling where no reduction due to engineering controls was assumed
Post-EC: refers to modeling where engineering controls with an assumed 90% efficiency were implemented

2.1.5 Vapor Degreasing

2.1.5.1 Process and Worker Activity Descriptions

1-BP is a potential replacement for chlorinated solvents in vapor degreasing. Vapor degreasing is used to remove dirt, grease, and surface contaminants in a variety of metal cleaning industries. The suitability of 1-BP for use in vapor degreasing is due to its high purity, compatibility with many metals, low corrosivity, and suitability for use in most modern vapor degreasing equipment. Figure 2-6 is an illustration of vapor degreasing operations, which can occur in a variety of industries.

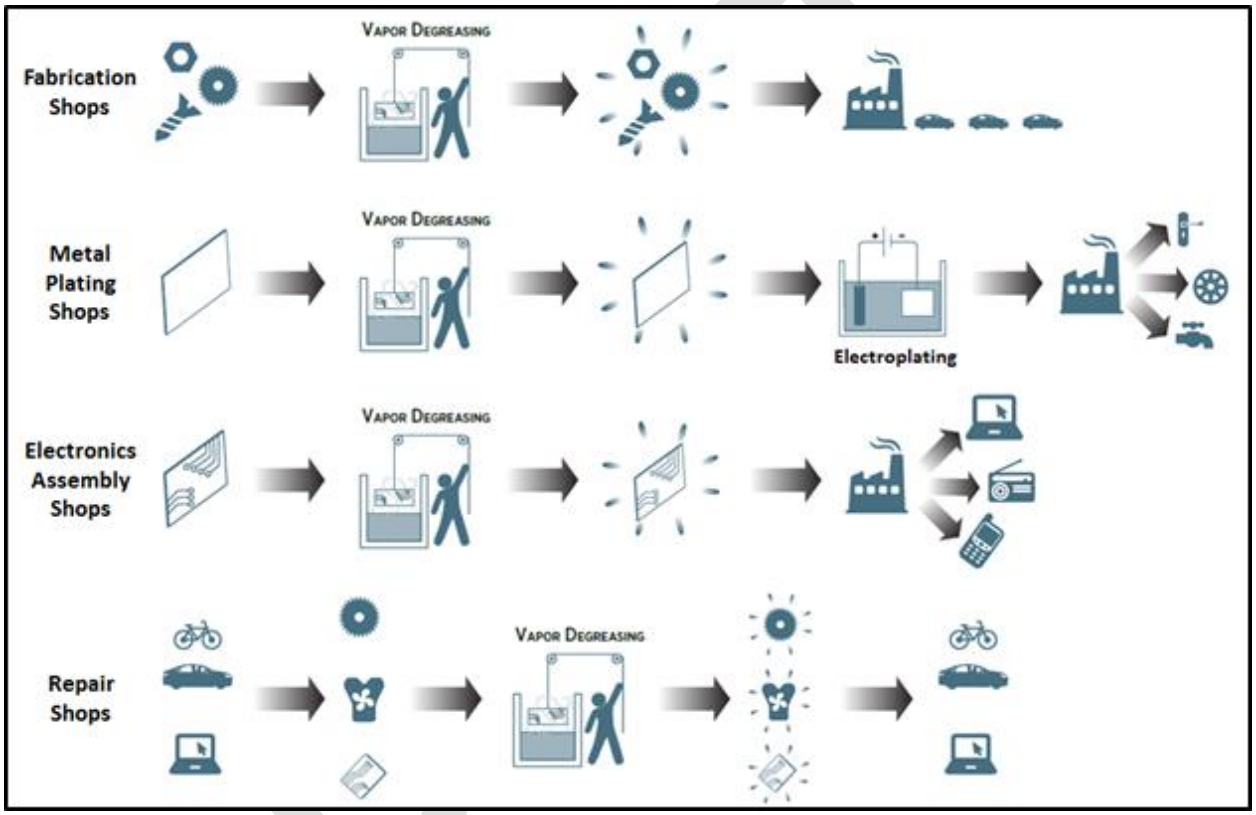


Figure 2-6 Use of Vapor Degreasing in a Variety of Industries

There are several types of vapor degreasing equipment, including batch degreaser, in-line degreaser, and airless, vacuum degreaser. The batch degreaser, traditionally an open-top unit, is a tank with condensing coils at the top (see Figure 2-7). Heating elements at the bottom of the degreaser heat the liquid solvent to above its boiling point. Solvent vapor rises to the height of chilled condensing coils on the inside walls of the unit, producing a hot vapor zone below the coils. The condensing coils cool the vapor, causing it to condense and return to the bottom of the degreaser (U.S. EPA, 2006a).

To clean dirty parts, the substrates are lowered into the vapor zone. The hot vapor condenses onto the substrate, which is cooler in temperature, and the condensation dissolves the grease

and carries it off the substrate surface as it drains into the solvent reservoir below. The process continues until the substrate temperature reaches that of the vapor, at which point the cleaned and dried substrate is lifted out of the vapor zone. The degreaser can also contain one or more immersion tanks below the vapor zone for additional cleaning and rinsing. 1-BP emissions and worker exposures from batch, open-top degreasers can occur from solvent dragout or vapor displacement when the substrates are raised out of or lowered into the equipment, respectively (Kanegsberg and Kanegsberg, 2011). Worker exposure is also possible while charging new solvent or disposing spent solvent.

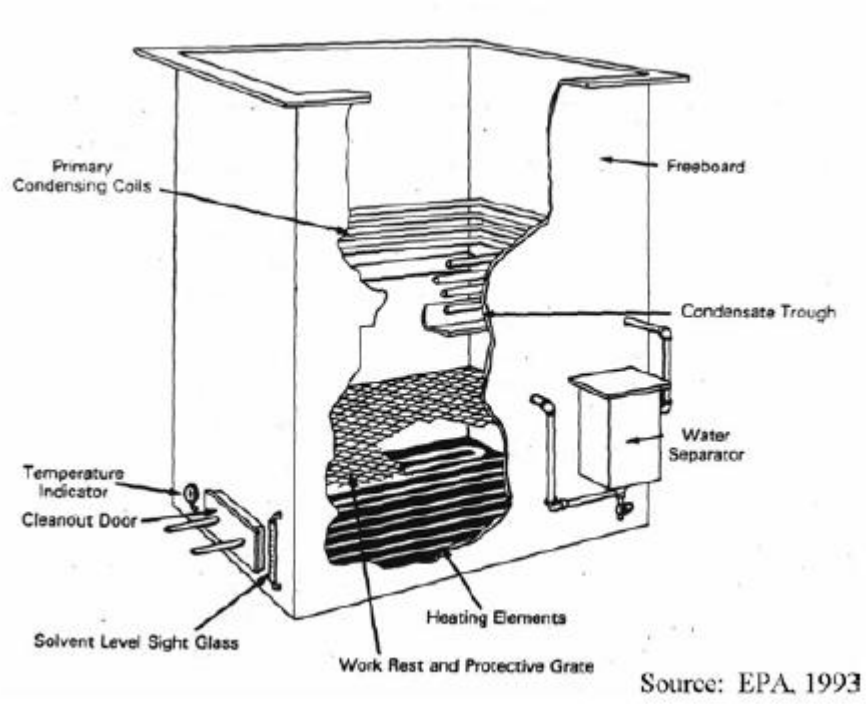


Figure 2-7 Open-Top Batch Vapor Degreaser (U.S. EPA, 2006a)

An in-line type degreaser consists of a material handling system that automatically conveys the workload in and out of the degreaser. In-line degreasers are used where there is a high volume of workload, typically custom designed for large scale industrial operations. These units utilize the same general cleaning techniques as batch units, but have different emission points due to differences in equipment configuration. In-line degreasers are semi-enclosed above the solvent/air interface, with the only openings at substrate entry and exit ports. Therefore, emissions are substantially lower than those from equal sized batch, open-top vapor degreasers. However, most in-line degreasers are larger than batch, open-top vapor degreasers. Some in-line degreasers are equipped with an exhaust system that pumps air from inside the cleaning machine to an outside vent (U.S. EPA, 2006a).

In airless degreaser systems, air is removed from an enclosed degreaser using a vacuum pump. The hot solvent vapor contacts the substrate via spraying action, condenses on the cooler substrate, and is removed by vacuum. The spraying and vacuum removal steps are then repeated until the substrate is cleaned. Because the system is under a vacuum, solvent can boil at

temperatures below their normal boiling points. These types of degreasers have very low solvent emissions; users of these systems have reported using the equipment for over five years without solvent changeout (Kanegsberg and Kanegsberg, 2011).

2.1.5.2 Estimate of the Number of Workers Potentially Exposed

EPA/OPPT estimated the number of workers potentially exposed to 1-BP in vapor degreasing using Bureau of Labor Statistics' OES data (2015) and (2012) U.S. Census SUBS. The method for estimating number of workers is detailed in Appendix F. The worker estimates were derived using industry- and occupation-specific employment data from these sources. The industry sectors and occupations that EPA/OPPT determined to be relevant to degreasing uses are presented below. EPA/OPPT was unable to determine which industry sectors and occupations perform specific degreasing types (e.g., vapor degreasing versus cold cleaning). It is possible that establishments under the same NAICS code perform a combination of vapor degreasing and cold cleaning.

There are 109,966 establishments among the industry sectors (see Appendix F). The number of businesses that use 1-BP for vapor degreasing is estimated at 500 to 2,500 businesses (U.S. EPA, 2007b). This translates to a 1-BP market penetration of 0.5 percent to 2.3 percent.

Table 2-8 presents the estimated number of workers and occupational non-users based on industry- and occupational-specific employment data. The low-end estimates correspond to a 0.5 percent market penetration, while the high-end estimates correspond to a 2.3 percent market penetration. The total number of potentially exposed workers and occupational non-users range from 4,712 to 23,558.

Table 2-8 Estimated Number of Workers Potentially Exposed to 1-BP in Degreasing Uses

Exposed Workers	Exposed Occupational non-users	Total Exposed	Estimated Number of Establishments	Workers per Site	Occupational non-users per Site
Low-end					
3,245	1,466	4,712	500	6	3
High-end					
16,226	7,332	23,558	2,500	6	3

Note: Number of workers and occupational non-users per site are calculated by dividing the exposed number of workers or occupational non-users by the number of establishments. Values are rounded to the nearest integer.

2.1.5.3 Assessment of Inhalation Exposure Based on Monitoring Data

Table 2-9 summarizes the 1-BP exposure data for pre-EC and post-EC vapor degreasing scenarios. EPA/OPPT obtained exposure monitoring data from several sources, including journal articles (e.g., (Hanley et al., 2010)), NIOSH HHEs, OSHA IMIS database, and data submitted to the EPA SNAP program. NIOSH HHEs are conducted at the request of employees, employers, or union officials, and provide information on existing and potential hazards present in the workplaces evaluated. OSHA IMIS data are workplace monitoring data from OSHA inspections; EPA SNAP program data are collected as part of the EPA/OPPT's effort to identify substitutes for ozone-depleting substances.

Data from these sources cover exposure at a variety of industries that conduct vapor degreasing, including telecommunication device manufacturing, aerospace parts manufacturing, electronics parts manufacturing, helicopter transmission manufacturing, hydraulic power control component manufacturing, metal product fabrication, optical prism and assembly, and printed circuit board manufacturing. It should be noted that sources that only contain a statistical summary of worker exposure monitoring, but exclude the detailed monitoring results, are not included in EPA/OPPT's analysis below.

Most of the gathered data were for batch open-top vapor degreasers with the only exception being data obtained from the EPA SNAP program, which did not specify the type of degreaser used. The EPA SNAP program data were included in the data analysis despite the uncertainty in the degreaser type. Additionally, the OSHA IMIS data from Da-Tech indicated that spray cleaning occurred while parts were inside the degreasers (OSHA, 2013). Such activities could further increase worker exposure.

To analyze the exposure monitoring data, EPA/OPPT categorized these data into pre-EC and post-EC scenarios. EPA/OPPT identified the data to be representative of a "pre-EC" scenario if they were gathered before implementation of engineering controls designed to reduce worker exposure to 1-BP. EPA/OPPT identified data to be "post-EC" if they were gathered after the implementation of engineering controls designed to reduce worker exposure to 1-BP at the facility. These controls can include local exhaust ventilation, dedicated ventilated degreasing room, or controls to the degreasing equipment such as larger and improved chillers.

EPA/OPPT defined a vapor degreasing "worker" as an employee who operates or performs maintenance tasks on the degreaser, such as draining, cleaning, and charging the degreaser bath tank. EPA/OPPT defined "occupational non-user" as an employee who does not regularly handle 1-BP or operate the degreaser but performs work in the area around the degreaser. The data sources do not describe their work activities in detail, and the exact proximity of these occupational non-users to the degreaser is unknown.

Pre-EC exposure data for vapor degreasing shows that workers handling the solvent and operating the degreasers are exposed to significant levels of 1-BP, with 95th and 50th percentile exposures of 47.7 and 8.20 ppm, respectively. In post-EC scenarios, worker exposures are reduced to 8.40 and 1.50 ppm at the 95th and 50th percentile levels, respectively, suggesting that good engineering controls can significantly reduce worker exposure to 1-BP during vapor degreasing. For occupational non-users, both pre-EC and post-EC inhalation levels of 1-BP are below 5 ppm.

Table 2-9 Statistical Summary of 1-BP 8-hr TWA Exposures (AC, ADC and LADC) for Vapor Degreasing Based on Monitoring Data

Category	Acute and Chronic, Non-Cancer Exposures (8-Hour TWAs in ppm) $AC_{1\text{-BP, 8-hr TWA}}$ and $ADC_{1\text{-BP, 8-hr TWA}}$		Chronic, Cancer Exposures (ppm) $LADC_{1\text{-BP, 8-hr TWA}}$		Data Points
	95th Percentile	50th Percentile	95th Percentile	50th Percentile	
Worker					
Pre EC	47.7	8.20	27.3	4.69	167
Post EC	8.40	1.50	4.80	0.857	26
Occupational non-users [a]					
Pre EC	4.90	0.440	2.80	0.251	7
Post EC	0.0200	0.0200	0.0114	0.0114	13

Source: (OSHA, 2013; U.S. EPA, 2006b). Note the (NIOSH, 2001) study only contains post-EC data.

[a] Occupational non-users refers to those employees who do not regularly handle the solvent or operate the degreaser but work in the degreaser area.

Note: the occupational non-users, post EC had the same exposure concentration 0.02 ppm at the 50th and 95th percentiles because in the 13 data points the reported exposure concentration had a very small range with multiple data points at 0.02 ppm. Equations and parameters for calculation of the AC, ADC, and LADC are described in Appendix H.

2.1.5.4 Assessment of Inhalation Exposure Based on Modeling

A more detailed description of the modeling approach is provided in Appendix J. Figure 2-8 illustrates the near-field / far-field model that can be applied to vapor degreasing (Keil et al., 2009). As the figure shows, volatile 1-BP vapors evaporate into the near-field, resulting in worker exposures at a concentration C_{NF}. The concentration is directly proportional to the evaporation rate of 1-BP, G, into the near-field, whose volume is denoted by V_{NF}. The ventilation rate for the near-field zone (Q_{NF}) determines how quickly 1-BP dissipates into the far-field, resulting in occupational non-user exposures to 1-BP at a concentration C_{FF}. V_{FF} denotes the volume of the far-field space into which the 1-BP dissipates out of the near-field. The ventilation rate for the surroundings, denoted by Q_{FF}, determines how quickly 1-BP dissipates out of the surrounding space and into the outside air. Appendix J outlines the equations uses for this model.

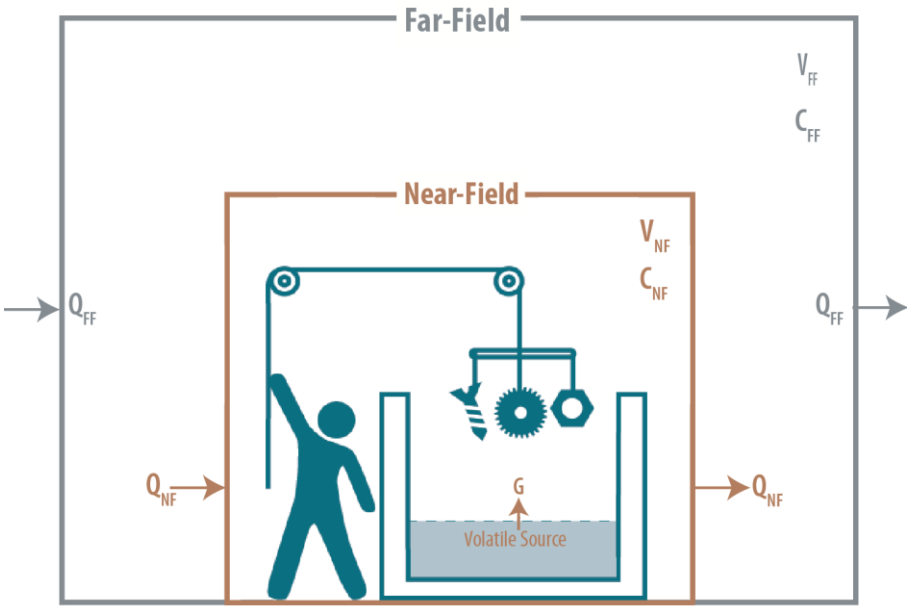


Figure 2-8 Schematic of the Near-Field/Far-Field Model for Vapor Degreasing

Appendix K presents the model parameters, parameter distributions, and assumptions for the 1-BP vapor degreasing model. To estimate the 1-BP vapor generation rate, the model references an emission factor developed by the California Air Resources Board (CARB) for the California Solvent Cleaning Emissions Inventories (CARB, 2011). CARB surveyed facilities that conduct solvent cleaning operations, and gathered site-specific information for 213 facilities. CARB estimated a 1-BP emission factor averaging 10.43 lb/employee-yr, with a standard deviation of 17.24 lb/employee-yr, where the basis is the total number of employees at a facility. The majority of 1-BP emissions were attributed to the vapor degreasing category.

It should be noted that the "vapor degreasing" category in CARB's study includes the batch-loaded vapor degreaser, aerosol surface preparation process, and aerosol cleaning process. It is not known what percentage, if any, of the 1-BP emission factor is derived from aerosol applications. This modeling approach assumes the 1-BP emission factor is entirely attributed to vapor degreasing applications. The emission factor is expected to represent emissions from batch-loaded degreasers used in California at the time of study. It is not known whether these are specifically open-top batch degreasers, although open-top is expected to be the most common design. The CARB survey data did not include emissions for conveyorized vapor degreasers.

The CARB emission factor is then combined with U.S. employment data for vapor degreasing industry sectors from the Economic Census[4]. The 1-BP RA identified 78 NAICS industry codes that are applicable to vapor degreasing. For these industry codes, the Census data set indicates a minimum industry average of 8 employees per site, with a 50th percentile and 90th percentile of

[4] For the purpose of modeling, EPA/OPPT used data from the 2007 Economic Census for the vapor degreasing NAICS codes as identified in the TCE RA (U.S. EPA, 2014c). The 2012 Economic Census did not have employment data (average number of employees per establishment) for all vapor degreasing NAICS codes of interest.

25 and 61 employees per site, respectively. A lognormal distribution is applied to the Census data set to model the distribution of the industry-average number of employees per site for the NAICS codes applicable to vapor degreasing.

These nationwide Census employment data are comparable to the 2008 California employment data cited in CARB's study. According to the CARB study, approximately 90 percent of solvent cleaning facilities in California had less than 50 employees (whereas the national Census data estimate 90 percent of facilities have less than or equal to 61 employees). It is important to note that the Census data report an average number of employees per site for each NAICS code. The number of employees for each individual site within each NAICS code is not reported. Therefore, the distribution EPA/OPPT calculated represents a population of *average* facility size for each NAICS code, and not the population of *individual* facility sizes over all NAICS codes.

The vapor generation rate, G (kg/unit-hr), is calculated *in-situ* within the model, as follows:

Equation 2-1 Equation for Calculating Vapor Degreasing Vapor Generation Rate

$$G = EF \times EMP / (2.20462 \times OH \times OD \times U)$$

Where EF = emission factor (lb/employee-yr)
EMP = Number of employees (employee/site)
OH = Operating hours per day (hr/day)
OD = Operating days per year (day/yr)
U = Number of degreasing units (unit/site)
2.20462 = Unit conversion from lb to kg (lb/kg)

EPA/OPPT performed a Monte Carlo simulation with one million iterations and the Latin Hypercube sampling method in @Risk[5] to calculate 8-hour TWA near-field and far-field exposure concentrations. Near-field exposure represents exposure concentrations for workers who directly operate the vapor degreasing equipment, whereas far-field exposure represents exposure concentrations for occupational non-users (i.e., workers in the surrounding area who do not handle the degreasing equipment).

The modeled 8-hr TWA results and the values in Table_Apx H-1 are used to calculate 8-hr acute exposure, ADC, and LADC (also see Appendix H).

Table 2-10 presents a statistical summary of the exposure modeling results. Estimates of Acute Concentration (AC), Average Daily Concentrations (ADC) and Lifetime Average Daily Concentration (LADC) for use in assessing risk were made using the approach and equations described in Appendix H.

[5] A risk analysis software tool (Microsoft Excel add-in) using Monte Carlo simulation

These exposure estimates represent modeled exposures for the workers and occupational non-users. For workers, the 50th percentile exposure is 1.76 ppm 8-hr TWA, with a 95th percentile of 25.61 ppm 8-hr TWA. Compared to literature studies:

- Hanley et al. (2010) reported a geometric mean of 2.63 ppm 8-hr TWA exposure with a range of 0.078 to 21.4 ppm 8-hr TWA among 44 samples;
- NIOSH (2001) reported a range of 0.01 to 0.63 ppm 8-hr TWA among 20 samples;
- A 2003 EPA analysis suggested that 87 percent of the samples were less than 25 ppm 8-hr TWA among 500 samples at vapor degreasing facilities (U.S. EPA, 2003).

The modeled mean near-field exposure is found to be generally comparable to the exposures reported in literature.

For occupational non-users, the modeled far-field exposure has a 50th percentile value of 0.671 ppm and a 95th percentile of 9.38 ppm 8-hr TWA. These modeled far-field results are somewhat higher than reported literature values. (Hanley et al., 2010) reported workers away from the degreasers are exposed at concentrations of 0.077 to 1.69 ppm 8-hr TWA, with a geometric mean of 0.308 ppm 8-hr TWA.

The post-EC scenarios reference Wadden et al. (1989) and NEWMOA (2001). The model assumes engineering controls can be 90 percent effective; this value is based on a LEV system for an open-top vapor degreaser (lateral exhaust hoods installed on two sides of the tank) (Wadden et al., 1989). This assumption is likely an overestimate because the study covered only reductions in degreaser machine emissions due to LEV and did not address other sources of emissions such as dragout, fresh and waste solvent storage and handling. Furthermore, a caveat in the study is that most LEV likely do not achieve ACGIH design exhaust flow rates, indicating that the emission reductions in many units may not be optimized. Actual exposure reductions from added engineering controls can be highly variable and can only be verified by monitoring studies.

The model assumes 98 percent exposure reduction can be achieved using equipment substitution. This value is based on the NEWMOA study, which states air emissions can be reduced by 98 percent or more when a closed-loop degreaser is used instead of an open-top vapor degreaser (NEWMOA, 2001).

The modeled post-EC scenarios suggest that 1-BP exposure during vapor degreasing could be effectively reduced using either equipment substitution or improved ventilation.

Table 2-10 Statistical Summary of 1-BP 8-hr TWA Exposures (AC, ADC and LADC) for Vapor Degreasing Based on Modeling

Category	Acute and Chronic, Non-Cancer Exposures (8-Hour TWAs in ppm) $AC_{1\text{-BP, 8-hr TWA}}$ and $ADC_{1\text{-BP, 8-hr TWA}}$		Chronic, Cancer Exposures (ppm) $LADC_{1\text{-BP, 8-hr TWA}}$	
	95th Percentile	50th Percentile	95th Percentile	50th Percentile
Workers (Near-Field)				
Pre EC	25.6	1.76	14.6	1.01
Post EC 90%	2.56	0.176	1.46	0.101
Post EC 98%	0.512	0.0352	0.293	0.0202
Occupational non-users (Far-Field)				
Pre EC	9.38	0.671	5.36	0.383
Post EC 90%	0.938	0.0671	0.536	0.0383
Post EC 98%	0.188	0.00134	0.0107	0.00767

AC = Acute Concentration; ADC = Average Daily Concentration and LADC = Lifetime Average Daily Concentration. See Appendix H.
Pre-EC: refers to modeling where no reduction due to engineering controls was assumed
Post-EC: refers to modeling where engineering controls with 90% efficiency were implemented or equipment substitution with 98% efficiency

2.1.6 Cold Cleaning Degreasing

2.1.6.1 Process and Worker Activity Descriptions

Cold cleaners are non-boiling solvent degreasing units. Cold cleaning operations include spraying, brushing, flushing, and immersion. Figure 2-9 shows the design of a typical batch-loaded, maintenance cold cleaner, where dirty parts are cleaned manually by spraying and then soaking in the tank. After cleaning, the parts are either suspended over the tank to drain or are placed on an external rack that routes the drained solvent back into the cleaner. Batch manufacturing cold cleaners could vary widely, but have two basic equipment designs: the simple spray sink and the dip tank. The dip tank design typically provides better cleaning through immersion, and often involves an immersion tank equipped with agitation (U.S. EPA, 1981). Emissions from batch cold cleaning machines typically result from (1) evaporation of the solvent from the solvent-to-air interface, (2) "carry out" of excess solvent on cleaned parts, and (3) evaporative losses of the solvent during filling and draining of the machine (U.S. EPA, 2006a).

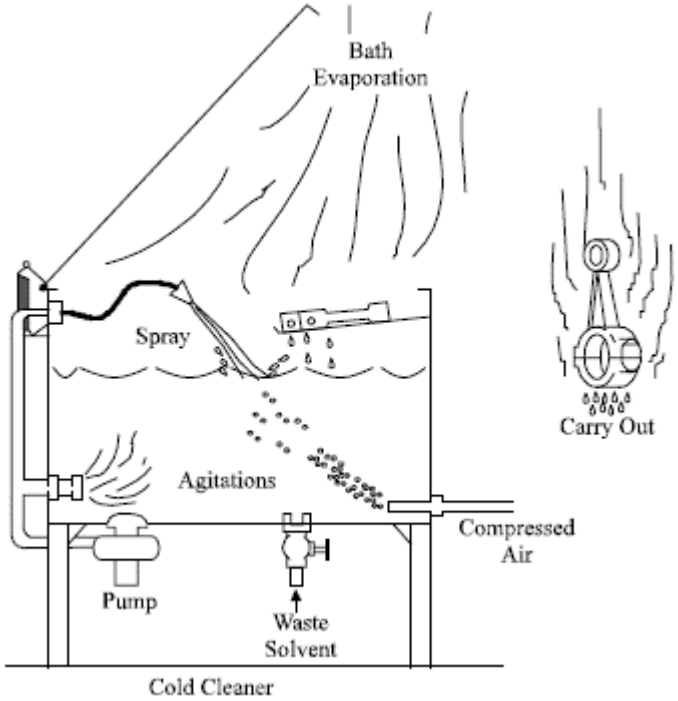


Figure 2-9 Typical Batch-Loaded, Maintenance Cold Cleaner (U.S. EPA, 1981)

Emissions from cold in-line (conveyorized) cleaning machines result from the same mechanisms, but with emission points only at the parts' entry and exit ports (U.S. EPA, 2006a).

The general worker activities for cold cleaning include placing the parts that require cleaning into a vessel. The vessel is usually something that will hold the parts but not the liquid solvent (i.e., a wire basket). The vessel is then lowered into the machine, where the parts could be sprayed, and then completely immersed in the solvent. After a short time, the vessel is removed from the solvent and allowed to drip/air dry. Depending on the industry and/or company, these operations may be performed manually (i.e., by hand) or mechanically. Sometimes parts require more extensive cleaning; in these cases, additional operations are performed including directly spraying solvent on the part, agitation of the solvent or parts, wipe cleaning and brushing (NIOSH, 2001; U.S. EPA, 1997b).

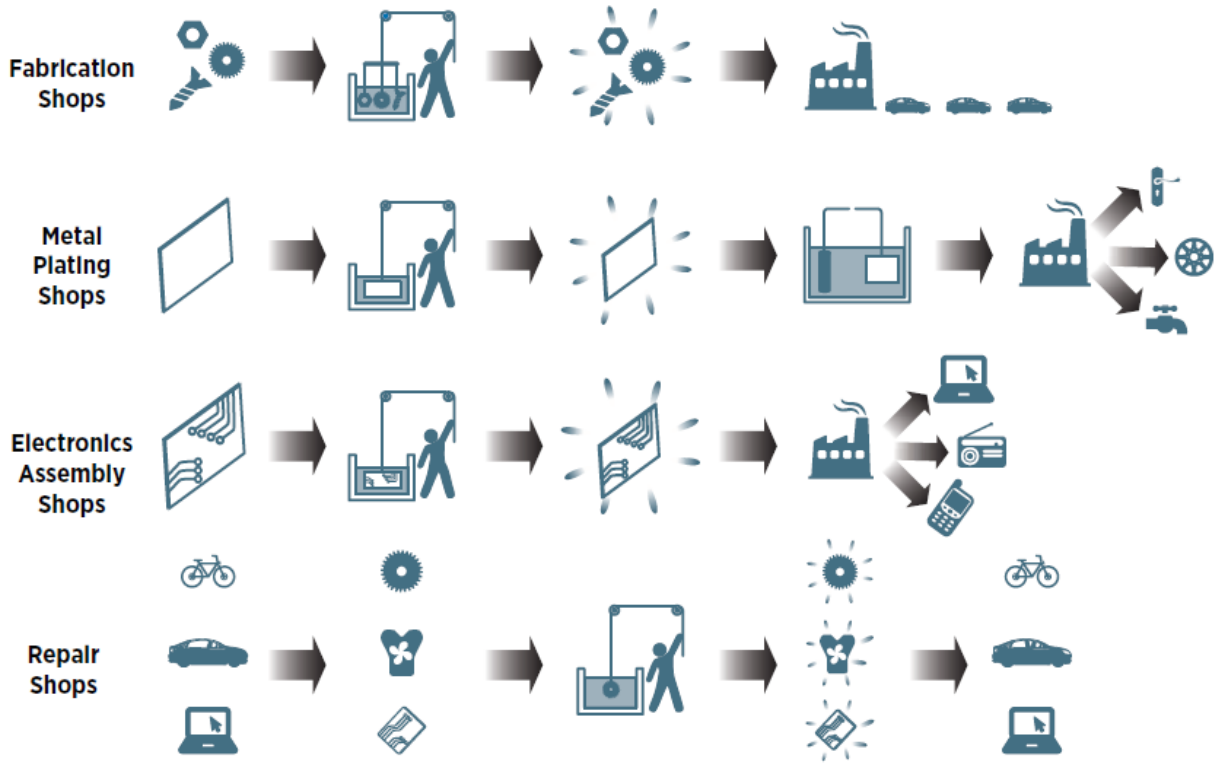


Figure 2-10 Illustration for Use of Cold Cleaner in a Variety of Industries

2.1.6.2 Estimate of the Number of Workers Potentially Exposed

There is no information to determine the number of workers and occupational non-users potentially exposed 1-BP during cold cleaning. The use of 1-BP is this sector is expected to be minimal. It is possible that some of the degreasing facilities presented in Section 2.1.5.2 also use 1-BP as a cold cleaning solvent.

2.1.6.3 Assessment of Inhalation Exposure Based on Monitoring Data

Table 2-11 presents OSHA IMIS data for two facilities: McFadden Lighting and Danville Metal Stamping. The first facility manufactures decorative, architectural, and church lighting, and uses 1-BP to clean parts in an immersion process in an area with general ventilation. The second facility manufactures parts for the aerospace industry, and uses 1-BP in a degreasing tank equipped with a spray nozzle. The degreasing operation is conducted in an area with local exhaust ventilation. The degreasing equipment and process activity in the two studies appear to refer to cold cleaning; however, the equipment is not described in detail in the OSHA IMIS data. The 95th and 50th percentile exposures for workers are 46.9 and 13.7 ppm 8-hr TWA, respectively. For occupational non-users, the exposure value is based on a single data point for a person described as "CSHO" (i.e. Chemical Safety and Health Officer), which is an official from OSHA or a state plan occupational safety and health program. The exposure for this individual measured 2.60 ppm 8-hr TWA. This data point represents a what-if inhalation exposure level for occupational non-users; the representativeness of this data point is unknown. It should be further

noted that IMIS data are obtained from OSHA inspections, and not intended to be representative of average worker exposure.

Table 2-11 Summary of Inhalation Exposure Monitoring Data for Cold Cleaning

Category	Acute and Chronic, Non-Cancer Exposures (8-Hour TWAs in ppm) $AC_{1\text{-BP, 8-hr TWA}}$ and $ADC_{1\text{-BP, 8-hr TWA}}$		Chronic, Cancer Exposures (ppm) $LADC_{1\text{-BP, 8-hr TWA}}$		Data Points
	95th Percentile	50th Percentile	95th Percentile	50th Percentile	
Workers					
Pre EC	46.9	13.7	26.8	7.83	10
Category	What-if		What-if		Data Points
Occupational non-users					
Pre EC	2.60		1.49		1

Source: (OSHA, 2013).
What-if: Represents a what-if inhalation exposure level for occupational non-user based on a single data point.

2.1.6.4 Assessment of Inhalation Exposure Based on Exposure Modeling

A more detailed description of the modeling approach is provided in Appendix J. The EPA AP-42, Compilations of Air Pollution Emission Factors contains emission factors and process information developed and compiled from source test data, material balance studies, and engineering estimates (U.S. EPA, 1981). Chapter 4.6 provides generic, non-methane VOC emission factors for several solvent cleaning operations, including cold cleaning and vapor degreasing. These emission factors suggest that cold cleaning emissions range from 3.2 to 57.1 percent of the emissions from a traditional open-top vapor degreaser (U.S. EPA, 1981). To model exposures during 1-BP cold cleaning, an exposure reduction factor, RF, with uniform distribution from 0.032 to 0.571 is applied to the vapor degreasing model.

Figure 2-11 presents the model approach for cold cleaning. Except for the exposure reduction factor, the model approach and input parameters for cold cleaning are identical to those previously presented for vapor degreasing. EPA/OPPT performed a Monte Carlo simulation with one million iterations and the Latin Hypercube sampling method in @Risk to estimate 8-hr TWA near-field and far-field exposures. EPA/OPPT then used these model exposure estimates to calculate acute exposure, ADC, and LADC. Note the cold cleaning model approach and the underlying data used (i.e. EPA AP-42) do not differentiate between a spray versus immersion cold cleaner.

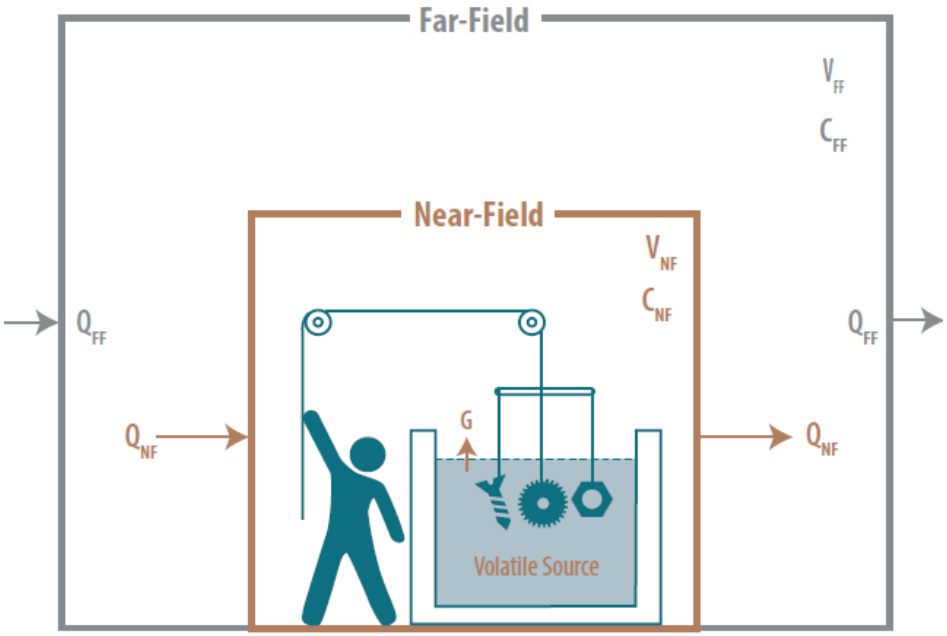


Figure 2-11 The Near-Field/Far-field Model for Cold Cleaning Scenario

Table 2-12 presents a statistical summary of the exposure modeling results. Estimates of Acute Concentration (AC), Average Daily Concentrations (ADC) and Lifetime Average Daily Concentration (LADC) for use in assessing risk were made using the approach and equations described in Appendix H. For workers, the pre-EC exposures are 0.442 ppm 8-hr TWA at the 50th percentile and 7.82 ppm 8-hr TWA at the 95th percentile. These exposure levels are substantially lower than actual monitoring data. This may be because the model assumes the cold cleaner only operates two hours per day, which could underestimate exposure if the equipment is operated for a longer duration. For occupational non-users, the pre-EC exposures are 0.168 ppm at the 50th percentile and 2.88 ppm 8-hr TWA at the 95th percentile. With engineering controls, these exposures are further reduced, with some being reduced to levels below the ACGIH TLV of 0.1 ppm. We assume the engineering control effectiveness would be similar to that of a vapor degreaser.

Table 2-12 Statistical Summary of 1-BP 8-hr TWA Exposures (AC, ADC and LADC) for Cold Cleaning Based on Modeling

Category	Acute and Chronic, Non-Cancer Exposures (8-Hour TWAs in ppm) $AC_{1\text{-}BP,\ 8\text{-}hr\ TWA}$ and $ADC_{1\text{-}BP,\ 8\text{-}hr\ TWA}$		Chronic, Cancer Exposures (ppm) $LADC_{1\text{-}BP,\ 8\text{-}hr\ TWA}$	
	95th Percentile	50th Percentile	95th Percentile	50th Percentile
Workers (Near-Field)				
Pre EC	7.82	0.442	4.47	0.253
Post EC 90%	0.782	0.0442	0.447	0.0253
Post EC 98%	0.156	0.00884	0.0894	0.00505
Occupational non-users (Far-Field)				
Pre EC	2.88	0.168	1.65	0.0962
Post EC 90%	0.288	0.0168	0.165	0.00962
Post EC 98%	0.0575	0.00336	0.0329	0.00192

AC = Acute Concentration; ADC = Average Daily Concentration and LADC = Lifetime Average Daily Concentration.

Pre-EC: refers to modeling where no reduction due to engineering controls was assumed.

Post-EC: refers to modeling where engineering controls with a 90% efficiency implemented or equipment substitution with 98% efficiency.

2.1.7 Aerosol Degreasing

2.1.7.1 Process and Worker Activity Descriptions

Aerosol degreasing is a process that uses an aerosolized solvent spray, typically applied from a pressurized can, to remove residual contaminants from fabricated parts. The aerosol droplets bead up on the fabricated part and then drip off, carrying away any contaminants and leaving behind a clean surface.

Figure 2-12 illustrates the typical process of using aerosol degreasing to clean components in commercial settings. One example of a commercial setting with aerosol degreasing operations is repair shops, where service items are cleaned to remove any contaminants that would otherwise compromise the service item's operation. Internal components may be cleaned in place or removed from the service item, cleaned, and then re-installed once dry (U.S. EPA, 2014a).

Figure 2-12 Overview of Aerosol degreasing

2.1.7.2 Estimate of the Number of Workers Potentially Exposed

NAICS industry sectors relevant to aerosol degreasing and BLS occupation codes where workers are potentially exposed to degreasing solvents are detailed in Appendix F. EPA/OPPT assumed the types of occupation with potential solvent exposure are similar between vapor degreasing and aerosol degreasing.

There are 222,940 establishments among the industry sectors presented in Table 2-13. The EPA/OPPT market report on 1-BP estimated that "*1,000 to 5,000 businesses used 1-BP-based aerosol solvents in 2002* (U.S. EPA, 2007b), as cited in (U.S. EPA, 2013c)". This translates to a market penetration of approximately 0.4 percent to 2.2 percent. Based on these estimates, approximately 2,466 to 12,329 workers and occupational non-users are potentially exposed to 1-BP as an aerosol degreasing solvent. It is unclear whether the number of establishments using 1-BP-based aerosol solvents has increased since 2002.

Table 2-13 Estimated Number of Workers Potentially Exposed to 1-BP in Aerosol Degreasing

Exposed Workers	Exposed Occupational non-users	Total Exposed	Estimated Number of Establishments	Workers per Site	Occupational non-users per Site
Low-end					
2,227	238	2,466	1,000	2	0.2
High-end					
11,137	1,192	12,329	5,000	2	0.2

Note: Number of workers and occupational non-users per site are calculated by dividing the exposed number of workers or occupational non-users by the number of establishments. The number of workers per site is rounded to the nearest integer. The number of occupational non-users per site is shown as 0.2, as it rounds down to zero.

2.1.7.3 Assessment of Inhalation Exposure Based on Monitoring Data

Table 2-14 summarizes 8-hr TWA PBZ monitoring data for aerosol degreasing obtained from (Stewart, 1998) and (Tech Spray, 2003). The Stewart (1998) study measured 1-BP worker PBZ during an aerosol spray can application on a test substrate consisting of a small electric motor; the scenario was intended to simulate workers performing typical repair and maintenance work. The (Tech Spray, 2003) study measured worker exposure in a test scenario that simulated cleaning of printed circuit boards for the repair of computers and electrical systems. Among the two test studies, the 95th and 50th percentile worker exposures were 31.6 and 16.1 ppm, respectively.

The Tech Spray study tested an exposure scenario where the aerosol degreasing occurred inside a non-vented booth. Subsequently, the company tested the same scenario in a vented booth. With a non-vented booth, worker exposure ranged from 13 to 32 ppm 8-hr TWA. With the vented booth, worker exposure was reduced to 5.50 ppm 8-hr TWA based on a single data point. The data suggest the significance of ventilation and its impact on worker exposure. The single data point for worker exposure with a vented booth represents a "what-if" exposure level for a post-EC scenario. The representativeness of this exposure level is unknown.

Table 2-14 Summary of Inhalation Exposure Monitoring Data for Aerosol Degreasing

Category	Acute and Chronic, Non-Cancer Exposures (8-Hour TWAs in ppm) $AC_{1\text{-BP, 8-hr TWA}}$ and $ADC_{1\text{-BP, 8-hr TWA}}$		Chronic, Cancer Exposures (ppm) $LADC_{1\text{-BP, 8-hr TWA}}$		Data Points
	95th Percentile	50th Percentile	95th Percentile	50th Percentile	
Workers [a]					
Pre EC	31.6	16.1	18.0	9.17	7
Category	What-if		What-if		Data Points
Post EC	5.50		3.14		1

Source: Stewart (1998); Tech Spray (2003), as cited in (U.S. EPA, 2006b).
What-if: Represents a what-if inhalation exposure level based on a single data point.
[a] Worker includes operators, technicians, mechanics, and maintenance supervisor.

In addition to the data summarized above, the Tech Spray study included a test scenario that measured short-term worker exposure that simulated an automotive repair shop. In this test, 1-BP was sprayed continuously over a 15-minute period. In reality, workers are only expected to spray 1-BP for a few minutes at a time; as such, the test was intended to simulate a "worst-case" scenario with heavy 1-BP usage. The 15-min short term exposure for operators ranged from 190 to 1,100 ppm. Further, the 15-minute short term exposure for a worker in an adjacent room measured 11 ppm ((Tech Spray, 2003), as cited in (U.S. EPA, 2006b)). The presence of 1-BP in the adjacent room suggests the infiltration of contaminated air into other work areas.

2.1.7.4 Assessment of Inhalation Exposure Based on Modeling

A more detailed description of the modeling approach is provided in Appendix J. Figure 2-13 illustrates the near-field/far-field for the aerosol degreasing scenario. As the figure shows, 1-BP in aerosolized droplets immediately volatilizes into the near-field, resulting in worker exposures at a concentration C_{NF}. The concentration is directly proportional to the amount of aerosol degreaser applied by the worker, who is standing in the near-field-zone (i.e., the working zone). The volume of this zone is denoted by V_{NF}. The ventilation rate for the near-field zone (Q_{NF}) determines how quickly 1-BP dissipates into the far-field (i.e., the facility space surrounding the near-field), resulting in occupational non-user exposures to 1-BP at a concentration C_{FF}. V_{FF} denotes the volume of the far-field space into which the 1-BP dissipates out of the near-field. The ventilation rate for the surroundings, denoted by Q_{FF}, determines how quickly 1-BP dissipates out of the surrounding space and into the outside air.

In this scenario, 1-BP vapors enter the near-field in non-steady "bursts," where each burst results in a sudden rise in the near-field concentration, followed by a more gradual rise in the far-field concentration. The near-field and far-field concentrations then decay with time until the next burst causes a new rise in near-field concentration. For the purpose of modeling, it is assumed that a worker applies the aerosol degreaser once per hour with seven applications in an eight-hour work day. EPA/OPPT assumes a worker does not use the aerosol degreaser during the first hour of the day. EPA/OPPT assumes an application rate of 26.7 g degreaser/m^2 and a characteristic throughput of 7.2 m^2/day, based on data for oven cleaning (Golsteijn et al., 2014). It is uncertain whether this use rate is representative of a typical aerosol degreasing facility. In

addition, EPA/OPPT assumed the facility operates 260 days per year; this value is based on EPA's Generic Scenario for Use of Vapor Degreasers (developed by ERG (2001), which estimates degreasers of all sizes operate 260 days per year. EPA/OPPT assumed aerosol degreasers operate at the same frequency. Model parameters and assumptions for aerosol degreasing are presented in Appendix K.

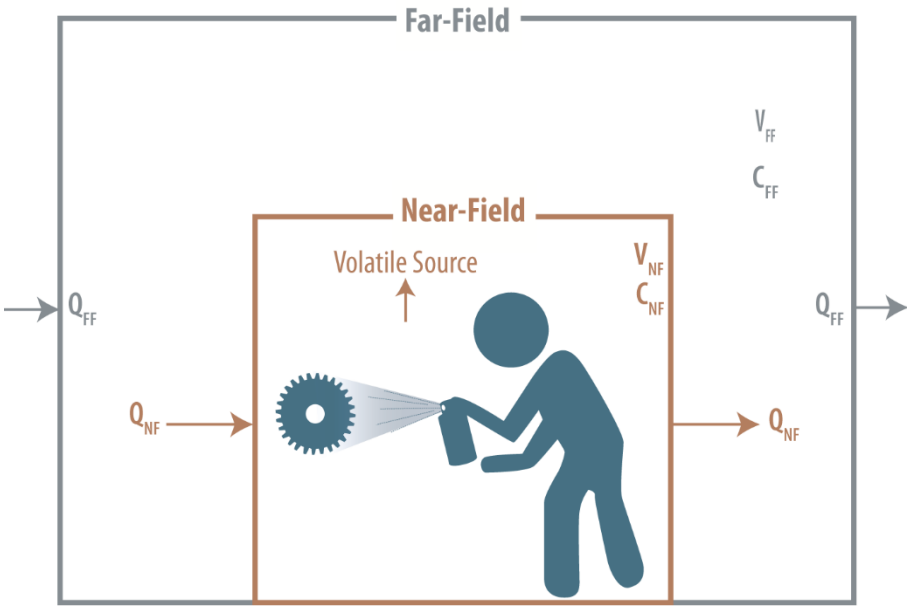


Figure 2-13 Schematic of the Near-Field/Far-Field Model for Aerosol degreasing

EPA/OPPT performed a Monte Carlo simulation with one million iterations and the Latin hypercube sampling method to model near-field and far-field exposure concentrations in the aerosol degreasing pre-EC scenario. Table 2-15 presents a statistical summary of the exposure modeling results. Estimates of Acute Concentration (AC), Average Daily Concentrations (ADC) and Lifetime Average Daily Concentration (LADC) for use in assessing risk were made using the approach and equations described in Appendix H.

For workers, the pre-EC exposures are 2.20 ppm 8-hr TWA at the 50th percentile, and 6.81 ppm 8-hr TWA at the 95th percentile. The model exposure levels are substantially lower than monitoring data. For occupational non-users, the model pre-EC exposures are 1.02 ppm at the 50th percentile and 3.42 ppm 8-hr TWA at the 95th percentile.

For the post-EC scenario, engineering control of local exhaust ventilation (LEV) is assumed to be 90 percent effective. Although worker and occupational non-user exposures are reduced by 90 percent, exposure level at the 95th and 50th percentile are still be above the ACGIH TLV of 0.1 ppm.

Table 2-15 Statistical Summary of 1-BP 8-hr TWA Exposures (AC, ADC and LADC) for Aerosol Degreasing Based on Modeling

Category	Acute and Chronic, Non-Cancer Exposures (8-Hour TWAs in ppm) $AC_{1\text{-}BP,\ 8\text{-}hr\ TWA}$ and $ADC_{1\text{-}BP,\ 8\text{-}hr\ TWA}$		Chronic, Cancer Exposures (ppm) $LADC_{1\text{-}BP,\ 8\text{-}hr\ TWA}$	
	95th Percentile	50th Percentile	95th Percentile	50th Percentile
Workers (Near-Field)				
Pre EC	6.81	2.20	3.89	1.26
Post EC 90%	0.681	0.220	0.389	0.126
Occupational non-users (Far-Field)				
Pre EC	3.42	1.02	1.95	0.583
Post EC 90%	0.342	0.102	0.195	0.0583

AC = Acute Concentration; ADC = Average Daily Concentration and LADC = Lifetime Average Daily Concentration. See Appendix H.
Pre-EC: refers to modeling where no reduction due to engineering controls was assumed
Post-EC: refers to modeling where engineering controls with a 90% efficiency were implemented

2.2 CONSUMER EXPOSURES

Consumer exposures have been assessed for the use of 1-BP in consumer products:

1. Aerosol spray adhesives (including spray adhesives and spray accelerant)
2. Aerosol spot removers
3. Aerosol cleaners and degreasers (including engine degreasing, brake cleaning, and electronics cleaning scenarios)

2.2.1 Approach and Methodology

EPA/OPPT selected consumer products containing 1-BP used as aerosol spray adhesives, aerosol spot removers, and aerosol cleaning and degreasing products for further risk evaluation. The decision to focus the assessment on these specific consumer products took into consideration (1) consumer use patterns, (2) information reported in Safety Data Sheets (SDS), and (3) potential risk to consumers.

EPA/OPPT searched the National Institutes of Health (NIH) Household Products Database, various government and trade association sources for products containing 1-BP, company websites for SDSs, *Kirk-Othmer Encyclopedia of Chemical Technology*, and the internet in general. The NIH Household Products Database and *Kirk-Othmer Encyclopedia of Chemical Technology* contained no relevant information on consumer products containing 1-BP. Through the other afore-mentioned search means, EPA/OPPT identified several products which contain 1-BP and are available to consumers (Table 2-16). There may be other consumer products containing 1-BP but not all SDSs display a complete list of chemical ingredients such that some products may contain 1-BP but cannot be confirmed by EPA/OPPT. The availability of products, listed in Table 2-16, ranging from 1 to 100 weight percent 1-BP raised sufficient concern to include these uses in this risk assessment. Additional uses and products (coin cleaning, refrigerant flush, and lubricant) were not further evaluated as reliable information regarding use practices such as mass of product used, room of use, method of use, and frequency of use were not readily available. While exposures from use of these products were not quantified, this does not imply that EPA/OPPT believes the exposure to be insignificant.

Table 2-16 Consumer Use Products Containing 1-BP

Use	Company	Product	% 1-BP (wt%)	Source
Aerosol Spray Adhesive	Maple Leaf Sales II	K-Grip 503	35-60	(Maple Leaf Sales II Inc., 2013)
	ITW TACC	STA'-PUT SP4H Canister Adhesive	35-60	(ITW Inc., 2014)
	Choice Brand Adhesives	751G	40-60	(Choice Brand Adhesives, 2010)
	Blair Rubber Company	Endurabond™ Normac 900R-NPB	60-85	(Blair Rubber Co., 2011)
	Satellite City [a]	NCF Accelerator	98-99	(Satellite City Instant Glues, 2015)
Aerosol Spot Remover	Albatross USA	Everblum Gold Cleaning Fluid	20-30	(Albatross USA Inc., 2015)
	EnviroTech	DrySolv Spray Testing & Spotter	>93	(Enviro Tech International, 2013)
	PettyJohn's Solutions	Homerun Cleaning Fluid	>96	(Pettyjohn's Solutions, 2012)
	The Sherwin-Williams Company [b]	SPRAYON LIQUI-SOL® Food Grade ULTRA-FORCE™ Safety Solvent & Degreaser	100	(Sherwin Williams, 2014)
Aerosol Cleaner or Degreaser	ITW Pro Brands	LPS Instant Super Degreaser	60-70	(ITW Pro Brands, 2015)
	ITW Pro Brands	LPS NoFlash Nu	60-70	(ITW Pro Brands, 2014)
	ZEP, Inc	Power Solv 5000	60-100	(ZEP, 2015)
	ACL, Inc	Precision Rinse NS	65-75	(ACL Inc., 2014)
	CRC Industries, Inc	Super Degreaser/Cleaner	90-100	(CRC Industries Inc., 2014)
	CRC Industries, Inc	Cable Clean RD	1-3	(CRC Industries Inc., 2015)
	MRO Solutions	525 Contact Cleaner	47-84	(MRO Solutions, 2015)
	Osborn	76334 High Tech Electronic Cleaner	50	(Osborn, 2015)
	ITW Chemtronics [b]	Electro-Wash NR	65-75	(ITW Chemtronics, 2008)
	ITW Chemtronics [b]	Kontact Restorer	65-75	(ITW Chemtronics, 2012)
	Sprayon	EL 2846 Non-Chlorinated Flash Free Electronic Solvent	96	(Sprayon Products, 2014)

Notes:
[a] Technically, the NCF Accelerator is added to another spray adhesive to make it dry more quickly.
[b] Not currently made by the manufacturer, but available on the secondary market.

In the absence of available emissions and monitoring data for use of consumer products containing 1-bromopropane (1-BP), a modeling approach was utilized to assess consumer exposure. Aerosol spray adhesive, spot remover, and cleaner and degreaser (brake cleaning, engine degreasing and electronics cleaning) scenarios were selected for exposure modeling.

2.2.1.1 Exposure Routes

Readily available information on the toxicity profile and physicochemical properties of 1-BP support inhalation as the primary route of exposure for human health concerns. Dermal exposures are possible; however, limited toxicological data are available for this route of exposure, and no toxicokinetic information is available to develop physiologically-based pharmacokinetic models or route-to-route extrapolations. Therefore, this assessment does not

evaluate aggregate exposures and may underestimate total exposures resulting from the uses of 1-BP due to this assumption.

Based on anticipated use patterns of aerosol spray adhesives, aerosol spot removers, and aerosol spray cleaners and degreasers by consumers and non-users in residential settings, acute exposures via the inhalation route were the primary scenarios of interest. EPA/OPPT assumed that consumer users would generally be male or female adults (>16 and older, including women of childbearing age), although exposures to adolescents or younger individuals may be possible. Acute inhalation exposure to 1-BP for both user and non-user were quantified using modeling approaches as monitoring data was not readily available to estimate air concentrations.

2.2.1.2 Overview of the E-FAST-2/CEM Model

The Exposure and Fate Assessment Screening Tool Version 2 (E-FAST2) Consumer Exposure Module (CEM) was selected for the consumer exposure modeling as the most appropriate model to use due to the lack of available emissions and monitoring data for the 1-BP uses under consideration. Moreover, EPA/OPPT did not have the input parameter data required to run more complex indoor air models for the consumer products under the scope of this assessment. CEM uses high-end input parameters/assumptions to generate conservative, upper-bound inhalation exposure estimates for aerosol spray products. The advantages of CEM are the following:

1. CEM model has been peer-reviewed.
2. CEM accommodates the inputs available for the products containing 1-BP in the indoor air model.
3. CEM uses the same calculation engine to compute indoor air concentrations from a source as the Multi-Chamber Concentration and Exposure Model (MCCEM), but does not require measured emission values (e.g. chamber studies).

The model used a two-zone representation of a house to calculate the potential acute dose rate (mg/kg-bw/day) of 1-BP for users and non-users. Zone 1 represents the area where the consumer is using the product, whereas Zone 2 represents the remainder of the house. Zone 2 was used for modeling passive exposure to non-users in the home (bystanders), such as children, adults, women of child bearing age, and the elderly.
The general steps of the calculation engine within the CEM model included:

1. Introduction of the chemical (i.e., 1-BP) into the room of use (Zone 1),
2. Transfer of the chemical to the rest of the house (Zone 2) due to exchange of air between the different rooms,
3. Exchange of the house air with outdoor air and,
4. Summation of the exposure doses as the modeled occupant moves about the house

The chemical of concern (i.e., 1-BP) enters the room air through two pathways: (1) overspray of the product and (2) evaporation from a thin film. One percent (1%) of the product was assumed to become instantly aerosolized (i.e. product overspray) and was available for inhalation.

The CEM model uses data from the evaporation of a chemical film to calculate the rate of the mass evaporating from the application surface covered during product use (DTIC DLA, 1981). The model assumes air exchanges from the room of use (Zone 1) and the rest of the house (Zone 2)

according to interzonal flow. The model also allows air exchange from the house (Zone 1 & 2) with the outdoor air.

EPA/OPPT used the default activity pattern in CEM based on the occupant being present in the home for most of the day. As the occupants moved around the house in the model, their exposure to the calculated air concentrations were summed to estimate a potential 24-hr dose.

The potential inhalation acute dose rates (ADR_{pot}) are computed iteratively by calculating the peak concentrations for each simulated 10-second interval and then summing the doses over 24 hrs. These calculations take into consideration the chemical emission rate over time, the volume of the house and the zone of use, the air exchange rate and interzonal airflow rate, the exposed individual's locations, body weights and inhalation rates during and after the product use. The reader is referred to EPA's E-FAST2 website (http://www.epa.gov/tsca-screening-tools/e-fast-exposure-and-fate-assessment-screening-tool-version-2014) and Appendix L to obtain additional information about the model, including the model documentation and algorithms used.

2.2.1.3 Consumer Model Scenario and Input Parameters for Indoor Exposure to Specific 1-BP Uses

Table 2-17 describes the acute inhalation indoor scenarios and populations of interest that EPA/OPPT evaluated in the consumer exposure assessment. As indicated in Section 2.2.1.1, EPA/OPPT believes that inhalation is the main exposure pathway. Exposure via ingestion from the use of these consumer products appears to be unlikely based on the intended method of use (i.e., spray application).

Table 2-17 Consumer Model Scenarios and Populations of Interest

Acute Inhalation Indoor Scenario	Population of Interest	
	Consumer User	Non-User
Aerosol Spray Adhesive Use	Adult Consumers >16 yrs old	Individuals of all ages
Aerosol Spot Remover Use	Adult Consumers >16 yrs old	Individuals of all ages
Aerosol Spray Cleaner and Degreaser Use (engine degreasing, brake cleaning, electronics cleaning)	Adult Consumers >16 yrs old	Individuals of all ages

To estimate exposures to these products, numerous input parameters are required to generate a single exposure estimate. These parameters include the characteristics of the house, the behavior of the consumer and the emission rate of the chemical into the room of use. In the absence of measured values for many of the needed inputs, the E-FAST2/CEM modeling for 1-BP used a combination of upper (90th) percentile, mean, and median input parameters and assumptions in the calculation of potential exposure for consumer users and non-users. This approach produced high-end (90th percentile) and central tendency (50th percentile) acute inhalation estimates that

are hypothetical. The general input parameters and assumptions are summarized in Table 2-18 and the input values specific to each use scenario are summarized and explained more fully in Appendix L.

Table 2-18 Product Use Input Parameters for CEM Modeling

Modeling Parameter	All Consumer Use Scenarios	Source and Description of Parameter Selection
Molecular weight (g/mol)	123	The Merck Index (2013); as shown in Table 1-1.
Vapor pressure (torr)	146.2	The Merck Index (2013); as shown in Table 1-1.
Frequency of use, acute (events/day)	1	Assumed to occur no more than once per day for acute exposures.
Air exchange rate - air exchanges per hour (ACH)	0.45	Recommended 50th percentile value of residential air exchange rate for all regions within the United States Koontz (1995), based on EPA (2011).
Overspray fraction	0.01	Selection based on professional judgment (Patrick Kennedy, 1990 as cited in E-FAST). It should be noted that the CEM model is insensitive to this parameter.
Emission rate constant ($hours^{-1}$)	183.09	Estimated using Chinn's algorithm (DTIC DLA, 1981), based on E-FAST model documentation. This algorithm utilizes molecular weight and vapor pressure to estimate emission rates.
Exposure duration, acute (days)	1	General (hypothetical) assumptions used for CEM modeling in absence of consumer product data for 1-Bromopropane.
Whole house volume (m^3)	492	Volume of house where product is applied. Mean value recommended for use as a central tendency for all single family homes, including mobile homes and multifamily units. This US EPA recommended value was taken from Exposure Factors Handbook (EFH) (2011)

Consumer behavior pattern parameters in CEM include the mass of product used, the duration of use and the frequency of use. Although the default values in CEM for these consumer behavior parameters are set to high end values, they were *not* used in this risk assessment. The other parameters (e.g. house volume) in CEM are set to mean or median values obtained from the literature. A combination of high end and mean or median values was utilized to produce high end acute inhalation exposure estimates, whereas a combination of mean and median values was used to produce central tendency acute inhalation exposure estimates.

To determine the appropriateness of the consumer behavior pattern parameters chosen in this risk assessment, EPA/OPPT examined the consumer categories available in the Westat (1987) survey. The authors of the Westat (1987) survey contacted thousands of Americans to gather information on consumer behavior patterns related to product categories that may contain halogenated solvents. The Westat (1987) survey data aligned reasonably well with the description of the products that were used in this consumer exposure assessment. The data informed the values that EPA/OPPT used for the mass of product used, and the time spent in the room of use

when considering all surveyed individuals who identified as users of spray adhesives, spot removers, engine cleaners, brake cleaners or electronics cleaners.

The input parameter for house volume was taken from the Exposure Factors Handbook (2011). The room volume for aerosol spray adhesives and aerosol spot removers was calculated as a proxy utility room measuring 9 ft x 10 ft, with 8 ft ceilings (U.S. EPA, 2014c). The area of use most frequently cited for aerosol degreasers and cleaners (used as engine degreasers and brake cleaners) was the outdoors. However, CEM does not have a module for outdoor use, therefore, the modeling for these use scenarios designated the room of use (zone 1) as the garage. While this presents a more conservative estimate, it should be noted that users surveyed in the Westat (1987) report also reported use in the garage. The E-FAST model does not include a garage volume in its default room parameters, thus the median garage volume from a 2007 indoor air quality study (Batterman et al., 2007) of 15 homes in Michigan was used as a reasonable proxy value. The room of use most frequently cited in the (1987) Westat survey for electronics cleaning was the living room; therefore a room volume of 48 m^3 (U.S. EPA, 2011) was used to estimate exposure from this use.

The user's body weight and inhalation rate were set to either the mean or the median values from the Exposure Factors Handbook (2011) for the simulations used in this assessment.

The air exchange rate in the room of use does not take into consideration open windows or the use of an exhaust fan. While it is possible that some users may employ these exposure reduction techniques inside their homes, the goal of the consumer exposure assessment was to provide an acute exposure estimate for ventilation conditions representing average household air exchange rates. Moreover, residential users would not necessarily have the type of indoor exposure reduction tools/equipment (e.g., gloves, exhaust ventilation) that workers are likely to have in occupational settings. Consumers may not necessarily be as aware of potential chemical hazards as workers and would not have a standard operating procedure in place to assure that they use exposure reduction techniques each time they use a product.

In this assessment it was assumed that there was no pre-existing concentration of 1-BP in the home before product use began. The outdoor air was also assumed to be free of 1-BP, meaning that the air exchange rate described the intake of air with no pre-existing 1-BP contamination.

The products were assumed to be sprayed on varying surfaces, where a thin film of the product was assumed to build up, evaporate, and contribute to the air concentration of the chemical in the room. We relied on modeled emission rates because data from chamber studies were not available. To generate emission rates, E-FAST2/CEM used empirical data from studies assessing the emission rates of pure solvents (DTIC DLA, 1981). E-FAST2/CEM used the Chinn study as surrogate data to calculate the rate of evaporation of 1-BP from the surface to the air in the home.

These solvent studies supported the use of an exponentially decaying emission rate for 1-BP from the application surface based on vapor pressure and molecular weight (DTIC DLA, 1981), the equations using the Chinn method are in Appendix L. The spot remover application should be well

modeled by the Chinn study since the spot remover product was over 90% 1-BP. On the other hand, the spray adhesive product may have more components, and the interaction of these chemicals could alter the evaporation rate of 1-BP. This introduces uncertainty into the assessment, however EPA/OPPT could not find a better data set available to model the emission rates. Within the current exposure assessment, the 24-hr exposure was not strongly dependent on the emission rate due to the amount of time the product user spends in the room of use (see Appendix L for details).

2.2.1.4 Consumer Model Results

The 'Aerosol Paint' default scenario within the Consumer Exposure Module (CEM) of the E-FAST model was chosen for conducting the modeling runs. This selection was the closest match to the spray adhesive scenario among the default CEM exposure scenarios. The common modeling inputs required to run CEM for all consumer scenarios evaluated in this assessment are provided in Table 2-18. Table 2-18 also has a brief explanation of the source of each parameter and the justification for the parameter selection. Other scenario-specific input parameters are provided in Appendix L. The body weight and inhalation rates for adults (age group 21 to 78) and other age groups are provided in the appendices.

CEM calculated air concentrations over the course of the simulation for the room of use and the rest of the house (Zone 1 and Zone 2). These concentrations were converted to acute dose rates (ADRs) using the body weight and respiration rate for each age group. The varying weight and respiration rates of the different age groups resulted in different doses; younger age groups had a higher ratio of inhalation rate to body mass creating a larger dose for a given air concentration of a chemical. However, the same air concentrations were used to generate the doses for each age group within the model's calculation engine. The standard output files for CEM did not include the air concentrations for the different parts of the house, only the doses were included.

Table 2-19 presents the results of the conversion from potential acute dose rates (mg/kg-bw/day) to indoor air concentrations (ppm) for the user and bystander, with both central tendency (50th percentile) and high end (90th percentile) estimated exposures for the consumer use scenarios. Calculations detailing the conversion from acute dose rates to air concentrations are provided in a supplemental Excel spreadsheet file.[6] The indoor air concentrations shown in Table 2-19 could be applied to users of different age groups. Although adults are generally the users of these products, EPA/OPPT cannot rule out scenarios where teenagers or younger children may be users or be in the same room with the user during use of the product.

[6] See attached document titled "Consumer Exposure Calculations.xlsx".

Table 2-19 Estimated[a] 1-BP Air Concentrations (Time Averaged Over 1 Day) Based on Residential Indoor Use of Spray Adhesives or Aerosol Removers

Consumer Use Scenario	Air Concentration[a] (ppm)			
	Central Tendency[b] (50th percentile)		High End[c] (90th percentile)	
	User[d]	Non-User[e]	User[d]	Non-User[e]
Aerosol Spray Adhesive	0.5	0.1	6	2
Aerosol Spot Remover	2	0.7	23	6
Aerosol Spray Cleaners and Degreasers				
Engine Degreasing Use	16	6	54	20
Brake Cleaning Use	5	2	22	8
Electronics Cleaning Use	0.5	0.2	7	3

Notes:

[a] See Appendix K for details about the model inputs and the method used to convert acute dose rates (ADRs) to air concentrations of 1-BP.

[b] Central tendency estimate based on using 50th percentile values for use patterns from Westat Survey (1987). See Appendix L for additional details.

[c] High end estimate based on using 90th percentile values for use patterns from Westat Survey, (1987). See Appendix L for additional details.

[d] Air concentrations for the user categories can be extended to different age groups, however, EPA/OPPT believes the users of these products to be adults.

[e] All age categories (<1 yrs; 1-2 yrs; 3-5 yrs; 6-10 yrs; 11-15 yrs; 16-20yrs; and >21 yrs)

Detailed CEM modeling results are provided in Appendix L

CEM has certain restrictions on the age that is assumed for simulated users, which in turn sets limits for the dose rates generated for different age groups. However, these restrictions should not be interpreted as suggesting that younger users would not be exposed. EPA/OPPT believes that the users of these products are generally adults, but teenagers or younger children may be users or may be in the same room with the user. Since there are not survey data for consumer behavior patterns or a way to create varying behavior patterns for different age groups, the indoor air concentrations shown in Table 2-19 could be extended to all users.

The model output reports the peak concentration of 1-BP, however this air concentration was not used in the risk assessment. The peak concentration was the highest concentration among all of the 10-second time intervals that CEM simulated within a 24-hr period. The peak concentration may only exist in the room of use for a short duration and was not considered a good indicator of what the concentration of 1-BP would be for longer time periods. Thus, we did not use the peak concentration in the risk assessment as it was not representative of a 24-hr exposure.

Lastly, a chronic consumer exposure assessment was not performed because the frequency of product used was considered to be too low to create chronic exposure concerns. Although CEM model results given in the supplemental information included chronic exposure estimates, they were not used in this assessment.

2.2.1.5 Sensitivity of Model Parameters

In order to explore the dependencies of chemical concentrations in air on modeled parameters, a sensitivity analysis was performed based on the nominal range sensitivity analysis method (Frey and Patil, 2002). Using this approach, a 'baseline scenario' is first defined which is a modeling scenario that consists of central tendency values. For this sensitivity analysis, we considered the spray adhesive scenario for adults as the baseline scenario. This baseline scenario was based on a consumer using a spray adhesive product containing 85% 1-BP in a residential setting. After identifying the base case, the next step is to systematically vary the input parameters one at a time and capture the subsequent model responses. For this sensitivity analysis, we chose the ADR and acute air concentrations as the representative model outputs to observe model responses.

Methodology

The sensitivity analysis was carried out in a two-tiered approach. The Tier 1 model runs were conducted in order to identify the key input parameters that the model was most sensitive to. After having identified the key input parameters, the Tier 2 runs were focused on a more detailed analysis of the model responses to these key input parameters. Thus, the Tier 2 runs could be considered to be a more 'refined' approach to measuring model sensitivity to key inputs. Model responses were analyzed by calculating the "index of sensitivity" for each model scenario. The "index of sensitivity" can be defined as the percent change in magnitude of the model output with respect to the baseline scenario output. Nine CEM input parameters were selected for the sensitivity testing and the remaining were treated as static parameters.

Tier 1 analysis

For the Tier 1 analysis, a plausible range of values was established for each input parameter. This range consisted of a low, medium (baseline scenario), and high value. These plausible values and the justification for the parameter selection for each input parameter are provided in Appendix K, Table_Apx L-5**.**

The plausible inputs for each parameter were varied one at a time and the model responses (i.e., changes in the ADR and acute concentration values) were noted. The results were first ranked by their output differences using the maximum response value minus the minimum response value of the plausible range and then by their index of sensitivity. The "index of sensitivity" was calculated by dividing the percent change in ADR by the percent change of the input values for each parameter. The rankings from both were averaged for an overall rank for each parameter tested. This exercise was repeated for the acute air concentration results.

The resulting ADRs (mg/kg-bw) and acute air concentrations (ppm) along with the rankings for each of the tested parameters are provided in Appendix K, Table_Apx L-6 and Table_Apx L-7.

The Tier 1 analysis indicated that the four most sensitive parameters affecting the ADR and the acute air concentration were as follows:

Acute Dose Rate

1. mass of product used per use;
2. whole house volume;
3. air exchange rate; and
4. body weight.

Acute air concentration

1. mass of product used per use;
2. whole house volume;
3. air exchange rate; and
4. consumer product weight fraction.

The parameter most influential in determining the acute dose rate and acute air concentration is the mass of product applied per use. The emission rate is directly dependent upon the chemical properties such as vapor pressure and because 1-BP is quite volatile, the mass of product used subsequently strongly influences the air concentration and dose rate. Because the modeled scenario follows the user over a 24 hour period limiting the period of use to 0.5 hrs in the utility room, the whole house volumes (the remaining 23.5 hours) plays a larger factor in influencing the final acute dose rate and acute air concentration. As shown in Appendix L Table_Apx L-6 and Table_Apx L-7, the air exchange rate and product weight fraction can influence the contaminant concentration but do not play as large a role in the final outcome. The above-mentioned 5 input parameters were chosen for the Tier 2 analysis.

Tier 2 Analysis

For the Tier 2 analysis, all the parameters were adjusted by equal increments from the base value. All of the baseline input values were adjusted by -10% and +10% to calculate sensitivity near the baseline value and by -50% and +50% to calculate sensitivity for values farther removed from the baseline value. The baseline scenario was the same baseline scenario that was used for the Tier 1 analysis with the exception of the consumer product weight fraction. Due to a limitation with this value (since the baseline consumer weight fraction was 85% and we could not increase that by 50% as the model would only consider weight fractions that were less than 100%) the consumer product weight fraction was lowered from 85% to 50% for the baseline scenario. The inputs for the Tier 2 analysis are provided in Appendix K, Table_Apx L-8.

Similar to the protocol followed in the Tier 1 analysis, the input parameters were varied one at a time and the model responses (ADR and acute concentration) were recorded. There were a total of four variable runs for each parameter. The sensitivity was calculated near the base value (-10% and +10%) and farther removed from the base value (-50% and +50%) for each of the tested parameters. Appendix K Table_Apx L-9 provides the calculated sensitivities for the parameters affecting the ADR and Table_Apx L-10 provides the calculated sensitivities for the parameter affecting the acute air concentration.

Results of the Tier 2 analysis indicate that the CEM model is most sensitive to changes in body weight when using the ADR as the model output since the air concentrations are consistent depending on whether you are the user or bystander. When the acute concentration is used as the model output, the CEM model is most sensitive to the mass of product used. It should be noted that the sensitivity analysis was conducted using some hypothetical values that were based solely on mathematical interpolation. Although some of these values might not correspond to actual product uses based on aerosol spray adhesive, spot remover, or degreasing/cleaning scenarios, they lend themselves in the overall understanding of the model sensitivity.

3 HUMAN HEALTH HAZARD ASSESSMENT

Figure 3-1 depicts the process EPA/OPPT used to review and select studies used in the 1-BP risk assessment. EPA/OPPT reviewed EPA assessments (U.S. EPA, 2007b), the primary peer reviewed literature and secondary sources (NTP, 2013; NTP-CERHR, 2003) identified through August 2015 to identify key endpoints (Section 3.2), meaning those that are relevant, sensitive and found in multiple studies. (EPA/OPPT notes that an EPA Integrated Risk Information System (IRIS) toxicological review is not currently available for 1-BP). Once key endpoints were identified, EPA/OPPT collected all publicly available data to refine the hazard characterization and conduct dose-response analysis and benchmark dose modeling.

A comprehensive summary table which includes all endpoints considered for this assessment can be found in Appendix O. Additional information on data quality criteria used for selection of key studies is provided in Appendix M. All endpoints were evaluated for consistency, sensitivity and human relevance. Based on this review, EPA/OPPT narrowed the focus of the 1-BP hazard characterization to liver toxicity, kidney toxicity, reproductive/developmental toxicity, neurotoxicity, and cancer (brief summaries are presented for each hazard endpoint in Section 3.2). In addition, a summary of key studies and endpoints carried forward in the risk assessment can be found in Table 3-1, including the no-observed- or lowest-observed-adverse-effect levels (NOAEL and LOAEL) for health endpoints by target organ/system, the corresponding benchmark dose lower confidence limits (BMDLs), when available, and the corresponding human equivalent concentrations (HECs), and uncertainty factors (UFs).

These key studies provided the dose-response information necessary for selection of points of departure (PODs)[7]. EPA defines a POD as the dose-response point that marks the beginning of a low-dose extrapolation. This point can be the lower bound on the dose for an estimated incidence, or a change in response level from a dose-response model (e.g., benchmark dose or BMD), a NOAEL value, or a lowest-observed-adverse-effect level (LOAEL) for an observed incidence, or a change in the level (i.e., intensity) of a given response. PODs were adjusted as appropriate to conform to the specific exposure scenarios evaluated.

[7] A point of departure (POD) is a dose-response point that marks the beginning of a low-dose extrapolation. This point can be the lower bound on dose for an estimated incidence or a change in response level from a dose-response model (BMD), or a NOAEL or LOAEL for an observed incidence, or change in level of response (U.S. EPA, 2002).

The dose-response assessment used for selection of PODs for cancer and non-cancer endpoints and the benchmark dose analysis used for use in the risk characterization are found in Section 3.4. Development of the 1-BP hazard and dose-response assessments considered principles set forth in various risk assessment guidance, and guidelines issued by the National Research Council and the U.S. EPA. Limited toxicological data are available by the oral and dermal routes. Because physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) models that would facilitate route-to-route extrapolation have not been identified for 1-BP, only studies conducted via the inhalation route of exposure were evaluated in this assessment. There are no relevant kinetic or metabolic information for 1-BP that would facilitate development of dosimetric comparisons. In accordance with EPA guidance, the exposure concentrations used in animal studies were adjusted according to the ratio of the blood:air partition coefficients, where a default ratio of 1 is applied when the partition coefficient for rats is greater than that of humans (U.S. EPA, 2002, 1994). For HEC calculations, these exposure concentrations were further adjusted from the exposure durations used in animal studies to durations deemed relevant for human exposure scenarios (e.g., 8-hours/day and 5 days/week for occupational exposures).

EPA/OPPT consulted EPA's Guidelines for Developmental Toxicity Risk Assessment when making the decision to use developmental toxicity studies to evaluate risks that may be associated with acute exposure to 1-BP during occupational or consumer use of spray adhesive, dry cleaning or degreasing products that contain 1-BP. This decision is based on EPA policy, and assumes that a single exposure during a critical window of fetal development may produce adverse developmental effects (U.S. EPA, 1991).

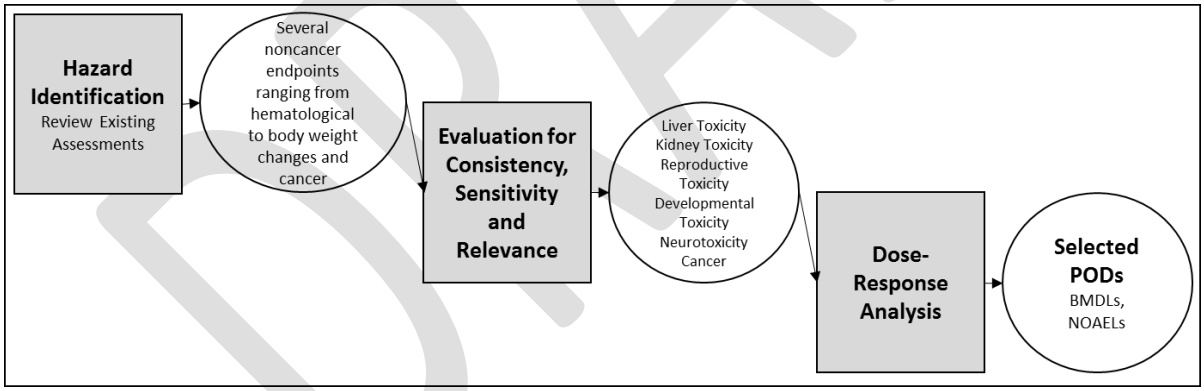


Figure 3-1 Hazard Identification and Dose-Response Process

3.1 Toxicokinetics

Studies in humans and laboratory animals show that 1-BP may be absorbed following oral, inhalation or dermal exposure; however, dermal and inhalation pathways are expected to be more relevant for occupational exposures (Frasch et al., 2011; Hanley et al., 2009; NIOSH, 2007; Garner et al., 2006; Jones and Walsh, 1979). The extent of absorption via the inhalation route depends on the rate of transfer from pulmonary capillaries to blood (i.e., blood/air partition coefficient), and the rate of metabolism in various tissue compartments.

The blood:air partition coefficients calculated for 1-BP in rats (11.7) and humans (7.08) indicate that it is readily absorbed (Meulenberg and Vijverberg, 2000). Upon uptake, 1-BP distribution via the systemic circulation follows the individual tissue/blood partition coefficients for respective tissue compartments. The fat:blood partition coefficient (calculated as the ratio of fat:air and blood:air partition coefficients) for 1-BP in rats (20) and humans (18) suggests that it may partition to fat (Meulenberg and Vijverberg, 2000). Higher partitioning to muscle, liver and fat has been predicted for 1-BP in female versus male rats (ECHA, 2012d).

Metabolism studies in rats and mice have shown that 1-BP can directly conjugate with glutathione forming N-acetyl-S-propyl cysteine, or be oxidized via cytochrome P450 enzymes (primarily CYP2E1) to reactive metabolites that can be further oxidized and/or conjugated with glutathione (Jones and Walsh, 1979; Barnsley et al., 1966) (Figure 3-2). Gluthathione conjugates formed via the glutathione-S-transferase catalyzed pathway are eventually excreted as mercapturic acid derivatives in urine. Although both pathways remain operative, the CYP2E1 pathway generally predominates at lower exposure concentrations (Garner et al., 2006).

Further evidence for the specific contribution of CYP2E1 to 1-BP metabolism is provided by studies with $Cyp2e1^{-/-}$ knockout mice (Garner et al., 2007) which show the elimination half-life in these animals to be more than twice that seen in wild type mice (3.2 vs. 1.3 hours, respectively) following 1-BP inhalation exposure. The ratio of glutathione conjugation to 2-hydroxylation reactions increased 5-fold in $Cyp2e1^{-/-}$ versus wild-type mice. Earlier work from this laboratory has shown that administration of 1-aminobenzotriazole (a general suicide inhibitor of P450) caused nearly complete elimination of 1-BP oxidative metabolism, and a compensatory shift toward GSH conjugation in rats (Garner et al., 2006).

1-BP is rapidly eliminated from the body primarily via exhalation, with lesser amounts excreted in urine and feces (Garner and Yu, 2014; Garner et al., 2006; Ishidao et al., 2002). In gas uptake studies with male and female rats, the elimination half-times calculated for 1-BP decreased with increasing air concentrations (Garner and Yu, 2014). Terminal elimination half-times in male and female mice following 1-BP inhalation exposure at $\leq$ 800 ppm ranged from 0.5 to 2 hrs (Garner and Yu, 2014; Garner et al., 2006). (Garner et al., 2006) investigated the metabolism of 1-BP in male F344 rats and B6C3F1 mice following inhalation or tail vein injection and determined that the proportion of 1-BP metabolized via CYP2E1 oxidation versus glutathione conjugation was inversely proportional to dose in rats, but independent of dose in mice.

Occupational exposure studies have consistently identified significant correlations between 1-BP concentrations in ambient air and the levels of 1-BP or its metabolites in urine (Ichihara et al., 2004b; Kawai et al., 2001). N-acetyl-S-(n-propyl)-L-cysteine (AcPrCys), produced via direct glutathione conjugation of 1-BP, was the primary urinary metabolite detected in exposed workers (Hanley et al., 2010, 2009; NIOSH, 2007; Valentine et al., 2007; Hanley et al., 2006).

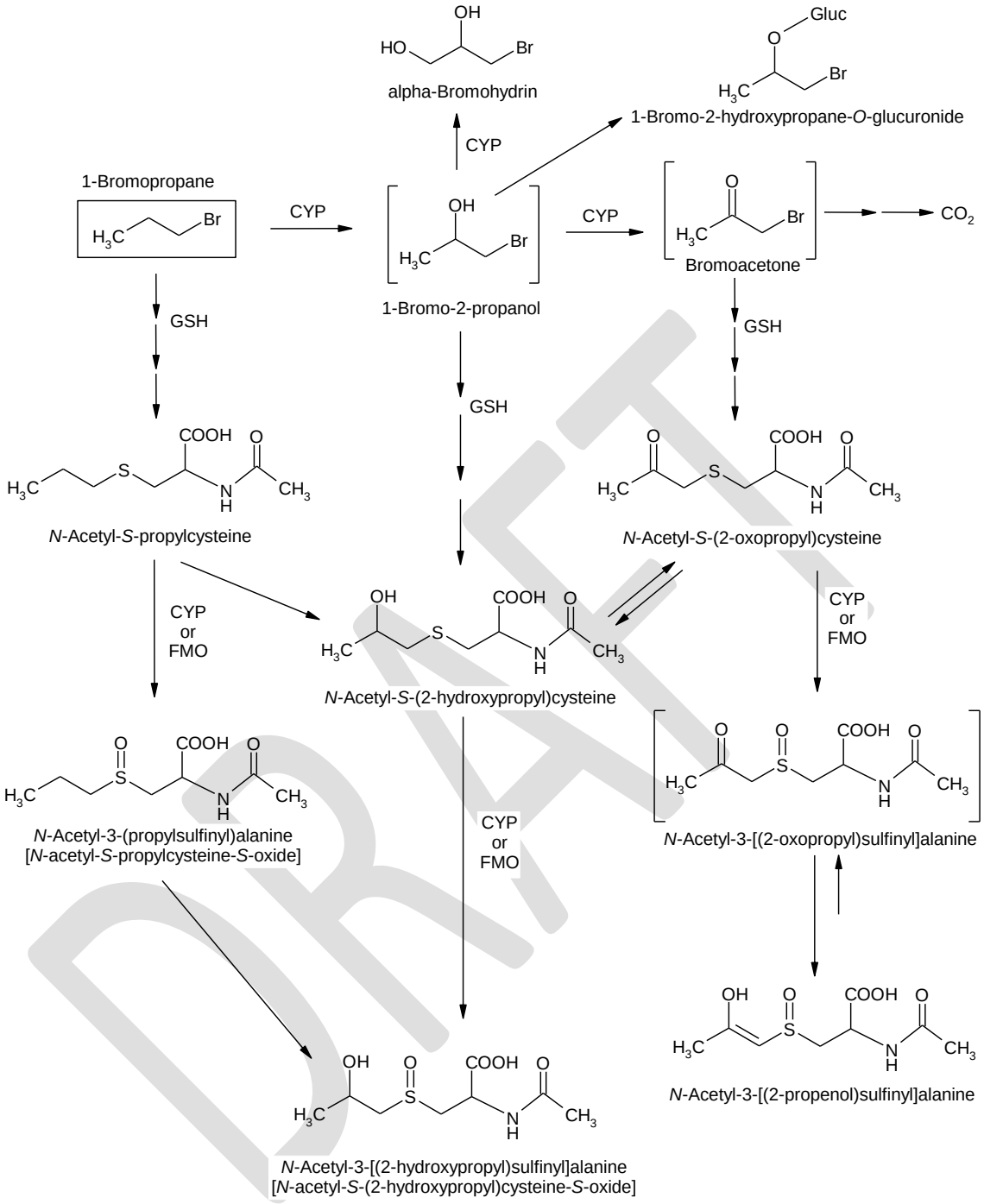


Figure 3-2 Metabolism of 1-Bromopropane in Male F-344 Rats and B6C3F1 Mice Following Inhalation Exposure or Tail Vein Injection*

*Structures in brackets are proposed intermediates and were not isolated in urine.
CYP = cytochrome P450 monooxygenase; FMO = flavin-containing monooxygenease; GSH = glutathione
Sources: Adapted from (NTP, 2013; Garner et al., 2007; Garner et al., 2006)

3.1.1 Biomarkers of Exposure

Several human and laboratory animal studies have investigated the utility of urinary biomarkers of 1-BP exposure (Mathias et al., 2012; Hanley et al., 2009; Valentine et al., 2007; Hanley et al., 2006; B'Hymer and Cheever, 2005; Ichihara et al., 2004a; Kawai et al., 2001). Bromide ion and N-acetyl-S-(n-Propyl)-L-Cysteine (AcPrCys) have shown the most promise at occupationally-relevant exposure concentrations.

1-BP is metabolized rapidly, via glutathione conjugation and cytochrome P-450 mediated oxidation, producing many metabolites which are subsequently excreted in urine. Glutathione conjugation leads to bromide ion release and formation of mercapturic acid derivatives. Bromide ion levels have been used as an internal biomarker of 1-BP exposure. They are slowly excreted from the body; the elimination half-life of bromide ions in blood generally ranges from 10.5 to 14 days (Mathias et al., 2012; Hanley et al., 2006). N-acetyl-S-(n-propyl)-L-cysteine (AcPrCys) is the primary urinary metabolite found in 1-BP exposed workers (see below); it also is considered to be a valid biomarker for 1-BP exposure (Mathias et al., 2012; Valentine et al., 2007).

Both Kawai (2001) and Ichihara (2004a) have shown a correlation between urinary 1-BP levels and 1-BP occupational exposure; however, the degree of correlation varied between studies. Kawai et al. (2001) reported a correlation coefficient of 0.9 for 1-BP concentrations in air and urine; the highest 1-BP concentration in air was 27.8 ppm (geometric mean = 1.42 ppm). Ichihara et al. (2004a) also reported a statistically significant correlation between 1-BP air concentrations and urinary levels measured on the same day ($r^2 = 0.39$; $p < 0.05$). NIOSH has suggested that urinary 1-BP levels may be a more suitable biomarker than urinary bromide concentrations; however, to ensure accuracy, samples must be tested immediately after collection using gas chromatography-mass spectrometry, which may be unfeasible or cost prohibitive (NIOSH, 2003).

Both urine and serum bromide ion levels have been used as biomarkers of 1-BP exposure in workers. Toraason et al. (2006) found a high correlation ($p < 0.0001$) between 1-BP exposure and bromide ion concentrations in serum (r^2= 0.7 to 0.8), and urine (r^2= 0.6 to 0.9) when evaluating personal breathing zone samples from approximately 50 workers. Workplace exposures ranged from 0.2 to 270 ppm (TWA), and the correlation coefficient for 1-BP air levels and urinary bromide levels was 0.5. Using gas chromatography with electron capture detection to evaluate samples taken from Japanese workers (n=33) following 1-BP exposure during an 8-hour shift of cleaning and painting, (Kawai et al., 2001) reported a good correlation (r^2= 0.5) between bromide levels in urine and 1-BP levels in air; however, control subjects exhibited high background levels of urinary bromide, which were subsequently linked to dietary exposure (Zhang et al., 2001). Hanley et al. (2006) measured urinary bromide levels to investigate the influence of non-occupational bromine exposure in 30 workers who used adhesives to make polyurethane foam seat cushions. Personal breathing zone samples indicated a geometric mean exposure of 92 ppm (range = 45-200 ppm) for sprayers and 11 ppm for workers in other parts of the plant. The composite (48-hour) urinary bromide concentrations for sprayers (n=12) ranged from 119 to 250 mg/g creatinine and for non-sprayers (n=17) ranged from 5.5 to 149 mg/g creatinine. The composite bromide concentration in unexposed control subjects (n=7) ranged from 2.6 to 5.9 mg/g creatinine. Daily bromide excretion was approximately four times greater for sprayers

than non-sprayers. Based on these results, urinary bromide concentration appears to be a useful index of 1-BP exposure.

Given the confounding factors identified (Kawai et al., 2001), a search for biomarkers of 1-BP exposure that are not influenced by dietary (or other non-occupational exposures) was initiated. (Mathias et al., 2012; Valentine et al., 2007) and Hanley et al. (2009) demonstrated that the mercapturic acid derivative, AcPrCys, could be used as a urinary biomarker of 1-BP exposure. Both the availability of sensitive methods with an acceptable limit of detection (LOD) for this metabolite, and its demonstrated persistence in urine suggest that it may serve as a reliable biomarker of exposure. In addition, 1-BP volatility and rapid elimination in exhaled breath suggests that the measurement of mercapturic acid derivatives in urine may be preferable to 1-BP measurements. Valentine et al. (2007) sampled blood and urine from women in a 1-BP production facility in China (Ichihara et al., 2004b). A significant increase in AcPrCys adducts on human globin was demonstrated using LC/MS/MS to evaluate samples taken from 26 1-BP exposed workers and 32 non-exposed controls. Worker exposures ranged from 0.34 ppm to 49.2 ppm, and urinary AcPrCys levels analyzed using GC/MS, increased with increasing 1-BP exposure (n=47). Hanley et al. (2009) used the same group of workers who applied spray adhesives to foam cushions as described above, to determine the utility of AcPrCys as a biomarker for 1-BP exposure. Higher levels of urinary AcPrCys were observed in sprayers than non-sprayers (geometric mean was approximately four times higher in sprayers). AcPrCys and bromide levels were highly correlated ($p < 0.0001$) in the same urine samples, and both showed statistically significant Spearman's correlation coefficients based on 1-BP TWA exposure concentrations. Mathias et al. (2012) evaluated the same cohort of workers, reporting the results of Hanley et al. (2009) and 3-bromopropionic acid (3-BPA), which was evaluated for its potential to induce mutagenic effects and tumor formation in toxicological studies. When urine samples were analyzed for 3-BPA, it was not detected in 50 samples (LOD = 0.01 µg/mL). The results of these analyses support the use of AcPrCys as a reliable biomarker for 1-BP occupational exposures.

3.1.2 Possible Mode of Action for 1-BP Toxicity

Various chemicals known to produce neuropathies in humans can be classified as hard or soft electrophiles according to the Hard and Soft Acid Base theory (Pearson, 1990). Based on this classification scheme, 1-BP is expected to induce adduct formation in vivo.

The primary metabolic pathways identified for 1-BP involve cytochrome P450 mediated oxidation (CYP2E1) and glutathione conjugation reactions which can produce numerous reactive intermediates (see Figure 3-3). Over 20 metabolites have been identified in rodent studies, including the four metabolites detected in urine samples taken from workers exposed to 1-BP (Hanley et al., 2009). The mode of action for 1-BP toxicity likely relates to the ability of these metabolites to react with critical cysteine, histidine and lysine amino acid residues which may ultimately impact the structural and functional integrity of the cell (Lopachin et al., 2009).

Various reactive metabolites (e.g., glycidol, α-bromohydrin, bromoacetone) and potential targets for cellular binding interactions (e.g., DNA, mitochondria) have been identified for 1-BP (NTP, 2013). Some 1-BP metabolites may exhibit alkylating activity. For example, further metabolism of

bromoacetone in a manner analogous to acetone (Casazza et al., 1984), would result in formation of 1-hydroxy-1-bromoacetone, which yields pyruvate and CO_2, or 3-bromo-1-hydroxypropanone (BOP). BOP has been shown to inhibit sperm energetics and motility via its conversion to bromolactaldehyde and bromopyruvaldehyde, ultimately yielding 3-bromopyruvate (Garner et al., 2007; Porter and Jones, 1995).

3-Bromopyruvate (3-BP) has been shown to produce many untoward effects, incuding lowered cell viability via production of reactive oxygen species (Qin et al., 2010) mitochondrial depolarization (Macchioni et al., 2011) and activation of mitochondrial apoptosis (Ko et al., 2004). It is a strong alkylating agent, and a known inhibitor of numerous enzymes, including glutamate decarboxylase (Fonda, 1976), glutamate dehydrogenase (Baker and Rabin, 1969), the mitochondrial pyruvate transporter (Thomas and Halestrap, 1981) and the pyruvate dehydrogenase complex (Apfel et al., 1984; Lowe and Perham, 1984). 3-BP induced alkylation and inhibition of glyceraldehyde-3-phosphate dehydrogenase can impair energy production via glycolysis (Da Silva et al., 2009; Ganapathy-Kanniappan et al., 2009) and induce apoptosis or necrosis as a result of ATP depletion due to impaired mitochondrial function (Kim et al., 2008).

The precise mechanism of action of 1-BP toxicity is not clearly understood, but likely relates to structural or functional modification of key signaling proteins as a result of cellular binding interactions induced by 1-BP or its metabolites. More research is needed to identify specific molecular targets and precursor events (e.g., organ-specific DNA adduct formation, oxidative stress responses) that precede toxicity. Since 1-BP can induce adverse effects in multiple organs acting directly as an alkylating agent, or indirectly via formation of reactive metabolites, different mechanisms may be operative in different target organs. At least four possible mechanisms (e.g., genotoxicity, oxidative stress, immunosuppression, and cell proliferation) have been proposed (NTP, 2013).

Several pathological conditions (e.g., alcoholism, diabetes), as well as chronic drug administration can induce CYP2E1 activity, and numerous cellular targets exist for 1-BP metabolites generated via CYP2E1 mediated oxidative metabolism. Interindividual variability in the expression and functional capacity of CYP2E1 has been observed (Neafsey et al., 2009) and genetic polymorphisms in CYP2E1 expression have been linked to altered disease susceptibility (Trafalis et al., 2010). Though inconsistencies exist in the available data, it is suggested that chronic exposure to CYP2E1 inducers such as ethanol and other solvents, as well as pharmaceuticals such as isoniazid, may increase the probability of developing malignancy, especially for carriers of certain CYP2E1 alleles (Trafalis et al., 2010).

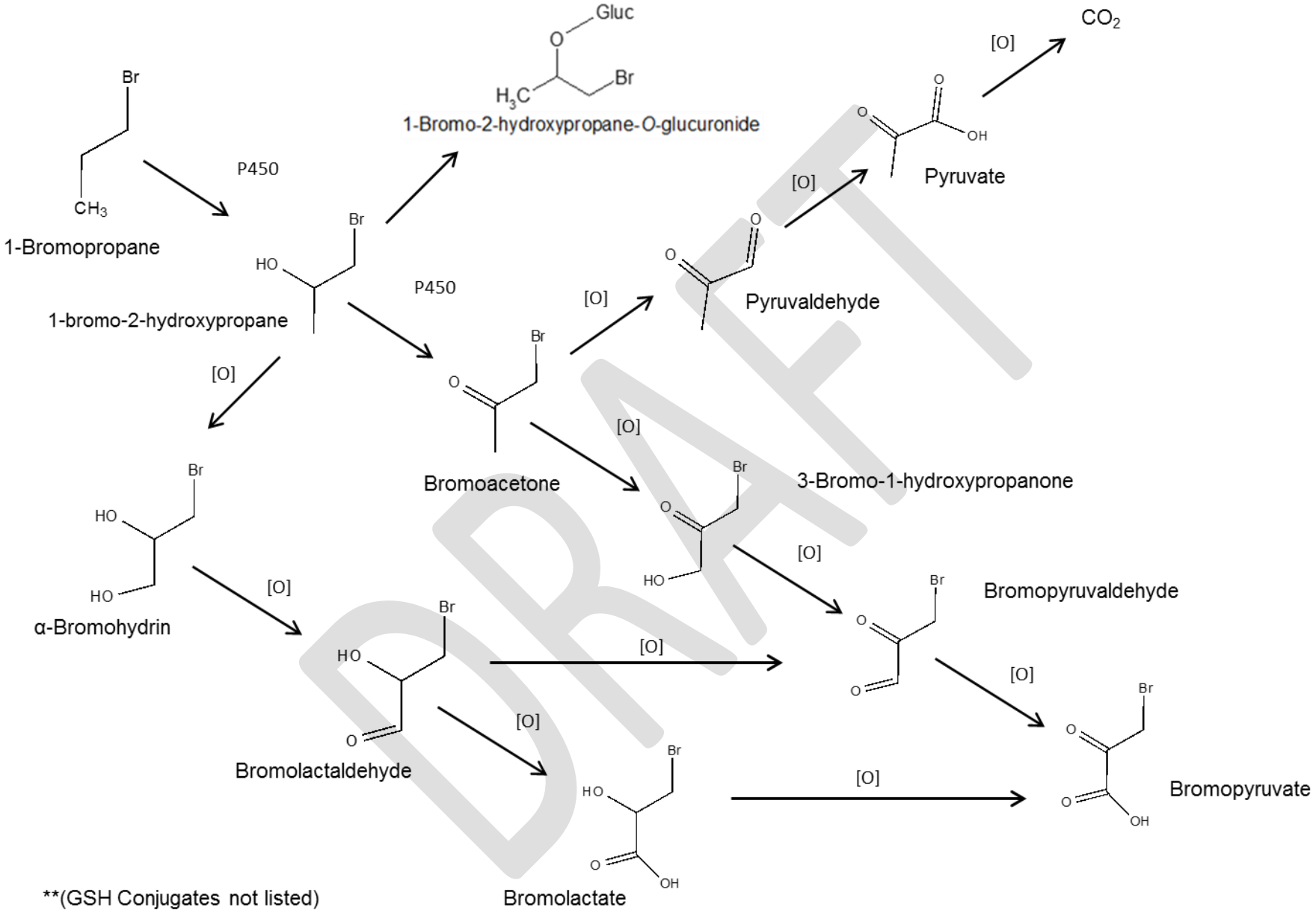


Figure 3-3 Proposed Intermediary Metabolism for 1-BP

(Garner et al., 2007; Garner et al., 2006)

3.1.3 PBPK Models

A PBPK model for 1-BP in rats was developed by (Garner et al., 2015). The model simulates 1-BP exposures via inhalation wherein distribution of 1-BP to tissues is assumed to be flow-limited. Metabolism of 1-BP was simulated with Michaelis-Menten kinetics for oxidative metabolism by cytochrome P450 and first order kinetics for GSH conjugation; parameters were fit to the time course data of chamber concentrations for 1-BP used in rat inhalation studies. Additional metabolic parameters were fit to time course data of chamber concentrations of 1-BP for rat inhalation studies when female rats were pretreated with either the cytochrome P450 inhibitor 1-aminobenzotriazole (ABT) or the GSH synthesis inhibitor D,L-buthionine (S,R)-sulfoximine (BSO). These results show the relative contributions of oxidative metabolism via cytochrome P450 and conjugation with GSH in female rats. Confidence in the PBPK model predictions for 1-BP concentrations in blood and tissues are limited by the lack of comparison of model predictions with measured data. The PBPK model was further extended to simulate human exposures by scaling the physiological parameters to humans, assuming the partition coefficients are the same in rats and humans and scaling metabolic parameters by $BW^{3/4}$. Cross species and route to route extrapolations with the Garner et al. (2015) model are precluded by the lack of data to inform a model of a species other than rat and a route other than inhalation.

3.2 Hazard Summary and Hazard Identification

This section summarizes the available cancer and non-cancer hazard information for 1-BP. A comprehensive summary table which includes all endpoints considered for this assessment is located in Appendix O. EPA/OPPT reviewed the available data and narrowed the focus of this assessment to six adverse health effect domains: (1) liver toxicity, (2) kidney toxicity, (3) reproductive toxicity, (4) developmental toxicity, (5) neurotoxicity, and (6) carcinogenicity. For non-cancer endpoints, emphasis was placed on acute/short term inhalation, and repeated-dose inhalation studies identified as most appropriate for hazard characterization and dose-response analysis.

3.2.1 Non-Cancer Hazard Identification

3.2.1.1 Toxicity Following Acute Exposure

In animals, deaths from acute inhalation exposure to 1-BP occurred only at high exposure concentrations. LC_{50} values in rats ranged from 7,000 to 14,374 ppm for 4-hour inhalation exposure (Elf Atochem, 1997; (Kim et al., 1999a). Deaths were associated with an acute inflammatory response and alveolar edema (Elf Atochem S.A., 1997). Similarly, for oral exposure, the LD_{50} was >2,000 mg/kg (Elf Atochem S.A., 1993a). No information on 1-BP toxicity following acute exposure in humans was located.

3.2.1.2 Liver Toxicity

Data from animal studies suggest the liver is a target for 1-BP. Reported effects include liver histopathology (e.g., hepatocellular vacuolation, swelling, degeneration and necrosis), increased liver weight, and clinical chemistry changes indicative of hepatotoxicity (Wang et al., 2012; NTP, 2011; Liu et al., 2009; Lee et al., 2007; Yamada et al., 2003; WIL Research, 2001; Kim et al., 1999a; Kim et al., 1999b; ClinTrials, 1997a, b). Hepatic endpoints selected for dose-response analysis

include datasets for histopathology (e.g., hepatocellular vacuolation) from subchronic duration inhalation studies in rats (WIL Research, 2001; ClinTrials, 1997a, b).

Hepatotoxicity was not directly evaluated in any of the human studies identified in the literature; however, one study evaluated liver function indirectly in a cohort of 86 Chinese workers exposed to 1-BP (median exposure levels up to 22.6 ppm) for an average of approximately 40 months (Li et al., 2010b) and no statistically significant clinical chemistry changes indicative of liver damage were observed.

3.2.1.3 Kidney Toxicity

Laboratory animal studies have provided evidence of renal toxicity following 1-BP exposure. Reported kidney effects include increased organ weight, histopathology (pelvic mineralization, tubular casts) and associated clinical chemistry changes (e.g., increased blood urea nitrogen) (NTP, 2011; Yamada et al., 2003; WIL Research, 2001; Kim et al., 1999a; ClinTrials, 1997a, b). Renal endpoints selected for dose-response analysis were for increased incidence of pelvic mineralization in male and female rats from a subchronic duration inhalation study by (Yamada et al., 2003; WIL Research, 2001).

No studies that directly evaluated 1-BP induced renal effects in humans were identified in the published literature; however, no significant clinical chemistry changes indicative of kidney damage were observed in a cohort of 86 Chinese workers exposed to 1-BP (median exposure levels up to 22.58 ppm) for an average of approximately 40 months (Li et al., 2010b) or in 45 workers exposed to a geometric mean concentration of 81.2 ppm for an average of 29 months (NIOSH, 2003).

3.2.1.4 Immunotoxicity

There is limited evidence for immune effects of 1-BP in animal studies. Two independent studies of immune function showed that 1-BP can suppress immune responses in rodents (Anderson et al., 2013; Lee et al., 2007). (Anderson et al., 2010) reported a decreased IgM plaque-forming response to immunization with sheep red blood cells (sRBC) in splenocytes harvested from female rats and mice following subchronic inhalation exposure to 1-BP (NOAEL = 500 ppm in rats; LOAEL [no NOAEL identified] = 125 ppm in mice). Associated effects in both species included decreases in T cells and increases in natural killer cells in the spleen; other effects reported in mice include reduced splenic cellularity and decreased absolute spleen weight. (Lee et al., 2007) also reported a decreased antibody response to sRBC and reduced splenic cellularity in female mice after a single oral dose of 1-BP (LOAEL [no NOAEL identified] = 200 mg/kg). Investigation of immune endpoints in other studies (limited to organ weights and histopathology of spleen, thymus, and other lymphoreticular tissues) showed no effects at concentrations as high as 1000 ppm in rats and 500 ppm in mice following subchronic inhalation exposure, and 500 ppm in rats and 250 ppm in mice following chronic inhalation exposure (NTP, 2011; Yamada et al., 2003; WIL Research, 2001; Ichihara et al., 2000a; Kim et al., 1999b; ClinTrials, 1997a, b). No information regarding 1-BP immunotoxicity in humans was located.

3.2.1.5 Reproductive Toxicity

Animal studies suggest that the reproductive system is a target of concern for 1-BP exposure. A two-generation reproduction study in rats reported adverse effects on male and female reproductive parameters (WIL Research, 2001). The majority of these effects exhibited a dose-response beginning at 250 ppm, with statistical significance observed at 500 ppm. Further details on each of these endpoints can be found in Appendix O.

Significant increases in the number of 'former' or 'unaccounted' implantation sites (i.e., the difference between the total number of implantation sites counted and the number of pups born) were reported by (WIL Research, 2001). EPA/OPPT considers this finding to be indicative of post-implantation loss (pre-implantation loss could not be determined because of a lack of data on the number of primordial follicles at 100, 250 and 500 ppm). F_0 females experienced a 48% reduction in fertility at 500 ppm and complete infertility at 750 ppm. Other effects reported in this study include dose-related decreases in mating indices, increased estrous cycle length, and a significant trend of increasing numbers of F_0 females with evidence of mating without delivery (a Cochran Armitage trend test conducted by EPA calculated a *p*-value <0.0001).

Statistically significant changes in reproductive endpoints in F_0 males include decreased absolute prostate and epididymal weights at exposures $\geq$ 250 and 500 ppm respectively, as well as decreased sperm motility, and decreased mating (500 ppm) and fertility indices (750 ppm) (WIL Research, 2001). The findings described above are supported by similar reports of reproductive toxicity from independent laboratory studies with rats and mice, including spermatogenic effects (decreased sperm count, altered sperm morphology and decreased sperm motility) and organ weight changes in males (decreased epididymis, prostate and seminal vesicle weights) as well as estrous cycle alterations and decreased numbers of antral follicles in females (NTP, 2011; Qin et al., 2010; Liu et al., 2009; Yu et al., 2008; Banu et al., 2007; Yamada et al., 2003; WIL Research, 2001; Ichihara et al., 2000b).

3.2.1.6 Developmental Toxicity

The developmental effects of 1-BP exposure have been evaluated on the basis of standard prenatal developmental toxicity studies, and a two-generation reproductive toxicity study in rats exposed via the inhalation route. Evidence for 1-BP induced developmental toxicity include dose related adverse effects on live litter size (WIL Research, 2001), postnatal survival (Furuhashi et al., 2006), pup body weight, brain weight and skeletal development (Huntingdon Life Sciences, 1999), (Huntingdon Life Sciences, 2001); (WIL Research, 2001). Further information on these endpoints can be found in Appendix O. No data were located on the developmental effects of 1-BP exposure in humans.

3.2.1.7 Neurotoxicity

Data from studies in humans and animals demonstrate that the nervous system is a sensitive target of 1-BP exposure. Both the central and peripheral nervous systems are affected. In animal inhalation studies, the degree or severity of neurotoxicity produced by 1-BP depends on the concentration as well as duration of exposure, with lower concentrations being effective at longer exposures. Most inhalation studies using concentrations of ≥1000 ppm reported ataxia progressing to severely altered gait, hindlimb weakness to loss of hindlimb control, convulsions,

and death (e.g., (Banu et al., 2007; Ishidao et al., 2002; Yu et al., 2001; Fueta et al., 2000; Ichihara et al., 2000a; Ohnishi et al., 1999; ClinTrials, 1997a, b). Concentrations of 400-1000 ppm produced neuropathological changes including peripheral nerve degeneration, myelin sheath abnormalities, and spinal cord axonal swelling (Wang et al., 2002; Yu et al., 2001; Ichihara et al., 2000a). Brain pathology has also been reported in several studies, including white and gray matter vacuolization, degeneration of Purkinje cells in the cerebellum and decreased noradrenergic but not serotonergic axonal density in frontal cortex and amygdala at exposures ≥400 ppm (Mohideen et al., 2013; Mohideen et al., 2011; Ohnishi et al., 1999; ClinTrials, 1997a, b). Decreased brain weight has been reported in adult and developmental studies (Subramanian et al., 2012; Wang et al., 2003; WIL Research, 2001; Ichihara et al., 2000a; Kim et al., 1999a; ClinTrials, 1997b). In a two-generation study (WIL Research, 2001), the NOAEL for decreased brain weight in F_1-generation males was 100 ppm (BMD modeling did not produce an acceptable fit); this value is brought forward for risk assessment representing neuropathological changes.

Physiological, behavioral, and biochemical measures have been used to characterize and develop dose-response data for neurological effects. Motor nerve conduction velocity and latency measured in the rat tail nerve were altered at concentrations ≥ 800 ppm with progressive changes from 4 to 12 weeks of exposure (Yu et al., 2001; Ichihara et al., 2000a). In the brain, electrophysiological changes in hippocampal slices were seen at concentrations of 400 ppm and above (Fueta et al., 2002a; Fueta et al., 2002b; Fueta et al., 2000); Fueta, 2004, 1717472; Fueta, 2007, 1519111; Ueno, 2007, 1717460}. Behavioral tests such as hindlimb grip strength, landing foot splay, traction (hang) time, gait assessment, motor activity, and water maze performance provide dose-response data and tend to be more sensitive than neuropathology or physiological changes, with effects at concentrations as low as 50-200 ppm (Banu et al., 2007; Honma et al., 2003; Ichihara et al., 2000a). Exposures to concentrations ≥ 50 ppm produce changes in neurotransmitters, biomarkers, and proteome expressions suggesting alterations in the function and maintenance of neural and astrocytic cell populations (Huang et al., 2015; Mohideen et al., 2013; Zhang et al., 2013; Huang et al., 2012; Subramanian et al., 2012; Huang et al., 2011; Mohideen et al., 2009; Suda et al., 2008; Yoshida et al., 2007; Wang et al., 2003; Wang et al., 2002). Although less extensively tested, oral or subcutaneous dosing of 1-BP resulted in similar findings as for inhalation exposure, with effects at ≥200 mg/kg-day (Guo et al., 2015; Zhong et al., 2013; Wang et al., 2012; Zhao et al., 1999). Neurological endpoints selected for dose-response analysis were datasets for decreased time hanging from a suspended bar (traction time) in rats in a 3 -week inhalation study (Honma et al., 2003) and decreased hind limb grip strength in rats in a 12 -week inhalation study (Ichihara et al., 2000a). These functional measures are relevant to peripheral neurotoxicity reported in human studies.

Human studies (case-control studies, industrial surveys, and case reports) corroborate that the nervous system is a sensitive target of 1-BP exposure in humans. Clinical signs of neurotoxicity (including headache, dizziness, weakness, numbness in lower extremities, ataxia, paresthesias, and changes in mood) and motor and sensory impairments were noted in the case reports of workers occupationally exposed to 1-BP for 2 weeks to 3 years at estimated concentrations exceeding averages of 100 ppm (Samukawa et al., 2012; Majersik et al., 2007; Raymond and Ford, 2007; Ichihara et al., 2002; Sclar, 1999), and in industrial surveys with average exposures greater

than 81 ppm (ranging from 2 weeks to 9 years) (NIOSH, 2003, 2002a, b). Cross-sectional studies of Chinese workers reported increased distal latency and decreased sural nerve conduction velocity in workers, although they were not statistically significant. Statistically significant decreased vibration sense in toes was observed across all exposure groups (0.07-106.4 ppm) compared to controls (Li et al., 2010a; Li et al., 2010b; Ichihara et al., 2004b). However, there were many methodological limitations in these studies, which are discussed in depth in Appendix O.

3.2.2 Cancer Hazard Identification

3.2.2.1 Genetic Toxicity

There is some evidence for mutagenicity and DNA damage associated with exposure to 1-BP in vitro, but the results are not conclusive as to whether and to what extent such effects may occur in mammals in vivo. 1-BP was mutagenic with or without metabolic activation in an assay for reverse mutation in *Salmonella typhimurium* conducted under closed conditions to control for loss of test material due to volatilization (Barber et al., 1981). Other tests for mutagenicity in bacteria were negative, but may not have been conducted in closed systems (e.g, (NTP, 2011; Kim et al., 1998). In mammalian cells tested in vitro, increased mutation frequency was observed in mouse lymphoma cells exposed to 1-BP with or without activation (Elf Atochem S.A., 1996a), and DNA damage was significantly increased in human leukocytes following in vitro exposure to 1-BP (Toraason et al., 2006). Tests conducted in vivo, however, were mostly negative, including assays for dominant lethal mutations and micronuclei induction in rats and mice (Kim et al., 1998); (Elf Atochem S.A., 1995); (NTP, 2011; Yu et al., 2008; Saito-Suzuki et al., 1982). An evaluation of the leukocytes of workers exposed to 1-BP showed no definitive evidence of DNA damage (i.e., damage was not significantly higher in workers exposed to the highest levels of 1-BP [sprayers] compared to those exposed to the lowest levels of 1-BP [non-sprayers]) (Toraason et al., 2006).

Positive results have been observed in several genotoxicity tests using known or postulated metabolites of 1-BP (including glycidol, propylene oxide, α-bromohydrin, 3-bromo-1-propanol, and 1-bromo-2-propanol) (NTP, 2014; IARC, 2000, 1994).

3.2.2.2 Carcinogenicity

Evidence from chronic cancer bioassays in rats and mice suggests that 1-BP may pose a carcinogenic hazard to humans. Significant increases in the incidences of skin tumors (keratoacanthoma/squamous cell carcinomas) in male F344 rats, rare large intestine adenomas in female F344 rats, and alveolar/bronchiolar adenomas or carcinomas (combined) in female B6C3F1 mice were observed following exposure to 1-BP via inhalation for 2 years (NTP, 2011). NTP concluded these data showed some evidence for carcinogenicity in male rats, clear evidence for carcinogenicity in female rats, no evidence for carcinogenicity in male mice, and clear evidence for carcinogenicity in female mice. No other animal data, and no human data, were located on the carcinogenicity of 1-BP.

1-BP has been shown to be a multi-target carcinogen in rats and mice. The exact mechanism/ mode of action of 1-BP carcinogenesis is not clearly understood. There are, however, an abundance of data that may provide a basis for weight of evidence consideration.

a. Ames test: Mixed results in the Ames test were reported in a number of 1-BP studies. Some of these studies were probably complicated by the high volatility of 1-BP and lack of use of closed systems and therefore should be invalidated. Among studies done in desiccator or closed systems, both positive and negative results have been reported.
b. Genotoxicity tests of mammalian cells: 1-BP caused mutations in cultured mammalian cells with or without metabolic activation and DNA damage in cultured human cells without metabolic activation. There was also limited evidence of DNA damage in leukocytes in 1-BP-exposed workers. Two in vivo micronucleus assays in bone marrow and circulating erythrocytes were negative; however, it should be mentioned that in vitro micronucleus assays have recently been suggested to be prone to yielding false negatives (e.g., (Benigni et al., 2012).
c. Metabolic activation to mutagenic intermediates: Rodent metabolic studies have indicated that 1-BP can be activated by CYP2E1 to at least five mutagenic intermediates (NTP, 2014; IARC, 2000, 1994), including two clearly mutagenic and carcinogenic chemicals, glycidol and propylene oxide, which are listed in NTP Report on Carcinogens as reasonably anticipated to be human carcinogens by the NTP (NTP, 2013). Glycidol has been shown to induce tumors in intestines, one of the carcinogenic targets of 1-BP. There is evidence that humans have CYP2E1 activity in lung and similar metabolic pathways for 1-BP as rodents.
d. Evidence for multi-species and multiplicity of cancer targets of 1-BP exists: In general, chemical carcinogens that induce cancer in more than one animal species and in multiple targets tend to act via mutagenic mechanism/mode of action. 1-BP has been shown to induce a variety of tumors in both rats and mice.
e. Structure-Activity Relationship (SAR) consideration: SAR has been routinely used as one of the criteria for consideration in EPA's Guidelines for Carcinogen Risk Assessment. From the SAR point of view, 1-BP is a low M.W. alkyl bromide that is generally known to be a good alkylating agent. In fact, 1-BP has been shown to bind to DNA in vitro. Bromoethane and 1-bromobutane, two of the closest analogs of 1-BP, were both reported to give positive results in the Ames test when tested in closed systems.
f. Other possible mechanism of action: Besides mutagenicity/genotoxicity, at least three other possible mechanisms – oxidative stress, immunosuppression, and cell proliferation—have been suggested by the NTP (NTP, 2013). These mechanisms can act synergistically to complete the multi-stage process of carcinogenesis. Although more research (e.g., organ-specific in vivo DNA adduct studies) is needed to ascertain mutagenicity as the key molecular event, there is no evidence that the other three mechanisms may play a more important role than mutagenicity.

Following EPA's Guidelines for Carcinogen Risk Assessment, overall, the totality of the available data/information and the weight of evidence support a justifiable basis to conclude a probable mutagenic mode of action for 1-BP carcinogenesis. 1-BP may be considered to be "*Likely to be Carcinogenic in Human*". Given the lack of information to inform a specific dose-response curve a linear extrapolation from the point of departure is recommended as the default risk assessment model per EPA's Guidelines for Carcinogen Risk Assessment.

3.3 Weight of Evidence/Multiple Lines of Evidence Supporting Critical Effects

3.3.1 Weight-of-Evidence for Reproductive and Developmental Toxicity

Reproductive and developmental toxicity were identified as critical targets for 1-BP exposure based on a constellation of effects reported in a number of studies, including a two-generation reproduction study by (WIL Research, 2001), which showed adverse effects on male and female reproductive parameters, as well as the developing fetus. Some of these endpoints were considered sufficient to include as PODs (see Section 3.4), while others were used as qualitative supportive evidence. Additional details on the results of this study can be found in Appendix O.

Quantitative and qualitative evidence of 1-BP induced reproductive toxicity in F_0 males include decreases in sperm motility, changes in normal sperm morphology, decreases in mating and fertility indices (WIL Research, 2001), and decreases in epididymal, prostate, and seminal vesicle weights following 1-BP inhalation exposure (NTP, 2011; WIL Research, 2001; Ichihara et al., 2000b). Evidence of reproductive toxicity in F_0 females include decreased numbers of corpora lutea, antral follicles, and implantation sites (NTP, 2011; Yamada et al., 2003; WIL Research, 2001). Other reported reproductive effects include increased estrous cycle length, and a significant trend of increasing numbers of F_0 females with evidence of mating without delivery (WIL Research, 2001). Reported impairments in male and female reproductive function resulted in a 48% reduction in fertility at 500 ppm and complete infertility at 750 ppm in F_0 mating pairs (WIL Research, 2001). Although the adverse reproductive effects of 1-BP exposure have not been directly evaluated in humans, the results from laboratory animal studies suggest that it may impair reproductive function.

Evidence supporting fetal development as a sensitive target of 1-BP exposure is provided by a number of laboratory animal studies. The current database consists of developmental toxicity studies that show severe effects resulting from prenatal exposures during gestation and postnatal exposure studies showing adverse developmental effects that manifest at various stages of development, and span multiple generations (WIL Research, 2001). Overall, the general consistency of findings indicative of impaired development reported in multiple studies from independent laboratories is taken as evidence of a causative association between 1-BP exposure and developmental toxicity. Reported adverse developmental effects following 1-BP exposure include dose-related decreases in live litter size (WIL Research, 2001), postnatal survival (Furuhashi et al., 2006), and pup body weight, brain weight and skeletal development (Huntingdon Life Sciences, 1999), (Huntingdon Life Sciences, 2001); (WIL Research, 2001). (WIL Research, 2001) also reported decreases in the number of implantation sites, and increases in 'unaccounted' implants for corresponding ovulatory events, reported as the difference between the total number of implantation sites counted and the number of pups born. EPA/OPPT interpreted this finding as an indication of post-implantation loss (pre-implantation loss could not be determined due to insufficient data on the number of primordial follicles). Additional qualitative evidence of impaired development following 1-BP exposure is provided by results from dominant lethal assays with 1-BP which show increased implantation loss in rats (only at week 8) subjected to five days of oral 1-BP exposure at 400 mg/kg (Saito-Suzuki et al., 1982) and

in mice (only at week 5) gavaged at 600 mg/kg for ten days prior to mating (Yu et al., 2008). The findings described above are supported by consistent reports of 1-BP induced adverse developmental effects from independent laboratory studies with rats and mice. No corresponding epidemiological studies have been identified; however, the concordance of results obtained from laboratory animal studies suggests that 1-BP may adversely affect human development.

3.3.2 Weight-of-Evidence for Neurotoxicity

Neurotoxicity has been identified as a critical effect for 1-BP based on over 15 years of behavioral, neuropathological, neurochemical, and neurophysiological studies in rodents as well as cross-sectional studies and case reports in humans (Section 3.2.1.7 and Appendices O-1, O-3, and O-4). Overall, there is considerable support for the finding of peripheral neurotoxicity, and consistency in reports of impaired peripheral nerve function (sensory and motor) and adverse neuromuscular impacts. The effects are progressive in terms of exposure duration and concentration, and range from subtle changes in nervous system function and neurochemistry progressing to physiological manifestations of neuron damage to structural evidence of neuronal pathology.

This spectrum of adverse manifestations of peripheral neurotoxicity is reproducible across almost all of the experimental studies, with a few notable exceptions. In addition, symptoms in humans, such as peripheral weakness, numbness, ataxia, and paraparesis, are concordant with the signs seen in many rodent studies. At high concentrations (≥1000 ppm), toxicological reports in rodents include observations such as hindlimb weakness, ataxia, altered gait, and other signs typical of peripheral neuropathy (Mohideen et al., 2013; Zhang et al., 2013; Banu et al., 2007; Honma et al., 2003; Fueta et al., 2002a; Fueta et al., 2002b; Ishidao et al., 2002; Yu et al., 2001; Fueta et al., 2000; Ichihara et al., 2000a; Kim et al., 1999a; Ohnishi et al., 1999; ClinTrials, 1997a, b). However, in a chronic bioassay (NTP, 2011) these signs were reported at 2000 ppm but not 1000 ppm; differences in timing and specificity of observations as well as training and blinding of personnel to dose assignment could account for the relative insensitivity of those specific outcomes. A number of papers that did not report any information at all about the general appearance and health of the animals were mostly mechanistic studies focused only on ex vivo endpoints (Huang et al., 2015; Huang et al., 2012; Huang et al., 2011; Mohideen et al., 2011; Mohideen et al., 2009 Subramanian, 2012, 1533580; Suda et al., 2008; Fueta et al., 2007; Ueno et al., 2007; Yoshida et al., 2007; Fueta et al., 2004; Wang et al., 2003; Wang et al., 2002). In human reports, severe neurological effects in workers occurred at relatively high exposures (>100 ppm) over a period of time of exposure ranging from weeks to months (Samukawa et al., 2012; CDC, 2008; Majersik et al., 2007; Raymond and Ford, 2007; Ichihara et al., 2002; Sclar, 1999).

There is generally agreement of 1-BP's neurotoxic effects across studies using measures of peripheral nerve integrity evaluated by electrophysiological and behavioral tests. Nerve conduction velocity and distal latency in motor neurons are decreased in animals (Yu et al., 2001; Ichihara et al., 2000a; Zhao et al., 1999) [subcutaneous exposure]). These experimental findings corroborate the studies of factory workers that describe decreased nerve conduction and/or peripheral sensory impairment (Li et al., 2010a; Li et al., 2010b; Ichihara et al., 2004a). The epidemiological studies are, however, somewhat limited by poorly defined exposures as well as concerns about the sensitivity and implementation of the test methods used to assess motor and sensory deficits. Using an objective measure of grip strength in rats, decreased function that

worsens with continued exposure has been reported in several laboratories (Wang et al., 2012; Banu et al., 2007; Ichihara et al., 2000a), [oral exposure]) except one (ClinTrials, 1997a).

A number of animal studies report histopathology of the nervous system (brain, spinal cord, and/or peripheral nerves) at concentrations as low as 400 ppm (Mohideen et al., 2013; Subramanian et al., 2012; Mohideen et al., 2011; Wang et al., 2002; Yu et al., 2001; Ichihara et al., 2000a; Ohnishi et al., 1999; ClinTrials, 1997b), but not in other studies that used even at higher concentrations (NTP, 2011; Fueta et al., 2004; Sohn et al., 2002; WIL Research, 2001; Kim et al., 1999a). There are a few conflicting reports from the same laboratory (ClinTrials, 1997a, b), [4 wk vs 13 wk studies]; (Sohn et al., 2002; Kim et al., 1999a). Such differences may be attributable to a number of experimental factors, including tissue preparation, fixation, staining, and sampling, measurement methodology, and training and blinding of personnel to dose group assignment.

Additional experimental animal studies report changes in brain weight, which is considered indicative of neurotoxicity even in cases where other histopathological changes are not evident (U.S. EPA, 1998); however, several studies do describe corresponding neuropathology (Wang et al., 2002; WIL Research, 2001; Kim et al., 1999a). Decreased brain weight was reported with subacute to subchronic exposures in adult rats (Subramanian et al., 2012; Wang et al., 2003; Ichihara et al., 2000a; Kim et al., 1999a; ClinTrials, 1997b), as well as decreased brain weight in offspring from a multi-generational study with lifetime exposures (WIL Research, 2001). Only two studies have measured brain weight and reported no effects: 1) (Wang et al., 2002), in which exposure was only 7 days and may not have been a sufficient exposure duration and/or concentration, and 2) the 13-wk study of (ClinTrials, 1997a), even though the same laboratory reported decreased brain weight at the same concentration with only 4 weeks of exposure (ClinTrials did not provide explanations for this contradictory finding).

Several studies report alterations in central nervous system neuronal communication, neurotransmitter levels, proteins, and oxidative stress markers, all of which are markers of neurotoxicity (U.S. EPA, 1998). It is notable that database consistency is partially a function of multiple studies from a few laboratories (Huang et al., 2015; Mohideen et al., 2013; Zhang et al., 2013; Huang et al., 2012; Subramanian et al., 2012; Huang et al., 2011; Mohideen et al., 2011; Mohideen et al., 2009; Suda et al., 2008; Fueta et al., 2007; Ueno et al., 2007; Fueta et al., 2004; Wang et al., 2003; Fueta et al., 2002a; Fueta et al., 2002b; Fueta et al., 2000). Other studies have reported cognitive deficits following 1-BP inhalation exposure (Guo et al., 2015; Zhong et al., 2013; Honma et al., 2003).

Overall, the sheer number of experimental studies, supported by the epidemiological studies, reporting clinical and neurohistological signs provide strong evidence for peripheral neuropathology. Where quantifiable endpoints that are sensitive to relatively low exposures have been measured across laboratories, there is generally good consistency in outcomes, with only a few notable exceptions. There is also agreement in findings of central nervous system dysfunction in laboratory rodents, but there are no corresponding studies in humans with which to compare. Thus, the strength and concordance of these lines of evidence provide good confidence in conclusions of adverse neurological findings with 1-BP.

3.3.3 Weight-of-Evidence for Cancer

Evidence from chronic cancer bioassays in rats and mice suggests that 1-BP may pose a carcinogenic hazard to humans. Significant increases in the incidences of skin tumors (keratoacanthoma/squamous cell carcinomas) in male F344 rats, rare large intestine adenomas in female F344 rats, and alveolar/bronchiolar adenomas or carcinomas (combined) in female B6C3F1 mice were observed following exposure to 1-BP via inhalation for 2 years (NTP, 2011). The exact mechanism/mode of action of 1-BP carcinogenesis is not clearly understood. There are, however, an abundance of data that may provide a basis for weight of evidence considerations; these include in vitro tests, similarity in metabolism across species, SAR and other potential mechanisms of action. Although the results from Ames and other genotoxicity tests for 1-BP have been mixed, two positive mammalian cell test results provide some evidence of genotoxicity/DNA damage. Rodent metabolic studies have indicated that 1-BP can be activated by CYP2E1 to at least five mutagenic metabolites/intermediates, including two that are clearly mutagenic and carcinogenic. Since humans have CYP2E1 activity in the lung and exhibit similar metabolic pathways for 1-BP as rodents, the evidence from multiple species (rats and mice) for multiple cancer types following 1-BP exposure supports a carcinogenic hazard to humans. From the SAR point of view, 1-BP is a low molecular weight alkyl bromide that is generally known to be a good alkylating agent and two of its closest analogs (bromoethane and 1-bromobutane) both have provided positive Ames test results in closed systems. Other possible mechanisms of action – oxidative stress, immunosuppression, and cell proliferation—can act synergistically to complete the multi-stage process of carcinogenesis. Per EPA Guidelines for Carcinogen Risk Assessment, overall, the totality of the available data/information and the weight of evidence support a justifiable basis to conclude a probable mutagenic mode of action for 1-BP carcinogenesis. 1-BP may be considered to be "*Likely to be Carcinogenic in Humans*". Linear extrapolation from the POD is recommended as the default risk assessment model.

3.3.4 Summary of Hazard Studies Used to Evaluate Acute and Chronic Exposures

EPA/OPPT considered adverse effects for 1-BP across organ systems and a comprehensive summary table is in Appendix O (Table_Apx O-2). The full list of effects was screened to those that are relevant, sensitive and found in multiple studies which include the following types of effects: hepatotoxicity, renal toxicity, immunotoxicity, developmental/reproductive toxicity, neurotoxicity, and cancer as described above. In general, adverse effects were observed in all of these systems in rats exposed to 1-BP by inhalation in the range of 100 – 1000 ppm (LOAELs). From these effects EPA/OPPT selected endpoints for both non-cancer and cancer that were amenable to quantitative analysis for dose-response assessment as discussed in more detail below in Section 3.4. In the following sections, EPA identifies the appropriate toxicological studies to be used for acute and chronic exposure scenarios.

3.4 Dose-Response Assessment

EPA/OPPT evaluated data from studies described above (Section 3.2) to characterize the dose-response relationships of 1-BP and selected studies and endpoints to quantify risks for specific exposure scenarios. One of the additional considerations was that the selected key studies had adequate information to perform dose-response analysis for the selected PODs. EPA/OPPT

defines a POD as the dose-response point that marks the beginning of a low-dose extrapolation. This point can be the lower bound on the dose for an estimated incidence, or a change in response level from a dose-response model (*i.e.*, BMD), a NOAEL or a LOAEL for an observed incidence or change in the level of response.

3.4.1 Non-Cancer Dose-Response Assessment

The non-cancer dose-response analysis in this assessment commenced with the review and selection of high quality toxicity studies that reported both adverse non-cancer health effects and quantitative dose-response data (Table_Apx O-2). As a result, the non-cancer dose-response assessment was organized into five health effect domains: (1) liver; (2) kidney; (3) reproductive; (4) developmental and (5) nervous system. Inhalation PODs were identified in earlier steps. HEC values were calculated for the inhalation PODs identified within each health effect domain. Endpoint and study-specific UFs were selected based on EPA guidance (U.S. EPA, 2002) and used as the benchmark MOEs for risk calculations. These UFs were applied to the PODs to account for (1) variation in susceptibility among the human population (i.e., inter-individual or intraspecies variability); (2) uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty); (3) uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure (i.e., extrapolating from subchronic to chronic exposure); and (4) uncertainty in extrapolating from a LOAEL rather than from a NOAEL, with default values of 10 applied for each (U.S. EPA, 2002).

Table 3-1 summarizes the hazard studies and health endpoints by target organ/system that EPA/OPPT considered suitable for risk evaluation of the exposure scenarios identified in this work plan risk assessment. Key studies in Table 3-1 are briefly described in the *Human Health Hazard Summary, Section 3.2*. Table 3-4 lists the lowest HECs by study type and duration (i.e., acute vs. chronic).

Benchmark dose (BMD) modeling was applied to these endpoints in a manner consistent with EPA Benchmark Dose Technical Guidance. When the models were adequate, the model results were used as PODs. For studies in which BMD modeling did not achieve an adequate fit to the data, the NOAEL or LOAEL value was used for the POD. Details regarding BMD modeling can be found in Appendix P. The PODs were converted from air concentrations in laboratory animals to HECs by accounting for the duration of exposure and applying an interspecies dose adjustment factor (DAF). The DAF was based on the ratio of the blood:gas partition coefficient for 1-BP, as recommended for a systemically acting gas (U.S. EPA, 1994). For 1 BP, the blood:air partition coefficient for rats is greater than that for humans, so a default ratio of 1 was applied (U.S. EPA, 1994). The HECs were adjusted from the respective study conditions to exposures of 8 hours per day for occupational exposure scenarios (acute and chronic) and to exposures of 24 hours per day for consumer exposure scenarios. For chronic exposure effects, air concentrations were adjusted to 5 days of exposure per week to reflect a 40 hour work week. HECs were rounded to two significant figures.

BMRs were selected for each endpoint. In cases where biologically relevant BMRs were not available the BMR was 10% for dichotomous endpoints and 1 standard deviation for continuous endpoints consistent with EPA Benchmark Dose Technical Guidance. A BMR of 10% was used for liver and kidney effects. A BMR of 1 standard deviation was used for reproductive effects. Lower

BMRs were used for developmental endpoints with 5% for pup body weight and 1% for brain weight to account for the increased severity of these endpoints (U.S. EPA, 1991). A BMR of 1 standard deviation was used for functional nervous system effects. When BMD modeling was successful, the PODs were the BMDLs determined for each endpoint. The PODs for endpoints selected following dose-response analysis were calculated either by benchmark dose (BMD) modeling (when the model fit was adequate) or a NOAEL/LOAEL approach based on the endpoint evaluated (see Section 3.4.1 and Table 3-1 for all of the PODs).

Given the different exposure scenarios considered (both acute and chronic for spray adhesives, dry cleaning, and degreasing activities for occupational exposure scenarios; and only acute for spot cleaners for consumer exposure scenarios), different endpoints were used based on the expected exposure durations. For non-cancer effects, and based on a weight-of-evidence analysis of toxicity studies from rats and humans, risks for developmental effects that may result from a single exposure were evaluated for acute (short-term) exposures, whereas risks for other adverse effects (e.g., toxicity to liver, kidney, reproduction, development and nervous system) were evaluated for repeated (chronic) exposures to 1-BP. Although developmental studies typically involve multiple exposures, they are considered relevant for evaluating single exposures because some developmental effects (e.g., fetal resorptions and mortality), may result from a single exposure during a critical period of development (Davis et al., 2009; Van Raaij et al., 2003; U.S. EPA, 1991). This is consistent with EPA's Guidelines for Reproductive Toxicity Risk Assessment which state that repeated exposure is not a necessary prerequisite for the manifestation of developmental toxicity. Consequently, EPA/OPPT concluded that developmental endpoints are applicable when assessing acute exposures, where it is assumed that the risk of their occurrence depends on the timing and magnitude of exposure. This is based on the presumption and EPA's policy that a single exposure during a critical window of development may produce adverse developmental effects (U.S. EPA, 1996, 1991). The rationale for using the range of toxic effects for chronic scenarios is based on the fact that relatively low dose and short term/sub-chronic exposures can result in long-term adverse consequences.

PODs for Acute Exposure

Acute exposure was defined for occupational settings as exposure over the course of a single work shift 8 hours and for consumers as a single day. Developmental toxicity (i.e. reduced number of live pups per litter) was the endpoint selected as most relevant for calculating risks associated with acute occupational or consumer exposure (WIL Research, 2001). The acute scenario covers exposures incurred during a single day, with varying time intervals assumed for worker (an 8 hour work shift), and consumer (a 24 hour day) exposure scenarios. Usually, the daily dose is not adjusted for duration of exposure because appropriate pharmacokinetic data are not available. In cases where such data are available, adjustments may be made to provide an estimate of equal average concentration at the site of action for the human exposure scenario of concern. However, the short half-life for 1-BP suggests there will not be increasing body burden over multiple exposure days, therefore, no duration adjustment is needed. Further support for using this endpoint for acute (short-term) exposures is the fact that the constellation of both male and female reproductive effects (in the F_0 males and females) collectively contributing to the decreases in live litter size, all occurred within a short window of exposure between ovulation and implantation. In addition, decreased live litter size occurred at relatively low exposures, suggesting

that this was a sensitive and relevant endpoint, suitable for use in the risk assessment. A BMR of 5% was used to address the severity of this endpoint (U.S. EPA, 2012a). The POD for the decreased live litter size was a BMDL of 31 ppm.

PODs for Chronic Exposure

Chronic exposure was defined for occupational settings as exposure reflecting a 40-hour work week. Non-cancer endpoints selected as most relevant for calculating risks associated with chronic (repeated) occupational exposures to 1-BP included toxicity to the liver, kidney, reproductive system, developmental effects, and the nervous system.

Table 3-1 summarizes the hazard studies and health endpoints by target organ/system that EPA/OPPT considered suitable for the risk evaluation of chronic exposure scenarios in the work plan risk assessment for 1-BP. Key studies in Table 3-1 are briefly described in the *Human Health Hazard Summary, Section 3.2,* along with other toxicity and epidemiological studies. BMD modeling was performed for these endpoints in a manner consistent with EPA Benchmark Dose Technical Guidance. BMRs were selected for each endpoint.

Hepatic endpoints selected for dose-response analysis include datasets for histopathology (e.g., hepatocellular vacuolation) from subchronic inhalation studies in rats (ClinTrials, 1997a, b) and (WIL Research, 2001). Benchmark dose modeling determined BMDL values of 143, 226 and 322 ppm for the three datasets modeled from these studies.

Renal endpoints selected for dose-response analysis include an increased incidence of pelvic mineralization in male and female rats from a subchronic inhalation study (WIL Research, 2001). Benchmark dose modeling determined BMDL values of 428 and 135 ppm, respectively, for these datasets.

Decreased epididymal weight, decreased prostate weight, decreased seminal vesicle weight, altered sperm morphology and decreased sperm motility were the male reproductive endpoints selected for dose-response analysis (WIL Research, 2001; Ichihara et al., 2000b). Increased estrous cycle length and decreased antral follicle count were the female reproductive endpoints selected for dose-response analysis (Yamada et al., 2003; WIL Research, 2001). The PODs for endpoints selected following dose-response analysis were calculated either by benchmark dose (BMD) modeling (when the model fit was adequate) or a NOAEL/LOAEL approach based on the reproductive endpoint evaluated (see Section 3.4 and Table 3-1 for all of the PODs). The PODs were 38, 227, 250, 313 and 338 ppm for decreased relative seminal vesicle weight (use of absolute seminal vesicle weight produced the same BMDL), decreased percent normal sperm, decreased percent motile sperm, and absolute left and right cauda epididymal weights respectively, in males. The PODs were 200 and 250 ppm for decreased antral follicle count and increased estrous cycle length respectively, in females.

Decreased live litter size (i.e. reduced number of live pups per litter) was the endpoint selected as most relevant for calculating risks associated with developmental toxicity following chronic, exposures (WIL Research, 2001). Decreased live litter size may result from single as well as repeated exposures at a developmentally critical period (Davis et al., 2009; Van Raaij et al., 2003;

U.S. EPA, 1991) and therefore was considered a relevant endpoint for chronic as well as acute exposures. In addition, decreased live litter size occurred at relatively low exposures, suggesting that this was a sensitive and relevant endpoint, suitable for use in the risk assessment. A BMR of 5% was used to address the severity of this endpoint (U.S. EPA, 2012a). The POD for the decreased live litter size was a BMDL of 43 ppm.

Neurological endpoints selected for dose-response analysis for chronic, repeated exposures were datasets for decreased time hanging from a suspended bar (traction time) in rats in a 3-week inhalation study (Honma et al., 2003) and decreased hind limb grip strength in rats in a 12-week inhalation study (Ichihara et al., 2000a). These functional measures are relevant to peripheral neurotoxicity reported in human studies. Benchmark dose modeling determined BMDL values of 18 and 214, respectively, for these datasets.

Table 3-1 List of Inhalation Endpoints Suitable for the Non-Cancer Dose-Response Analysis of 1-BP

Target Organ/ System	Species, sex (#animals/dose)	Range of Doses or Concentrations[1] (ppm)	Duration[2]	POD Type (ppm)[3]	Effect	HEC (ppm)[4]	Uncertainty Factors (UFs) for Benchmark MOE[5]	Reference
Liver	Rat (male) (n=25/group)	100 to 750	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until sacrifice for F_0	$BMDL_{10}$= 143.5	Increased incidence of vacuolization of centrilobular hepatocytes (F_0)	150	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(WIL Research, 2001)
Liver	Rat (male) (n=15/group)	100 to 600	6 hours/day, 5 days/week for 13 weeks	$BMDL_{10}$= 226.1	Increased incidence of cytoplasmic vacuolization	170	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(ClinTrials, 1997a)
Liver	Rat (female) (n=25/group)	100 to 750	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until GD 20; from PND 5 until weaning of offspring (~PND 21) for F_0	$BMDL_{10}$= 322.1	Increased incidence of vacuolization of centrilobular hepatocytes (F_0)	340	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(WIL Research, 2001)
Kidney	Rat (female) (n=25/group)	100 to 750	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until GD 20; from PND 5 until weaning of offspring (~PND 21) for F_0	$BMDL_{10}$= 135.0	Increased incidence of pelvic mineralization (F_0)	140	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(WIL Research, 2001)

Target Organ/ System	Species, sex (#animals/dose)	Range of Doses or Concentrations[1] (ppm)	Duration[2]	POD Type (ppm)[3]	Effect	HEC (ppm)[4]	Uncertainty Factors (UFs) for Benchmark MOE[5]	Reference
Kidney	Rat (male) (n=25/group)	100 to 750	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until sacrifice for F_0	$BMDL_{10}$= 428.3	Increased incidence of pelvic mineralization (F_0)	450	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(WIL Research, 2001)
Reproductive System	Rat (male) (n=8-9/group)	200 to 800	8 hours/day, 7 days/week for 12 weeks	$BMDL_{1SD}$= 38	Decreased absolute/relative seminal vesicle weight	53	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(Ichihara et al., 2000b)
Reproductive System	Rat (female) (n=22-25/group)	100 to 500	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until sacrifice for F_0	$BMDL_{1SD}$= 188	Decreased number of implantation sites	200	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(WIL Research, 2001)
Reproductive System	Rat (male) (n=15-25/group)	100 to 750	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until sacrifice for F_0	NOAEL*= 250	Decreased percent motile sperm (F_0)	260	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(WIL Research, 2001)

Target Organ/ System	Species, sex (#animals/dose)	Range of Doses or Concentrations[1] (ppm)	Duration[2]	POD Type (ppm)[3]	Effect	HEC (ppm)[4]	Uncertainty Factors (UFs) for Benchmark MOE[5]	Reference
Reproductive System	Rat (female) (n=22-25/group)	100 to 750	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until GD 20; from PND 5 until weaning of offspring (~PND 21) for F_0	NOAEL*= 250	Increase in estrous cycle length (F_0)	260	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(WIL Research, 2001)
Reproductive System	Rat (female) (n=10/group)	200 to 800	8 hours/day, 7 days/week for 7 or 12 weeks	LOAEL*= 200	Decreased number of antral follicles (F_0)	280	UF_S=1; UF_A=10; UF_H=10; UF_L=10; *Total UF=1000*	(Yamada et al., 2003)
Reproductive System	Rat (male) (n=25/group)	100 to 750	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until sacrifice for F_0	$BMDL_{1SD}$= 313	Decreased left cauda epididymis absolute weight (F_0)	330	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(WIL Research, 2001)
Reproductive System	Rat (male) (n=24-25/group)	100 to 750	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until sacrifice for F_0	$BMDL_{1SD}$= 327	Decreased percent normal sperm morphology (F_0)	340	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(WIL Research, 2001)
Reproductive System	Rat (male) (n=25/group)	100 to 750	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until sacrifice for F_0	$BMDL_{1SD}$= 338	Decreased right cauda epididymis absolute weight (F_0)	350	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(WIL Research, 2001)

Target Organ/ System	Species, sex (#animals/dose)	Range of Doses or Concentrations[1] (ppm)	Duration[2]	POD Type (ppm)[3]	Effect	HEC (ppm)[4]	Uncertainty Factors (UFs) for Benchmark MOE[5]	Reference
Reproductive System	Rat (n=25/group)	100 to 750	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until sacrifice for F_0	$BMDL_{10}$= 356	Decreased Male and Female Fertility Index (F_0)	370	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(WIL Research, 2001)
Developmental Effects	Rat (n=25/group)	100 to 500	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until GD 20 for the F_1 litters	$BMDL_5$= 41	Decreased live litter size (F_1) at PND 0	Acute[6]: 31 Chronic[6]: 43	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(WIL Research, 2001)
Developmental Effects	Rat (female) (n=15-22/group)	100 to 500	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until GD 20; from PND 5 until weaning of offspring (~PND 21)	$BMDL_1$= 50	Decreased brain weight in F_2 females at PND 21	53	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(WIL Research, 2001)
Developmental Effects	Rat (female) (n=25/group)	100 to 500	6 hours/day during gestation plus ≥ 21 weeks after PND21	$BMDL_1$= 82	Decreased brain weight in adult F_1 females	86	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(WIL Research, 2001)

Target Organ/ System	Species, sex (#animals/dose)	Range of Doses or Concentrations[1] (ppm)	Duration[2]	POD Type (ppm)[3]	Effect	HEC (ppm)[4]	Uncertainty Factors (UFs) for Benchmark MOE[5]	Reference
Developmental Effects	Rat (male) (n=15-22/group)	100 to 500	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until GD 20; from PND 5 until weaning of offspring (~PND 21)	$BMDL_1$= 98	Decreased brain weight in F_2 males at PND 21	100	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(WIL Research, 2001)
Developmental Effects	Rat (male) (n=24-25/group)	100 to 500	6 hours/day during gestation plus ≥ 21 weeks after PND21	LOAEL* = 100	Decreased brain weight in adult F_1 males	110	UF_S=1; UF_A=10; UF_H=10; UF_L=10; *Total UF=1000*	(WIL Research, 2001)
Developmental Effects	Rat (male) (n=15-22/group)	100 to 500	6 hours/day during gestation until GD 20 and from PND 5 until weaning (~PND 21) for F_2	$BMDL_5$= 116	Decreased pup body weights on PND 21 (F_2 males)	120	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(WIL Research, 2001)
Developmental Effects	Rat (male) (n=10-24/group)	100 to 500	6 hours/day during gestation until GD 20 and from PND 5 until weaning (~PND 21) for F_1	$BMDL_5$= 123	Decreased pup body weights on PND 28 (F_1 males)	130	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(WIL Research, 2001)
Developmental Effects	Rat (female) (n=15-22/group)	100 to 500	6 hours/day during gestation until GD 20 and from PND 5 until weaning (~PND 21) for F_2	NOAEL* = 250	Decreased pup body weights on PND 14 (F_2 females)	260	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(WIL Research, 2001)

Target Organ/ System	Species, sex (#animals/dose)	Range of Doses or Concentrations[1] (ppm)	Duration[2]	POD Type (ppm)[3]	Effect	HEC (ppm)[4]	Uncertainty Factors (UFs) for Benchmark MOE[5]	Reference
Developmental Effects	Rat (male) (n=15-22/group)	100 to 500	6 hours/day during gestation until GD 20 and from PND 5 until weaning (~PND 21) for F_2	$BMDL_5$= 288	Decreased pup body weights on PND 14 (F_2 males)	300	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(WIL Research, 2001)
Developmental Effects	Rat (female) (n=15-22/group)	100 to 500	6 hours/day during gestation until GD 20 and from PND 5 until weaning (~PND 21) for F_2	$BMDL_5$= 303	Decreased pup body weights on PND 21 (F_2 females)	320	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(WIL Research, 2001)
Nervous System	Rat (male) (n=5/group)	10 to 1000	8 hours/day, 7 days/week for 3 weeks	$BMDL_{1SD}$ = 18.2	Decreased time hanging from a suspended bar (traction time)	25	UF_S=10; UF_A=10; UF_H=10; UF_L=1; *Total UF=1000*	(Honma et al., 2003)
Nervous System	Rat (male) (n=25/group)	100 to 750	6 hours/day during pre-mating, throughout mating, and until GD 20 (≥ 16 weeks)	NOAEL* = 100	Decreased brain weight in F_0 males	110	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(WIL Research, 2001)
Nervous System	Rat (male) (n=8-9/group)	200 to 800	8 hours/day, 7 days/week for 12 weeks	$BMDL_{1SD}$= 213.8	Decreased hind limb grip strength	300	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(WIL Research, 2001)

Target Organ/ System	Species, sex (#animals/dose)	Range of Doses or Concentrations[1] (ppm)	Duration[2]	POD Type (ppm)[3]	Effect	HEC (ppm)[4]	Uncertainty Factors (UFs) for Benchmark MOE[5]	Reference
Nervous System	Rat (female) (n=25/group)	100 to 750	6 hours/day during pre-mating, throughout mating, and until GD 20 (≥ 16 weeks)	$BMDL_{1SD}$ = 509	Decreased brain weight in F_0 females	530	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(WIL Research, 2001)

[1]Control concentrations are not included in the table.

[2] Acute exposures defined as those occurring within a single day. Chronic exposures defined as 10% or more of a lifetime (U.S. EPA, 2011).

[3]POD type can be NOAEL, LOAEL, or BMDL. For BMDLs, the subscript indicates the associated BMR. The BMRs are a percentage relative deviation (e.g., 10% relative deviation $BMDL_{10}$) or 1 standard deviation change ($BMDL_{1SD}$) from the mean for continuous data.

[4]HECs are adjusted from the study conditions by the equation HEC_{EXRESP} = POD x duration adjustment × DAF where the DAF is the ratio of blood:gas partition coefficients (animal:human). For 1-BP, the blood:air partition coefficient for rats is greater than that for humans, so a default ratio of 1 is applied (U.S. EPA, 1994). The baseline used for the duration adjustment was an 8 hours/day exposure for occupational exposure scenarios and 24 hours/day exposure for consumer exposure scenarios. For acute exposure the duration adjustment was (hours per day exposed ÷ 8) and for chronic exposure (occupational scenarios) was (hours per day exposed ÷ 8) × (days per week exposed ÷ 5) to reflect a 40-hour work week. All of the endpoints used the chronic exposure duration adjustment except for the decreased live litter size (F_1) at PND 0 as described above in Section 3.4.1. HECs are rounded to two significant digits.

[5]UF_S = subchronic to chronic UF (default value = 10); UF_A = interspecies UF (default value of 10); UF_H = intraspecies UF (default value = 10); UF_L = LOAEL to NOAEL UF (default value = 10) (U.S. EPA, 2002).

[6]The HEC for decreased live litter size was adjusted for acute and chronic occupational exposures as described in footnote 4.

* BMD modeling did not adequately fit the variance in the data so the NOAEL or LOAEL is presented.

3.4.2 Carcinogenic Dose-Response Assessment

No data were located on the carcinogenicity of 1-BP in humans. In animals, the carcinogenicity of 1-BP was evaluated in well-designed studies conducted in rodents (NTP, 2011). Male and female rats and mice were exposed to 1-BP via inhalation 6 hours/day, 5 days/week for 2 years. Cancer findings included significant increases in the incidences of: 1) skin tumors (keratoacanthoma/squamous cell carcinomas) in male F344 rats, 2) rare large intestine adenomas in female F344 rats, and 3) alveolar/bronchiolar adenomas and carcinomas (combined) in female B6C3F1 mice.

Dose-Response Modeling

Dose-response modeling of the (NTP, 2011) cancer data was performed by EPA. A brief summary of the methodology is presented here and more details are available in Appendix P-3. Benchmark dose modeling was performed for all three statistically significantly increased tumor types from the NTP study (i.e., skin tumors in male rats, intestinal tumors in female rats and lung tumors in female mice). All dichotomous models in the BMD software (BMDS Version 2.6) were fit to the incidence data for each of the three tumor types. The benchmark response level (BMR) used was 0.1% added risk (corresponding to a 1-in-1,000 working lifetime added risk of cancer). Because extrapolation to a 0.1% response level is sensitive to model selection, a model-averaging (MA) technique (Wheeler and Bailer, 2007) was used. This technique uses statistics (bootstrapping technique) to weigh, based on fit, the models providing acceptable fit to the experimental dataset (as evidenced by a chi-square goodness-of-fit value > 0.10). Model-averaging software was restricted to avoid supralinear models, which exhibit properties at the low dose that are not considered biologically plausible. The resulting model-average benchmark concentrations (MA BMCs) associated with 0.1% added risk and their 95% lower confidence limits (MA BMCLs) are shown in Table 3-2 for each of the three cancer datasets.

Table 3-2 Model-Average BMC and BMCL Estimates of 1-BP Exposure Associated with a 0.1% Added Risk of Tumors in Rodents

Species; Tumor Type	MA BMC (ppm)	MA BMCL (ppm)
Male F344 rats; keratoacanthoma/squamous cell carcinoma (combined)	3.73	2.25
Female F344 rats; large intestine adenoma	13.5	4.85
Female B6C3F1 mice; alveolar/bronchiolar adenoma or carcinoma (combined)	0.85	0.64

Extrapolation to Humans

The BMC and BMCL values shown in Table 3-2 represent the concentrations estimated by the model to generate the target response in rodents exposed 6 hours/day for 5 days/week. These data were extrapolated to humans based on occupational exposure to 1-BP during a 40-hour work week (8 hours/day, 5 days/week) using the following methodology:

1. Conversion of MA BMC/BMCLs (ppm) to benchmark dose values (BMD/BMDL in mg/kg-day) by adjusting for the experimental exposure duration 6 hours/day[8];
2. Conversion of BMD/BMDLs in rodents to human equivalent BMD/BMDLs on the basis of the mg/kg-day dose scaled by body weight to the 0.75 power[9]; and
3. Adjustment of the human equivalent BMD/BMDLs (mg/kg-day) to BMC/BMCLs (ppm) that reflect exposure for an 8-hour work day[10].

The human equivalent BMC and BMCL (BMC_{HEC} and $BMCL_{HEC}$) estimates based on a BMR of 0.1% added risk are shown in Table 3-3.

Table 3-3 BMC and BMCL Estimates of 1-BP Exposures Associated with a 0.1% Added Risk of Tumors in Humans Exposed 40 hours/week (8 hours/day, 5 days/week) (ppm)

Species; Tumor Type	BMC_{HEC}	$BMCL_{HEC}$
Male F344 rats; keratoacanthoma/squamous cell carcinoma (combined)	1.75	1.05
Female F344 rats; large intestine adenoma	6.17	2.22
Female B6C3F1 mice; alveolar/bronchiolar adenoma or carcinoma (combined)	0.39	0.30

Derivation of Inhalation Unit Risk

As shown in Table 3-3, the data for lung tumors (based on the combined incidence of alveolar/bronchiolar adenoma or carcinoma) in female mice generated the lowest BMC_{HEC}/$BMCL_{HEC}$ values; these values are considered protective for the other tumor types. The $BMCL_{HEC}$ (0.30 ppm) represents the 95% lower confidence limit estimate of the occupational exposure concentration expected to produce a 1-in-1,000 lifetime added risk of lung cancer. This value was selected as the POD for the inhalation unit risk (IUR) value because it reflects the statistical variability of the data and is more health-protective than the central estimate (BMC_{HEC}). Although data suggest a probable genotoxic mode of action (MOA), the exact MOA of 1-BP-induced tumorigenesis is not known. In the absence of more definitive knowledge regarding the MOA of 1-BP, the inhalation unit risk was calculated using the default linear approach, as follows:

$$\begin{aligned} IUR &= BMR \div BMCL \\ &= 0.001 \div 0.30 \text{ ppm} \\ &= 3 \times 10^{-3} \text{ per ppm } (7 \times 10^{-7} \text{per } \mu g/m^3) \end{aligned}$$

[8]BMD/BMDL (mg/kg-day) = BMC/BMCL (ppm) x (6 hours/24 hours) x (5.031 mg/m^3 per ppm) x default inhalation rate (m^3/day) x default body weight (kg); where the default inhalation rate and body weight values are 0.36 m^3/day and 0.380 kg for male F344 rats, 0.24 m^3/day and 0.229 kg for female F344 rats, and 0.06 m^3/day and 0.0353 kg for female B6C3F1 mice in chronic studies (U.S. EPA, 1988).

[9]Human equivalent BMD/BMDL (mg/kg-day) = BMC/BMCL (mg/kg-day) x (default body weight in rats or mice [kg]/default body weight in humans [kg]) $^{0.25}$; where default body weight values are 0.380 kg for male F344 rats, 0.229 kg for female F344 rats, 0.0353 kg for female B6C3F1 mice, and 70 kg for humans (U.S. EPA, 1988; ICRP, 1975).

[10]BMC/BMCL (ppm) = (1 ppm per 5.031 mg/m^3) x (default body weight in humans [kg]/default minute volume for human occupational exposure based on an 8-hour shift [m^3/day]); where default body weight and minute volume values are 70 kg and 9.6 m^3/day (U.S. EPA, 1994).

The IUR was used in the EPA/OPPT risk assessment to estimate added cancer risks for the inhalation occupational exposures scenarios. There is high confidence in the IUR because it was based on good quality animal data. Moreover, current weight of evidence suggests that 1-BP operates through at least four possible mechanisms in different target organs – genotoxicity, oxidative stress, immunosuppression, and cell proliferation to complete a multi-stage process of carcinogenesis.

EPA/OPPT did not use the IUR to calculate the theoretical cancer risk associated with a single (acute) exposure to spray adhesive, degreasing, and dry cleaning activities containing 1-BP. Published methodology for extrapolating cancer risks from chronic to short-term exposures to mutagenic carcinogens caveat that extrapolation of lifetime theoretical added cancer risks to single exposures has great uncertainties (NRC, 2001).

As NRC (2001) explains, "*There are no adopted state or federal regulatory methodologies for deriving short-term exposure standards for workplace or ambient air based on carcinogenic risk, because nearly all carcinogenicity studies in animals and retrospective epidemiologic studies have entailed high-dose, long-term exposures. As a result, there is uncertainty regarding the extrapolation from continuous lifetime studies in animals to the case of once-in-a-lifetime human exposures. This is particularly problematical, because the specific biologic mechanisms at the molecular, cellular, and tissue levels leading to cancer are often exceedingly diverse, complex, or not known. It is also possible that the mechanisms of injury of brief, high-dose exposures will often differ from those following long-term exposures. To date, U.S. federal regulatory agencies have not established regulatory standards based on, or applicable to, less than lifetime exposures to carcinogenic substances*."

Thus, the EPA/OPPT work plan risk assessment for 1-BP does not estimate added cancer risks for acute exposures because the relationship between a single short-term exposure to 1-BP and the induction of cancer in humans has not been established in the current scientific literature.

3.5 Summary of Health Hazard

Table 3-1 summarizes the hazard studies, health endpoints (PODs) by target organ/system, HEC and UFs that are relevant for the risk evaluation of acute and chronic exposure scenarios. Table 3-4 lists the lowest HECs by study type and duration category (acute vs. chronic). Appendix O contains a comprehensive summary table of adverse effects.

Table 3-4 Lowest HECs for Non-Cancer Effects for 1-BP

Exposure Duration for Risk Analysis	Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentra-tions[1] (ppm)	Duration[2]	POD Type (ppm)[3]	Effect	HEC (ppm)[4]	Uncertainty Factors (UFs) for Benchmark MOE[5]	Reference
CHRONIC OCCUPATIONAL	Liver	Rat (male) (n=25/ group)	Inhalation	100 to 750	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until sacrifice	$BMDL_{10}$ = 143.5	Increased incidence of vacuolization of centrilobular hepatocytes (F_0)	150	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(WIL Research, 2001)
	Kidney	Rat (female) (n=25/ group)	Inhalation	100 to 750	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until GD 20; from PND 5 until weaning of offspring (~PND 21)	$BMDL_{10}$ = 135.0	Increased incidence of pelvic mineralization (F_0)	140	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(WIL Research, 2001)
	Reproductive System	Rat (male) (n=8-9)/ group	Inhalation	200 to 800	8 hours/day, 7 days/week for 12 weeks	$BMDL_{1SD}$= 38	Decreased absolute/ relative seminal vesicle weight	53	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(WIL Research, 2001)
	Developmental Effects	Rat (n=25/ group)	Inhalation	100 to 500	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until GD 20 for the F_1 litters	$BMDL_5$= 41	Decreased live litter size (F_1) at PND 0	43	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(WIL Research, 2001)
	Nervous System	Rat (male) (n=5/ group)	Inhalation	10 to 1000	8 hours/day, 7 days/week for 3 weeks	$BMDL_{1SD}$ = 18.2	Decreased time hanging from a suspended bar (traction time)	25	UF_S=10; UF_A=10; UF_H=10; UF_L=1; *Total UF=1,000*	(Honma et al., 2003)

Exposure Duration for Risk Analysis	Target Organ/ System	Species	Route of Exposure	Range of Doses or Concentra-tions[1] (ppm)	Duration[2]	POD Type (ppm)[3]	Effect	HEC (ppm)[4]	Uncertainty Factors (UFs) for Benchmark MOE[5]	Reference
ACUTE OCCUPATIONAL	Developmental Effects	Rat (male) (n=24-25/ group)	Inhalation	100 to 500	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until sacrifice in males; or until GD 20 and from PND 5 until weaning of offspring (~PND 21) in females	$BMDL_5$ = 41	Decreased live litter size (F_1)	31	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(WIL Research, 2001)
ACUTE CONSUMER	Developmental Effects	Rat (male) (n=24-25/ group)	Inhalation	100 to 500	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until sacrifice in males; or until GD 20 and from PND 5 until weaning of offspring (~PND 21) in females	$BMDL_5$ = 41	Decreased live litter size (F_1)	10	UF_S=1; UF_A=10; UF_H=10; UF_L=1; *Total UF=100*	(WIL Research, 2001)

[1]Control concentrations are not included in the table.

[2] Acute exposures defined as those occurring within a single day. Chronic exposures defined as 10% or more of a lifetime (U.S. EPA, 2011).

[3]POD type can be NOAEL, LOAEL, or BMDL. For BMDLs, the subscript indicates the associated BMR. The BMRs are a percentage relative deviation (e.g. 10% relative deviation $BMDL_{10}$) or 1 standard deviation change ($BMDL_{1SD}$) from the mean for continuous data.

[4] HECs are adjusted from the study conditions by the equation HEC_{EXRESP} = POD x duration adjustment × DAF. The DAF is the ratio of blood:gas partition coefficients (animal:human). For 1-BP, the blood:air partition coefficient for rats is greater than that for humans, so a default ratio of 1 is applied (U.S. EPA, 1994). For acute exposure the duration adjustment was (hours per day exposed ÷ 8 or 24) and for chronic exposure the duration adjustment was (hours per day exposed ÷ 8) × (days per week exposed ÷ 5) to reflect a 40-hour work week. The effects all used the chronic exposure duration adjustment except for the decreased live litter size (F_1) at PND 0 as described above in Section 3.4.1. The differences in the HECs between the occupational and consumer exposures are due to the baseline used for the duration adjustment of acute occupational and consumer exposures; occupational exposures was 8 hours/day, and consumer exposures was 24 hours/day. HECs are rounded to two significant digits.

[5]UF_S = subchronic to chronic UF (default value = 10); UF_A = interspecies UF (default value of 10); UF_H = intraspecies UF (default value = 10); UF_L = LOAEL to NOAEL UF (default value = 10) (U.S. EPA, 2002).

* BMD modeling did not adequately fit the variance in the data so the LOAEL is presented

4 HUMAN HEALTH RISK CHARACTERIZATION

1-BP exposure is associated with a variety of cancer and non-cancer effects deemed relevant to humans for risk estimations for the chronic scenarios and populations addressed in this risk assessment. Based on a weight-of-evidence analysis of the available toxicity studies from rats and humans, these effects include liver toxicity, kidney toxicity, reproductive toxicity, developmental toxicity and neurotoxicity. The rationale for using the range of toxic effects for chronic exposures is based on the fact that relatively low dose, short term/sub-chronic exposures can result in long-term adverse consequences. The adverse developmentally toxic effects are also deemed important for risk estimation for the acute exposure scenarios and populations addressed in this risk assessment. The rationale for using 1-BP associated developmental effects for evaluating risks associated with acute exposures is based on the understanding that a relatively short critical window of vulnerability exists in humans and in rodents and short half-life of the chemical and reactive nature of the metabolites of 1-BP with cellular components (e.g., DNA and proteins) in multiple organ systems.

1-BP is carcinogenic in animals. The cancer risk assessment uses the EPA/OPPT derived IUR based on lung tumors in female mice. The weight-of-evidence analysis for the cancer endpoint was sufficient to support a probable mutagenic mode of action for 1-BP carcinogenesis.

4.1 RISK ESTIMATION APPROACH

Table 4-1, Table 4-2, and Table 4-3 show the use scenarios, populations of interest and toxicological endpoints used for acute and chronic exposures, respectively.

Table 4-1 Use Scenarios, Populations of Interest and Toxicological Endpoints for Assessing Occpational Risks Following Acute Exposures to 1-BP Used In Spray Adhesives, Dry Cleaning, and Degreasing

Populations And Toxicological Approach	Occupational Use Scenarios of 1-BP at Commercial Facilities Including Spray Adhesives, Dry Cleaning, and Degreasing
Population of Interest and Exposure Scenario:	***Users:*** Adult pregnant[1] worker (>16 years old) exposed to 1-BP for a single 8-hr exposure[2,3]. ***Occupational Non-user:*** Adult pregnant women [1] (>16 years old) exposed to 1-BP indirectly by being in the same work area of building.
Health Effects of Concern, Concentration and Time Duration	Non-Cancer Health Effects: Decreased live litter size (F_1) (WIL Research, 2001) [4] **1.** *Non-Cancer Hazard values or Point of Departures (PODs)*: 8-hr HEC: 31 ppm Cancer Health Effects: Cancer risks following acute exposures were not estimated. Relationship is not known between a single short-term exposure to 1-BP and the induction of cancer in humans.
Uncertainty Factors (UF) used in Non-Cancer Margin of Exposure (MOE) calculations	(UF_S=1) x (UF_A=10) x (UF_H=10) x (UF_L=1) [5] = 100 Total UF=Benchmark MOE=100

Notes:

[1] The risk assessment for acute exposures focused on the most sensitive life stage in humans, which is women of childbearing age and fetus (i.e., pregnant worker) due to concerns for developmental effects.

[2] Exposure estimate was adjusted to an 8-hr exposure estimate in order to combine it with the 8-hr HECs.

[3] It is assumed no substantial buildup of 1-BP in the body between exposure events due to 1-BP's short biological half-life (< 2 hours).

[4] The risk assessment for acute exposures focused on developmental toxicity effects as the most sensitive health effect when compared to other potential acute effects (i.e., neurotoxicity).

[5] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF

Table 4-2 Use Scenarios, Populations of Interest and Toxicological Endpoints for Assessing Consumer Risks Following Acute Exposures to 1-BP Use In Aerosol Spray Adhesives, Aerosol Spot Removers, and Aerosol Cleaners and Degreasers

Population and Toxicological Approach	CONSUMER USE SCENARIOS				
			Aerosol Spray Cleaning and Degreasing		
	Aerosol Spray Adhesives Use	Aerosol Spot Removers Use	Engine Degreasers	Brake Cleaners Use	Electronics Cleaners Use
Population of Interest	Women of child bearing age[1] consumers (>16 yrs old)				
Exposure Scenario[2]: *Users, High End*	A single 0.5-hr exposure[3].	A single 0.5-hr exposure[3].	A single 1.0-hr exposure[3].	A single 0.8-hr exposure[3].	A single 0.3-hr exposure[3].
Exposure Scenario[2]: *Users, Central Tendency*	A single 0.07-hr exposure[3].	A single 0.08-hr exposure[3].	A single 0.25-hr exposure[3].	A single 0.25-hr exposure[3].	A single 0.03-hr exposure[3].
Population of Interest and Exposure Scenario: *Non-User*	Women of child bearing age non-users [4] and individuals of multiple age groups that are exposed to indirect 1-BP exposures by being in the rest of the house.				
Health Effects of Concern, Concentration and Time Duration	Non-Cancer Health Effects: Decreased live litter size (F_1) (WIL Research, 2001) [5] **1.** *Non-Cancer Hazard values or Point of Departures (PODs)*: 24-hr HEC: 10 ppm Cancer Health Effects: Cancer risks following acute exposures were not estimated. Relationship is not known between a single short-term exposure to 1-BP and the induction of cancer in humans.				
Uncertainty Factors (UF) used in Non-Cancer Margin of Exposure (MOE) calculations	(UF_S=1) x (UF_A= 10) x (UF_H=10) x (UF_L=1) [6] = 100 Total UF=Benchmark MOE=100				

Notes:

[1] The risk assessment for acute exposures focused on the most sensitive life stage in humans, which is women of childbearing age and fetus (i.e., pregnant user) due to concerns for developmental effects.

[2] E-FAST/CEM provided the 24-hr acute exposure estimate and the HECs were adjusted to 24-hrs.

[3] It is assumed no substantial buildup of 1-BP in the body between exposure events due to 1-BP's short biological half-life (<2 hours).

[4] EPA/OPPT believes that the users of these products are generally adults, but teenagers and even children may be users or be in the same room with the user.

[5] The risk assessment for acute exposures focused on developmental toxicity effects as the most sensitive health effect when compared to other potential acute effects (i.e., neurotoxicity).

[6] UF_S=subchronic to chronic UF; UF_A=interspecies UF; UF_H=intraspecies UF; UF_L=LOAEL to NOAEL UF

Table 4-3 Use Scenarios, Populations of Interest and Toxicological Endpoints for Assessing Occupational Risks Following Chronic Exposures to 1-BP Used In Spray Adhesives, Dry Cleaning, and Degreasing

Populations and Toxicological Approach	Occupational Use Scenarios of 1-BP at Commercial Facilities Including Spray Adhesives, Dry Cleaning, and Degreasing
Population of Interest and Exposure Scenario: *Users*	Adult worker (>16 years old) [1,2] exposed to 1-BP for the entire 8-hr workday for 260 days per year for 40 working years.
Population of Interest and Exposure Scenario: *Occupational Non-users*	Adult worker (>16 years old) [1,2] repeatedly exposed to indirect 1-BP exposures by being in the same work area of building.
Health Effects of Concern, Concentration and Time Duration	Non-Cancer **1.** Non-cancer health effects: A range of possible chronic non-cancer adverse effects in liver, kidney, nervous system, reproductive system and developmental effects **2.** Non-Cancer Hazard values or Point of Departures (PODs): The lowest POD (i.e., 8-hr HEC expressed in ppm) within each health endpoint domain. See Table 3-4. Cancer **1.** Cancer health effects: Possible cancer effects in the lung from chronic exposure (NTP, 2011). **2.** Cancer Inhalation Unit Risk (IUR): 3×10^{-3} per ppm
Uncertainty Factors (UF) Used in Non-Cancer Margin of Exposure (MOE) calculations	Study- and endpoint-specific UFs. See Table 3-4.

Notes:
[1] Adult workers (>16 years old) include both healthy female and male workers.
[2] The risk assessment for chronic exposures for developmental effects focused on the most sensitive life stage in humans, which are women of child-bearing age and fetus (i.e., pregnant worker). For other health effects (e.g., liver, kidney, etc.), healthy female or male workers were assumed to be the population of interest.

Acute or chronic MOEs (MOE_{acute} or $MOE_{chronic}$) were used in this assessment to estimate non-cancer risks using Equation 4-1.

Equation 4-1 Equation to Calculate Non-Cancer Risks Following Acute or Chronic Exposures Using Margin of Exposures

$$MOE_{acute\ or\ chronic} = \frac{Non-cancer\ Hazard\ value\ (POD)}{Human\ Exposure}$$

Where:

MOE = Margin of exposure (unitless)
Hazard value (POD) = HEC (ppm)

Human Exposure = Exposure estimate (in ppm) from occupational or consumer exposure assessment. ADCs were used for non-cancer chronic risks and acute concentrations were used for acute risks (see sections 2.1.2 through 2.1.7).

EPA/OPPT used margin of exposures (MOEs)[11] to estimate acute or chronic risks for non-cancer based on the following:

1. the lowest HECs within each health effects domain reported in the literature;
2. the endpoint/study-specific UFs applied to the HECs per the EPA Guidance (U.S. EPA, 2002); and
3. the exposure estimates calculated for 1-BP uses examined in this risk assessment (see *Section 2 Exposure Assessment*).

MOEs allow for the presentation of a range of risk estimates. The occupational exposure scenarios considered both acute and chronic exposures. All consumer uses considered only acute exposure scenarios. Different adverse endpoints were used based on the expected exposure durations. For non-cancer effects, risks for developmental effects were evaluated for acute (short-term) exposures, whereas risks for other adverse effects (toxicity to the liver, kidney, nervous system, developmental effects, and the reproductive system) were evaluated for repeated (chronic) exposures to 1-BP.

For occupational exposure calculations, the 8 hr TWA was used to calculate MOEs for risk estimates for acute and chronic exposures.

The total UF for each non-cancer POD was the benchmark MOE used to interpret the MOE risk estimates for each use scenario. The MOE estimate was interpreted as human health risk if the MOE estimate was less than the benchmark MOE (i.e. the total UF). On the other hand, the MOE estimate indicated negligible concerns for adverse human health effects if the MOE estimate exceeded the benchmark MOE. Typically, the larger the MOE, the more unlikely it is that a non-cancer adverse effect would occur.

Risk estimates were calculated for all of the studies per health effects domain that EPA/OPPT considered suitable for the risk evaluation of acute and chronic exposure scenarios in the work plan risk assessment for 1-BP.

Added cancer risks for repeated exposures to 1-BP were estimated using Equation 4-2. Estimates of added cancer risks should be interpreted as the incremental probability of an individual developing cancer over a lifetime as a result of exposure to the potential carcinogen (i.e., incremental or added individual lifetime cancer risk).

[11] Margin of Exposure (MOE) = (Non-cancer hazard value, POD) ÷ (Human Exposure). Equation 4-1. The benchmark MOE is used to interpret the MOEs and consists of the total UF shown in Table 3-4. See Section 4.1 for an explanation of the benchmark MOE.

Equation 4-2 Equation to Calculate Added Cancer Risks

$$Risk = Human\ Exposure \times IUR$$

Where:

Risk = Added cancer risk (unitless)
Human exposure = Exposure estimate (LADC in ppm) from occupational exposure assessment
IUR = Inhalation unit risk (3 x 10^{-3} per ppm)

4.2 RISK ESTIMATION FOR ACUTE, NON-CANCER INHALATION EXPOSURES

Non-cancer risk estimates for acute inhalation exposures to 1-BP were derived for both occupational scenarios and consumer uses. Cancer risk estimates for acute inhalation exposures to 1-BP were not derived for occupational or consumer uses because the published methodology for extrapolating cancer risks from chronic to short-term exposures to mutagenic carcinogens caveat that extrapolation of lifetime theoretical added cancer risks to single exposures has great uncertainty (NRC, 2001).

The risk assessment for acute inhalation exposures used developmental toxicity data to evaluate the risks associated following acute exposures with the TSCA use scenarios identified for 1-BP under the scope of this assessment. As indicated previously, EPA's policy supports use of developmental studies to evaluate the risks of acute exposures. This policy is based on the presumption that a single exposure to a chemical during a critical window of development may produce adverse developmental effects (U.S. EPA, 1991). Thus, EPA/OPPT based its acute risk assessment on developmental toxicity (i.e., decreased live litter size), the lowest HEC identified for an acute exposure duration (WIL Research, 2001), which is representative of a sensitive subpopulation (i.e., adult women of child-bearing age and their offspring).

The risk assessment for acute exposures used the hazard value from the (WIL Research, 2001) two-generation reproductive toxicity study to evaluate risks for each occupational and consumer exposure scenario.

EPA/OPPT chose to focus on the high-end acute exposure estimates to calculate non-cancer risks (MOEs) for the occupational (95th percentile) and consumer (90th percentile) populations. Non-cancer acute MOE calculations for the 50th percentile (central tendency) exposure estimates are provided in the supplemental Excel spreadsheet[12]. Non-cancer risk estimates for acute occupational exposure scenarios are presented in Table 4-4 through Table 4-14 below. Risk estimates were calculated for all of the occupational exposure scenarios described in Section 2.1. Non-cancer risk estimates for acute consumer exposure scenarios are presented in Table 4-15.

Risks were identified for most of the acute occupational exposure scenarios (user and occupational non-user alike) even with the use of engineering controls (post-EC), with few exceptions. These exceptions include post-EC MOE values for the vapor degreasing (monitoring

[12] See attached document titled "Supplemental File 1-BP Non-Cancer MOE Risk Estimates.xlsx".

and modeling data for the occupational non-user, Table 4-9 and Table 4-10) and cold cleaning (modeling data for both the worker and occupational non-user, Table 4-12) uses. Similar findings were noted for the 50th percentile exposure estimates in most cases (see supplemental Excel spreadsheet[13]). For the 90th percentile exposure estimates, risks were identified for all of the acute inhalation consumer exposure scenarios (Table 4-15). For the 50th percentile exposure estimates, risks were identified for all of the consumer exposure scenarios (user and non-user), except for the aerosol spray adhesive non-user where the MOE was at the benchmark MOE of 100 (see supplemental Excel spreadsheet[13]). In all cases where risk was identified, the MOE values were approximately 1 to 2 orders of magnitude below the benchmark MOE of 100.

Table 4-4 Non-Cancer Risk Estimates for Acute Inhalation Exposures Following Occupational Use of 1-BP in Spray Adhesives Based on Monitoring Data

Health Effect, Endpoint and Study	Acute HEC (ppm)	Acute Exposure 95th Percentile Estimates						Benchmark MOE (= Total UF)
		WORKER (SPRAYER) MOE[1]		WORKER (NON-SPRAYER) MOE[1]		OCCUPATIONAL NON-USER MOE[1]		
		Pre EC	Post EC	Pre EC	Post EC	Pre EC	Post EC	
DEVELOPMENTAL EFFECTS Decreased live litter size (F_1) (WIL Research, 2001)	31	**0.12**	**0.74**	**0.15**	**1.07**	**0.24**	**5.66**	100

Notes: [1]MOEs (HEC in ppm/exposure estimate in ppm) lower than the Benchmark MOE (Total UF) indicate potential health risks and are denoted in **bold**.

Table 4-5 Non-Cancer Risk Estimates for Acute Inhalation Exposures Following Occupational Use of 1-BP in Dry Cleaning Based on Monitoring Data

Health Effect, Endpoint and Study	Acute HEC (ppm)	Acute Exposure 95th Percentile Estimates		Benchmark MOE (= Total UF)
		WORKER MOE[1]	OCCUPATIONAL NON-USER MOE[1]	
		Pre EC	Pre EC	
DEVELOPMENTAL EFFECTS Decreased live litter size (F_1) (WIL Research, 2001)	31	**0.62**	**1.50**	100

Notes: [1]MOEs (HEC in ppm/exposure estimate in ppm) lower than the Benchmark MOE (Total UF) indicate potential health risks and are denoted in **bold.**
Only monitoring data characterized as "Pre-EC" by this assessment was available for dry cleaning. See Section 2.1.3.

Table 4-6 Non-Cancer Risk Estimates for Acute Inhalation Exposures Following Occupational Use of 1-BP in Dry Cleaning Based on Modeling

Health Effect, Endpoint and Study	Acute HEC (ppm)	Acute Exposure 95th Percentile Estimates						Benchmark MOE (= Total UF)
		WORKERS: MACHINE UNLOADING AND FINISHING (NEAR-FIELD)MOE[1]		WORKERS: SPOT CLEANING (NEAR-FIELD) MOE[1]		OCCUPATIONAL NON-USERS (FAR-FIELD)		
		Pre EC	Post EC	Pre EC	Post EC	Pre EC	Post EC	
DEVELOPMENTAL EFFECTS Decreased live litter size (F_1) (WIL Research, 2001)	31	**0.5**	**5.1**	**4.5**	**45**	**6.4**	**64**	100

Notes: [1]MOEs (HEC in ppm/exposure estimate in ppm) lower than the Benchmark MOE (Total UF) indicate potential health risks and are denoted in **bold**.

[13]See attached document titled "Supplemental File 1-BP Non-Cancer MOE Risk Estimates.xlsx".

Table 4-7 Non-Cancer Risk Estimates for Acute Inhalation Exposures Following Occupational Use of 1-BP in Spot Cleaning at Dry Cleaners Based on Monitoring Data

Health Effect, Endpoint and Study	Acute HEC (ppm)	Acute Exposure 95th Percentile Estimates	Benchmark MOE (= Total UF)
		WORKER MOE[1]	
		Pre EC	
DEVELOPMENTAL EFFECTS Decreased live litter size (F_1) (WIL Research, 2001)	31	**17.5**	100

Notes: [1]MOEs (HEC in ppm/exposure estimate in ppm) lower than the Benchmark MOE (Total UF) indicate potential health risks and are denoted in **bold**.

Table 4-8 Non-Cancer Risk Estimates for Acute Inhalation Exposures Following Occupational Use of 1-BP in Spot Cleaning at Dry Cleaners Based on Modeling

Health Effect, Endpoint and Study	Acute HEC (ppm)	Acute Exposure 95th Percentile Estimates				Benchmark MOE (= Total UF)
		WORKER (NEAR-FIELD) MOE[1]		OCCUPATIONAL NON-USER (FAR-FIELD) MOE		
		Pre EC	Post EC with 90% Efficiency	Pre EC	Post EC with 90% Efficiency	
DEVELOPMENTAL EFFECTS Decreased live litter size (F_1) (WIL Research, 2001)	31	**3.28**	**32.8**	**8.2**	**82**	100

Notes: [1]MOEs (HEC in ppm/exposure estimate in ppm) lower than the Benchmark MOE (Total UF) indicate potential health risks and are denoted in **bold**.

Table 4-9 Non-Cancer Risk Estimates for Acute Inhalation Exposures Following Occupational Use of 1-BP in Vapor Degreasing Based on Monitoring Data

Health Effect, Endpoint and Study	Acute HEC (ppm)	Acute Exposure 95th Percentile Estimates				Benchmark MOE (= Total UF)
		WORKER MOE[1]		OCCUPATIONAL NON-USERS MOE[1]		
		Pre EC	Post EC	Pre EC	Post EC	
DEVELOPMENTAL EFFECTS Decreased live litter size (F_1) (WIL Research, 2001)	31	**0.65**	**3.69**	**6.33**	1550	100

Notes: [1]MOEs (HEC in ppm/exposure estimate in ppm) lower than the Benchmark MOE (Total UF) indicate potential health risks and are denoted in **bold**.

Table 4-10 Non-Cancer Risk Estimates for Acute Inhalation Exposures Following Occupational Use of 1-BP in Vapor Degreasing Based on Modeling

Health Effect, Endpoint and Study	Acute HEC (ppm)	Acute Exposure 95th Percentile Estimates						Benchmark MOE (= Total UF)
		WORKER (NEAR-FIELD) MOE[1]			OCCUPATIONAL NON-USER (FAR-FIELD) MOE[1]			
		Pre EC	Post EC with 90% Efficiency	Post EC with 98% Efficiency	Pre EC	Post EC with 90% Efficiency	Post EC with 98% Efficiency	
DEVELOPMENTAL EFFECTS Decreased live litter size (F_1) (WIL Research, 2001)	31	**1.21**	**12.1**	**61**	**3.30**	**33.0**	165	100

Notes: [1]MOEs (HEC in ppm/exposure estimate in ppm) lower than the Benchmark MOE (Total UF) indicate potential health risks and are denoted in **bold**.

Table 4-11 Non-Cancer Risk Estimates for Acute Inhalation Exposures Following Occupational Use of 1-BP in Cold Cleaning Based on Monitoring Data

Health Effect, Endpoint and Study	Acute HEC (ppm)	Acute Exposure 95th Percentile Estimates	Acute 'What If' Estimates	Benchmark MOE (= Total UF)
		WORKER MOE[1]	OCCUPATIONAL NON-USER MOE[1]	
		Pre EC	Pre EC	
DEVELOPMENTAL EFFECTS Decreased live litter size (F_1) (WIL Research, 2001)	31	**0.66**	**11.92**	100

Notes: [1]MOEs (HEC in ppm/exposure estimate in ppm) lower than the Benchmark MOE (Total UF) indicate potential health risks and are denoted in **bold**.

Table 4-12 Non-Cancer Risk Estimates for Acute Inhalation Exposures Following Occupational Use of 1-BP in Cold Cleaning Based on Modeling

Health Effect, Endpoint and Study	Acute HEC (ppm)	Acute Exposure 95th Percentile Estimates						Benchmark MOE (= Total UF)
		WORKER (NEAR-FIELD) MOE[1]			OCCUPATIONAL NON-USER (FAR-FIELD) MOE[1]			
		Pre EC	Post EC with 90% Efficiency	Post EC with 98% Efficiency	Pre EC	Post EC with 90% Efficiency	Post EC with 98% Efficiency	
DEVELOPMENTAL EFFECTS Decreased live litter size (F_1) (WIL Research, 2001)	31	**4.0**	**40**	198	**10.8**	108	538	100

Notes: [1]MOEs (HEC in ppm/exposure estimate in ppm) lower than the Benchmark MOE (Total UF) indicate potential health risks and are denoted in **bold**.

Table 4-13 Non-Cancer Risk Estimates for Acute Inhalation Exposures Following Occupational Use of 1-BP in Aerosol Degreasing Based on Monitoring Data

Health Effect, Endpoint and Study	Acute HEC (ppm)	Acute Exposure 95th Percentile Estimates		Benchmark MOE (= Total UF)
		WORKER MOE[1]		
		Pre EC	Post EC	
DEVELOPMENTAL EFFECTS Decreased live litter size (F_1) (WIL Research, 2001)	31	**0.98**	**5.64**	100

Notes: [1]MOEs (HEC in ppm/exposure estimate in ppm) lower than the Benchmark MOE (Total UF) indicate potential health risks and are denoted in **bold**.

Table 4-14 Non-Cancer Risk Estimates for Acute Inhalation Exposures Following Occupational Use of 1-BP in Aerosol Degreasing Based on Modeling

Health Effect, Endpoint and Study	Acute HEC (ppm)	Acute Exposure 95th Percentile Estimates				Benchmark MOE (= Total UF)
		WORKER (NEAR-FIELD) MOE[1]		OCCUPATIONAL NON-USER (FAR-FIELD) MOE[1]		
		Pre EC	Post EC with 90% Efficiency	Pre EC	Post EC with 90% Efficiency	
DEVELOPMENTAL EFFECTS Decreased live litter size (F_1) (WIL Research, 2001)	31	**4.55**	**45.5**	**9.1**	**91**	100

Notes: [1]MOEs (HEC in ppm/exposure estimate in ppm) lower than the Benchmark MOE (Total UF) indicate potential health risks and are denoted in **bold**.

Table 4-15 Non-Cancer Risk Estimates for Acute Inhalation Exposure Following Consumer Uses of 1-BP

Health Effect Domain, Endpoint and Study	Acute HEC (ppm)*	AEROSOL SPRAY ADHESIVE MOE[1]		AEROSOL SPOT REMOVER MOE[1]		AEROSOL SPRAY CLEANERS AND DEGREASERS						Benchmark MOE (= Total UF)
						ENGINE DEGREASER MOE[1]		BRAKE CLEANER MOE[1]		ELECTRONICS CLEANER MOE[1]		
		User[2]	Non-User[3]	User[2]	Non-User[3]	User[2]	Non-User[3]	User[2]	Non-User[3]	User[2]	Non-User[3]	
DEVELOPMENTAL EFFECTS Decreased live litter size (F_1) (WIL Research, 2001)	10	**1.7**	**5**	**0.435**	**1.7**	**0.185**	**0.5**	**0.454**	**1.25**	**1.43**	**3.33**	100

Notes:

* The acute consumer HECs were adjusted for 24 hour exposure (see Table 3-1)

[1]MOEs (HEC in ppm/exposure estimate in ppm) lower than the Benchmark MOE (Total UF) indicate potential health risks and are denoted in **bold**.

[2]MOEs for the use categories can be extended to different age groups; however, EPA/OPPT believed the users of these products to be adults.

[3]All age categories (< 1 yrs; 1-2 yrs; 3-5 yrs; 6-10 yrs; 11-15 yrs; 16-20 yrs; and > 21 yrs)

4.3 RISK ESTIMATION FOR CHRONIC, NON-CANCER AND CANCER INHALATION EXPOSURES

Non-cancer and cancer risk estimates for chronic exposures were only derived for occupational scenarios since consumer exposures were not considered chronic in nature.

4.3.1 Non-Cancer Risks for Chronic Occupational Exposure Scenarios

EPA/OPPT estimated the non-cancer risks associated with chronic exposures following 1-BP use in spray adhesive, dry cleaning, and degreasing applications in the workplace. Since 1-BP exposure may be associated with a variety of non-cancer health effects, this assessment estimated risks for liver toxicity, kidney toxicity, reproductive toxicity, developmental toxicity and neurotoxicity following chronic inhalation exposures. EPA/OPPT used the HEC specific to each health effect domain for calculating risk estimates (MOEs). Non-cancer risk estimates for chronic exposures for each occupational use scenario and the lowest HECs for each health effect domain (shown in Table 3-4) are presented below (Table 4-16 through Table 4-26). Risk estimates for a range of health effects were calculated (See excel spreadsheet provided in the supplemental materials).

EPA/OPPT focused on the 95th percentile (high-end) chronic exposure estimates to calculate non-cancer risks (MOEs) for occupational populations at risk. Non-cancer MOE calculations for the 50th percentile (central tendency) exposure estimates are provided in a supplemental Excel spreadsheet (See footnote 12). Monitoring data are presented for all occupational exposure scenarios (i.e., spray adhesives, dry cleaning, spot cleaning, vapor degreasing, cold cleaning and aerosol degreasing); modeling data are presented for all occupational exposure scenarios except spray adhesives.

Spray Adhesives
Based on monitoring data for the 50th (central tendency) and 95th (high-end) percentile exposure estimates, workers and occupational non-users (i.e., sprayers and non-sprayers) in spray adhesive facilities showed risks for all of the health effects examined regardless of the type of engineering controls used (Table 4-16).

Dry Cleaning and Spot Cleaning
Monitoring data for the 50th and 95th percentile exposure estimates from dry cleaning facilities reporting 1-BP use in machines (Table 4-17), and workers using 1-BP formulations when spot cleaning (Table 4-19) showed risks (to workers and occupational non-users) for all of the health effects examined. The MOE for spot cleaning for liver and kidney toxicity in workers based on monitoring data was very close to the benchmark MOE (84.75 and 79.10, respectively, vs. 100; Table 4-19). Exposure data was only available for pre-EC scenarios.

Modeling data for dry cleaning facilities using 1-BP in machines (Table 4-18) and spot cleaning (Table 4-20), showed risks for all health effects examined in workers and occupational non-users (pre-EC). Risks for neurological and developmental effects in workers remained even after engineering controls were applied (post-EC). For occupational non-users (post-EC) for dry cleaning and spot cleaning, the MOE for developmental toxicity was very close to or slightly

over the benchmark MOE (89 and 113, respectively, vs. 100). The 50th percentile exposure estimates for dry cleaning available for pre-EC and post-EC scenarios showed risks for neurological and developmental effects in workers, but only risks for neurological effects were identified for occupational non-users. The 50th percentile exposure estimate for spot cleaning (pre-EC) showed risks for neurological and developmental effects (for workers and occupational non-users).

Vapor Degreasing
Monitoring data for workers using 1-BP for vapor degreasing showed risks for all health effects examined regardless of the type of engineering controls applied (Table 4-21). Likewise, occupational non-users in these facilities also showed risks for all five health effects in the absence of engineering controls (pre-EC), but did not show risks when engineering controls were applied. For the 50th percentile exposure estimates, risks were shown for neurological and developmental effects regardless of the availability of engineering controls for the worker, but not for the occupational non-user when engineering controls were applied.

When using modeling data for workers and occupational non-users using 1-BP for vapor degreasing, risks were shown for all five health effects in the pre-EC scenarios (Table 4-22). Likewise, risks were shown for workers and occupational non-users for neurological effects regardless of the availability of engineering controls. When engineering controls were applied, the MOE for developmental toxicity for workers was very close to the benchmark MOE (84 vs. 100). No risks were shown for developmental effects in occupational non-users when engineering controls were applied. For the 50th percentile exposure estimates, workers showed risks for all health effects (pre-EC); for the occupational non-user (pre-EC), risks for adverse neurological and developmental effects were shown.

Cold Cleaning
Monitoring data for 1-BP in cold cleaning activities showed risks for each of the five health effects examined in workers and occupational non-users (Table 4-23). Data was available only for pre-EC scenarios. The 50th percentile exposure estimates also showed risks for all five health effects.

When using modeling data, workers and occupational non-users showed risks for adverse neurological effects regardless of the type of engineering controls applied (Table 4-24). No risks were shown for developmental effects in either workers or occupational non-users when engineering controls were applied. Neither workers nor occupational non-users showed risks for the remaining health effects when engineering controls were applied. The 50th percentile exposure estimates showed risks for adverse neurological and developmental effects in workers and occupational non-users before engineering controls were applied (pre-EC). Occupational non-users without engineering controls (pre-EC) showed risks for developmental effects.

Aerosol Degreasing
Monitoring data for 1-BP use in aerosol degreasing activities showed risks for each of the five adverse health effects in workers regardless of the type of engineering controls applied (Table

4-25). Data was not available for occupational non-users. The (pre-EC) 50th percentile exposure estimates for workers also showed risks for each of the five adverse health effects examined.

Modeling data for 1-BP use in aerosol degreasing activities showed risks for workers and occupational non-users for each of the five health effects examined pre-EC (Table 4-26). Risk for adverse neurological effects in workers and occupational non-users were shown regardless of the availability of engineering controls. Risks were shown for developmental effects in workers even after engineering controls were applied. No risks were shown for developmental effects in occupational non-users when engineering controls were applied. For the (pre-EC) 50th percentile exposure estimates, risks were shown for adverse neurological and developmental effects in workers and occupational non-users.

Conclusions

Overall, risks were observed across all of the uses in workers and occupational non-users for both monitoring and modeling data in most cases. High-end exposures (95th percentile) without engineering controls (pre-EC) using monitoring and modeling data showed risks for workers and occupational non-users for all five health effects in all the uses evaluated. Both monitoring data and modeling exposure estimates showed risks for adverse effects on the nervous system and development at the high-end (95th percentile) exposures for occupational non-users regardless of the availability of engineering controls for most uses. Risks were reduced when engineering controls were applied (post-EC) in only one use for adverse effects on the nervous system; vapor degreasing (monitoring data for occupational non-users). Risks were reduced when engineering controls were applied (post-EC) in only a few uses for adverse effects on development. These included spot cleaning at dry cleaning (modeling data for occupational non-user); vapor degreasing (monitoring data for occupational non-users; modeling data for occupational non-users), cold cleaning (modeling data for workers and occupational non-users), and aerosol degreasing (modeling data for occupational non-users). Furthermore, there are risks for workers and occupational non-users for the central tendency exposures (50th percentile) before engineering controls are applied (pre-EC) in all of the uses evaluated for adverse effects on the nervous system and development.

Table 4-16 Non-Cancer Risk Estimates for Chronic Inhalation Exposures Following Occupational Use of 1-BP in Spray Adhesives Based on Monitoring Data

Health Effect, Endpoint and Study	Chronic HEC (ppm)	Chronic Exposure 95th Percentile Estimates						Benchmark MOE (= Total UF)
		WORKER (SPRAYER) MOE[1]		WORKER (NON-SPRAYER) MOE[1]		OCCUPATIONAL NON-USER MOE[1]		
		Pre EC	Post EC	Pre EC	Post EC	Pre EC	Post EC	
LIVER Increased hepatocellular vacuolization (WIL Research, 2001)	150	**0.59**	**3.58**	**0.71**	**5.20**	**1.17**	**27.37**	100
KIDNEY Increased pelvic mineralization (WIL Research, 2001)	140	**0.55**	**3.34**	**0.66**	**4.85**	**1.09**	**25.55**	100
REPRODUCTIVE SYSTEM Decreased seminal vesicle weight (Ichihara et al., 2000b)	53	**0.21**	**1.26**	**0.25**	**1.84**	**0.41**	**9.67**	100
DEVELOPMENTAL EFFECTS Decreased live litter size (F_1) (WIL Research, 2001)	43	**0.17**	**1.03**	**0.20**	**1.49**	**0.33**	**7.85**	100
NERVOUS SYSTEM Decreased traction time (Honma et al., 2003)	25	**0.10**	**0.60**	**0.12**	**0.87**	**0.19**	**4.56**	1,000

Notes: [1]MOEs (HEC in ppm/exposure estimate in ppm) lower than the Benchmark MOE (Total UF) indicate potential health risks and are denoted in **bold**.

Table 4-17 Non-Cancer Risk Estimates for Chronic Inhalation Exposures Following Occupational Use of 1-BP in Dry Cleaning Machines Based on Monitoring Data

Health Effect, Endpoint and Study	Chronic HEC (ppm)	Chronic Exposure 95th Percentile Estimates		Benchmark MOE (= Total UF)
		WORKER MOE[1]	OCCUPATIONAL NON-USER MOE[1]	
		Pre EC	Pre EC	
LIVER Increased hepatocellular vacuolization (WIL Research, 2001)	150	**2.99**	**7.27**	100
KIDNEY Increased pelvic mineralization (WIL Research, 2001)	140	**2.79**	**6.78**	100
REPRODUCTIVE SYSTEM Decreased seminal vesicle weight (Ichihara et al., 2000b)	53	**1.06**	**2.57**	100
DEVELOPMENTAL EFFECTS Decreased live litter size (F_1) (WIL Research, 2001)	43	**0.86**	**2.08**	100
NERVOUS SYSTEM Decreased traction time (Honma et al., 2003)	25	**0.50**	**1.21**	1,000

Notes: [1]MOEs (HEC in ppm/exposure estimate in ppm) lower than the Benchmark MOE (Total UF) indicate potential health risks and are denoted in **bold**.

Table 4-18 Non-Cancer Risk Estimates for Chronic Inhalation Exposures Following Occupational Use of 1-BP in Dry Cleaning Machines Based on Modeling

Health Effect, Endpoint and Study	Acute HEC (ppm)	Acute Exposure 95th Percentile Estimates						Benchmark MOE (= Total UF)
		WORKERS: MACHINE UNLOADING AND FINISHING (NEAR-FIELD)MOE[1]		WORKERS: SPOT CLEANING (NEAR-FIELD) MOE[1]		OCCUPATIONAL NON-USERS (FAR-FIELD)		
		Pre EC	Post EC	Pre EC	Post EC	Pre EC	Post EC	
LIVER Increased hepatocellular vacuolization (WIL Research, 2001)	150	**2.5**	**25**	**21.7**	217	**31.0**	310	100
KIDNEY Increased pelvic mineralization (WIL Research, 2001)	140	**2.3**	**23**	**20.2**	202	**28.9**	289	100
REPRODUCTIVE SYSTEM Decreased seminal vesicle weight (Ichihara et al., 2000b)	53	**0.9**	**9**	**7.7**	**77**	**11.0**	110	100
DEVELOPMENTAL EFFECTS Decreased live litter size (F_1) (WIL Research, 2001)	43	**0.7**	**7**	**6.2**	**62**	**8.9**	**89**	100
NERVOUS SYSTEM Decreased traction time (Honma et al., 2003)	25	**0.4**	**4**	**3.6**	**36**	**5.2**	**52**	1,000

Notes: [1]MOEs (HEC in ppm/exposure estimate in ppm) lower than the Benchmark MOE (Total UF) indicate potential health risks and are denoted in **bold**.

Table 4-19 Non-Cancer Risk Estimates for Chronic Inhalation Exposures Following Occupational Use of 1-BP in Spot Cleaning at Dry Cleaners Based on Monitoring Data

Health Effect, Endpoint and Study	Chronic HEC (ppm)	Chronic Exposure 95th Percentile Estimates WORKER MOE[1] Pre EC	Benchmark MOE (= Total UF)
LIVER Increased hepatocellular vacuolization (WIL Research, 2001)	150	**84.75**	100
KIDNEY Increased pelvic mineralization (WIL Research, 2001)	140	**79.10**	100
REPRODUCTIVE SYSTEM Decreased seminal vesicle weight (Ichihara et al., 2000b)	53	**29.94**	100
DEVELOPMENTAL EFFECTS Decreased live litter size (F_1) (WIL Research, 2001)	43	**24.29**	100
NERVOUS SYSTEM Decreased traction time (Honma et al., 2003)	25	**14.1 2**	1,000

Notes: [1]MOEs (HEC in ppm/exposure estimate in ppm) lower than the Benchmark MOE (Total UF) indicate potential health risks and are denoted in **bold**.

Table 4-20 Non-Cancer Risk Estimates for Chronic Inhalation Exposures Following Occupational Use of 1-BP in Spot Cleaning at Dry Cleaners Based on Modeling

Health Effect, Endpoint and Study	Chronic HEC (ppm)	Chronic Exposure 95th Percentile Estimates				Benchmark MOE (= Total UF)
		WORKER (NEAR-FIELD) MOE[1]		OCCUPATIONAL NON-USER (FAR-FIELD) MOE		
		Pre EC	Post EC with 90% Efficiency	Pre EC	Post EC with 90% Efficiency	
LIVER Increased hepatocellular vacuolization (WIL Research, 2001)	150	**16**	159	**40**	396	100
KIDNEY Increased pelvic mineralization (WIL Research, 2001)	140	**15**	148	**37**	369	100
REPRODUCTIVE SYSTEM Decreased seminal vesicle weight (Ichihara et al., 2000b)	53	**6**	**56**	**14**	140	100
DEVELOPMENTAL EFFECTS Decreased live litter size (F_1) (WIL Research, 2001)	43	**5**	**46**	**11**	113	100
NERVOUS SYSTEM Decreased traction time (Honma et al., 2003)	25	**3**	**26**	**7**	**66**	1,000

Notes: [1]MOEs (HEC in ppm/exposure estimate in ppm) lower than the Benchmark MOE (Total UF) indicate potential health risks and are denoted in **bold**.

Table 4-21 Non-Cancer Risk Estimates for Chronic Inhalation Exposures Following Occupational Use of 1-BP in Vapor Degreasing Based on Monitoring Data

Health Effect, Endpoint and Study	Chronic HEC (ppm)	Chronic Exposure 95th Percentile Estimates				Benchmark MOE (= Total UF)
		WORKER MOE[1]		OCCUPATIONAL NON-USERS MOE[1]		
		Pre EC	Post EC	Pre EC	Post EC	
LIVER Increased hepatocellular vacuolization (WIL Research, 2001)	150	**3.1**	**17.9**	**30.6**	7500	100
KIDNEY Increased pelvic mineralization (WIL Research, 2001)	140	**2.9**	**16.7**	**28.6**	7000	100
REPRODUCTIVE SYSTEM Decreased seminal vesicle weight (Ichihara et al., 2000b)	53	**1.1**	**6.3**	**10.8**	2650	100
DEVELOPMENTAL EFFECTS Decreased live litter size (F_1) (WIL Research, 2001)	43	**0.9**	**5.1**	**8.8**	2150	100
NERVOUS SYSTEM Decreased traction time (Honma et al., 2003)	25	**0.5**	**3.0**	**5.1**	1250	1,000

Notes: [1]MOEs (HEC in ppm/exposure estimate in ppm) lower than the Benchmark MOE (Total UF) indicate potential health risks and are denoted in **bold**.

Table 4-22 Non-Cancer Risk Estimates for Chronic Inhalation Exposures Following Occupational Use of 1-BP in Vapor Degreasing Based on Modeling

Health Effect, Endpoint and Study	Chronic HEC (ppm)	Chronic Exposure 95th Percentile Estimates						Benchmark MOE (= Total UF)
		WORKER (NEAR-FIELD) MOE[1]			OCCUPATIONAL NON-USER (FAR-FIELD) MOE[1]			
		Pre EC	Post EC with 98% Efficiency	Post EC with 90% Efficiency	Pre EC	Post EC with 98% Efficiency	Post EC with 90% Efficiency	
LIVER Increased hepatocellular vacuolization (WIL Research, 2001)	150	**5.9**	294	**59**	**16**	798	160	100
KIDNEY Increased pelvic mineralization (WIL Research, 2001)	140	**5.5**	275	**55**	**15**	745	149	100
REPRODUCTIVE SYSTEM Decreased seminal vesicle weight (Ichihara et al., 2000b)	53	**2.1**	104	**21**	**6**	282	**57**	100
DEVELOPMENTAL EFFECTS Decreased live litter size (F_1) (WIL Research, 2001)	43	**1.70**	**84**	**17**	**5.0**	229	**46**	100
NERVOUS SYSTEM Decreased traction time (Honma et al., 2003)	25	**1.0**	**49**	**10**	**3.0**	**133**	**27**	1,000

``Notes: [1]MOEs (HEC in ppm/exposure estimate in ppm) lower than the Benchmark MOE (Total UF) indicate potential health risks and are denoted in **bold**.

Table 4-23 Non-Cancer Risk Estimates for Chronic Inhalation Exposures Following Occupational Use of 1-BP in Cold Cleaning Based on Monitoring Data

Health Effect, Endpoint and Study	Chronic HEC (ppm)	Chronic Exposure 95th Percentile Estimates		Benchmark MOE (= Total UF)
		WORKER MOE[1]	OCCUPATIONAL NON-USER MOE[1]	
		Pre EC	Pre EC	
LIVER Increased hepatocellular vacuolization (WIL Research, 2001)	150	**3.20**	**57.69**	100
KIDNEY Increased pelvic mineralization (WIL Research, 2001)	140	**2.99**	**53.85**	100
REPRODUCTIVE SYSTEM Decreased seminal vesicle weight (Ichihara et al., 2000b)	53	**1.13**	**20.38**	100
DEVELOPMENTAL EFFECTS Decreased live litter size (F_1) (WIL Research, 2001)	43	**0.92**	**16.54**	100
NERVOUS SYSTEM Decreased traction time (Honma et al., 2003)	25	**0.53**	**9.62**	1,000

Notes: [1]MOEs (HEC in ppm/exposure estimate in ppm) lower than the Benchmark MOE (Total UF) indicate potential health risks and are denoted in **bold**.

Table 4-24 Non-Cancer Risk Estimates for Chronic Inhalation Exposures Following Occupational Use of 1-BP in Cold Cleaning Based on Modeling

Health Effect, Endpoint and Study	Chronic HEC (ppm)	Chronic Exposure 95th Percentile Estimates						Benchmark MOE (= Total UF)
		WORKER (NEAR-FIELD) MOE[1]			OCCUPATIONAL NON-USER (FAR-FIELD) MOE[1]			
		Pre EC	Post EC with 98% Efficiency	Post EC with 90% Efficiency	Pre EC	Post EC with 98% Efficiency	Post EC with 90% Efficiency	
LIVER Increased hepatocellular vacuolization (WIL Research, 2001)	150	**19**	962	192	**52**	2604	521	100
KIDNEY Increased pelvic mineralization (WIL Research, 2001)	140	**18**	897	179	**49**	2431	487	100
REPRODUCTIVE SYSTEM Decreased seminal vesicle weight (Ichihara et al., 2000b)	53	**7**	340	**68**	**18**	920	184	100
DEVELOPMENTAL EFFECTS Decreased live litter size (F_1) (WIL Research, 2001)	43	**5.0**	276	**55**	**15.0**	747	149	100
NERVOUS SYSTEM Decreased traction time (Honma et al., 2003)	25	**3.0**	**160**	**32**	**9**	**434**	**87**	1,000

Notes: [1]MOEs (HEC in ppm/exposure estimate in ppm) lower than the Benchmark MOE (Total UF) indicate potential health risks and are denoted in **bold**.

Table 4-25 Non-Cancer Risk Estimates for Chronic Inhalation Exposures Following Occupational Use of 1-BP in Aerosol Degreasing Based on Monitoring Data

Health Effect, Endpoint and Study	Chronic HEC (ppm)	Chronic Exposure 95th percentile Estimate		Benchmark MOE (= Total UF)
		WORKER MOE[1]		
		Pre EC	Post EC	
LIVER Increased hepatocellular vacuolization (WIL Research, 2001)	150	**4.75**	**27.27**	100
KIDNEY Increased pelvic mineralization (WIL Research, 2001)	140	**4.44**	**25.45**	100
REPRODUCTIVE SYSTEM Decreased seminal vesicle weight (Ichihara et al., 2000b)	53	**1.68**	**9.64**	100
DEVELOPMENTAL EFFECTS Decreased live litter size (F_1) (WIL Research, 2001)	43	**1.36**	**7.82**	100
NERVOUS SYSTEM Decreased traction time (Honma et al., 2003)	25	**0.79**	**4.55**	1,000

Notes: [1]MOEs (HEC in ppm/exposure estimate in ppm) lower than the Benchmark MOE (Total UF) indicate potential health risks and are denoted in **bold**.

Table 4-26 Non-Cancer Risk Estimates for Chronic Inhalation Exposures Following Occupational Use of 1-BP in Aerosol Degreasing Based on Modeling

Health Effect, Endpoint and Study	Chronic HEC (ppm)	Chronic Exposure 95th percentile Estimate				Benchmark MOE (= Total UF)
		WORKER (NEAR-FIELD) MOE[1]		OCCUPATIONAL NON-USER (FAR-FIELD) MOE[1]		
		Pre EC	Post EC with 90% Efficiency	Pre EC	Post EC with 90% Efficiency	
LIVER Increased hepatocellular vacuolization (WIL Research, 2001)	150	**22**	220	**44**	439	100
KIDNEY Increased pelvic mineralization (WIL Research, 2001)	140	**21**	206	**41**	409	100
REPRODUCTIVE SYSTEM Decreased seminal vesicle weight (Ichihara et al., 2000b)	53	**8.0**	**78**	**15**	155	100
DEVELOPMENTAL EFFECTS Decreased live litter size (F_1) (WIL Research, 2001)	43	**6.0**	**63**	**13**	126	100
NERVOUS SYSTEM Decreased traction time (Honma et al., 2003)	25	**4.0**	**37**	**7**	**73**	1,000

Notes: [1]MOEs (HEC in ppm/exposure estimate in ppm) lower than the Benchmark MOE (Total UF) indicate potential health risks and are denoted in **bold**.

4.3.2 Cancer Risks for Occupational Scenarios

EPA/OPPT estimated the added cancer risks associated with chronic exposures following 1-BP use in spray adhesive, dry cleaning, and degreasing applications in the workplace. The added cancer risk estimation for 1-BP consisted of multiplying the occupational scenario-specific estimates (i.e., LADC) for both workers and occupational non-users by EPA's inhalation unit risk (IUR) to estimate the added cancer risk. Added cancer risks were expressed as number of cancer cases per million. Figure 4-1 through Figure 4-11 present the incremental individual lifetime cancer risks for the 95th percentile for exposures to 1-BP occurring during the occupational use of spray adhesives, vapor degreasing, dry cleaning, cold cleaning, and aerosol degreasing activities. Occupational exposure estimates for the 50th percentile/central tendency, as well as the entire suite of calculations of cancer risks (including estimates with the 90% engineering control effectiveness) are provided in the supplemental Excel spreadsheet[14].

It was assumed that the exposure frequency (*i.e.*, the amount of days per year for workers or occupational non-users exposed to 1-BP) was 260 days per year and the occupational exposure duration was 40 years over a 70-year lifespan. It is recognized that these exposure assumptions are likely yielding conservative cancer risk estimates, but EPA/OPPT does not have additional information for further refinement.

[14]See attached document titled "Supplemental File 1-BP Cancer Risk Estimates.xlsx".

EPA typically uses a benchmark cancer risk level between $1x10^{-4}$ and $1x10^{-6}$ for determining the acceptability of the cancer risk in a population. Since the benchmark cancer risk level will be determined during risk management, the occupational estimates for added cancer risk were compared to the benchmark levels of 10^{-4}, 10^{-5}, and 10^{-6} incremental or added individual lifetime risk. The benchmark levels were:

1. $1x10^{-6}$: the probability of 1 chance in 1 million of an individual developing cancer
2. $1x10^{-5}$: the probability of 1 chance in 100,000 of an individual developing cancer, which is equivalent to 10 cancer cases in 1 million
3. $1x10^{-4}$: the probability of 1 chance in 10,000 of an individual developing cancer, which is equivalent to 100 cancer cases in 1 million

All three benchmark cancer risk estimates of $1x10^{-4}$, $1x10^{-5}$ and $1x10^{-6}$ (and beyond) were exceeded for all of the uses in workers and occupational non-users for both monitoring and modeling data regardless of the type of engineering controls (pre- and post-EC) with only a few exceptions and only after engineering controls were applied (post-EC). These included vapor degreasing (monitoring data for occupational non-users only exceeded $1x10^{-5}$, Figure 4-6) and cold cleaning (modeling data for occupational non-users only exceeded $1x10^{-5}$, Figure 4-9). Based on monitoring data, spray adhesives showed the greatest cancer risk, followed by dry cleaning, cold cleaning, vapor degreasing, aerosol degreasing, and spot cleaning at dry cleaners. In most cases, benchmark cancer risk estimates were similar between monitoring and modeling within each use.

Figure 4-1 Cancer Risk Estimates for Occupational Use of 1-BP in Spray Adhesives Based on Monitoring Data

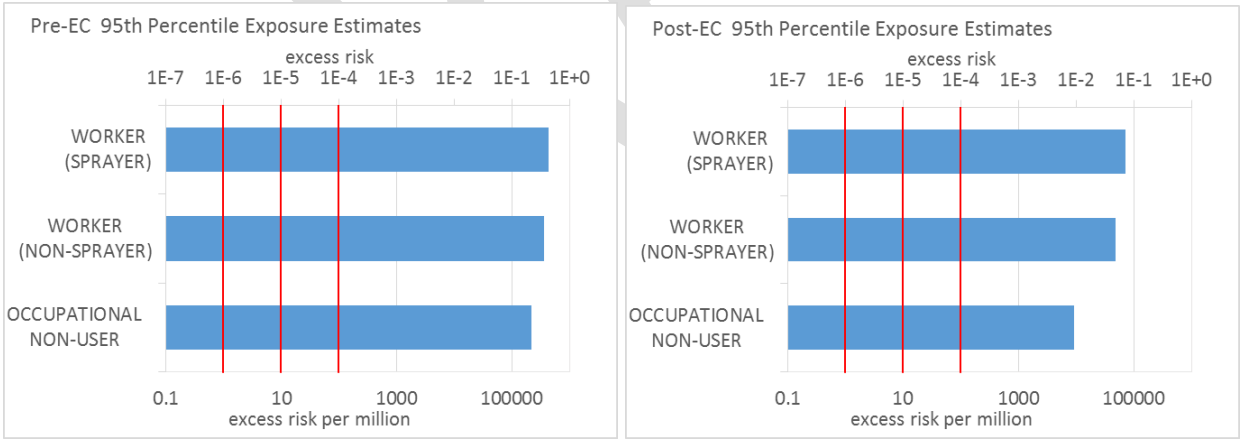


Figure 4-2 Cancer Risk Estimates for Occupational Use of 1-BP in Dry Cleaning Based on Monitoring Data

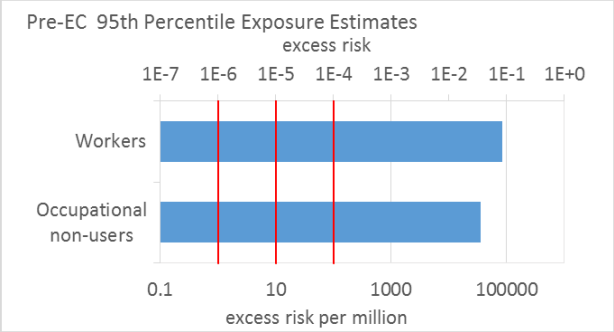


Figure 4-3 Cancer Risk Estimates for Occupational Use of 1-BP in Dry Cleaning Based on Modeling

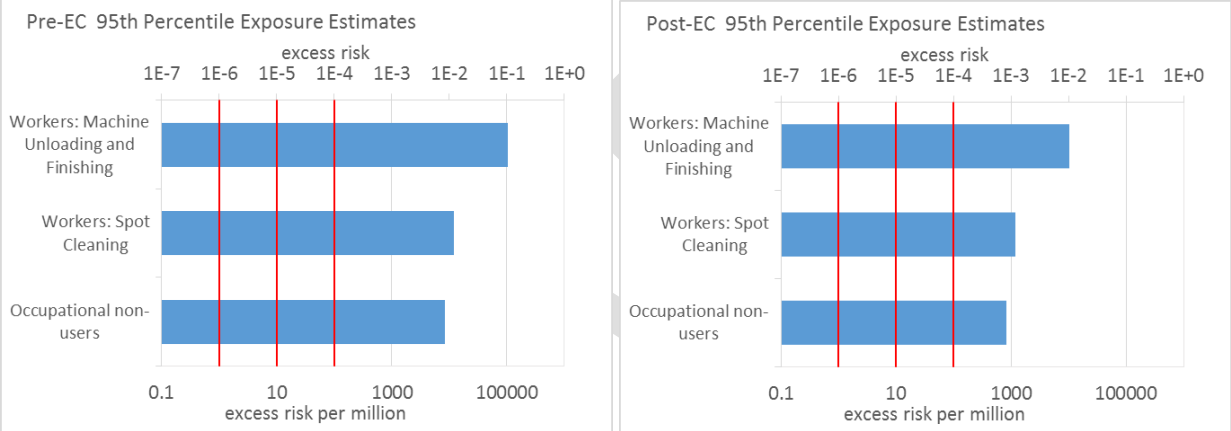


Figure 4-4 Cancer Risk Estimates for Occupational Uses of 1-BP in Spot Cleaning at Dry Cleaners Based on Monitoring Data

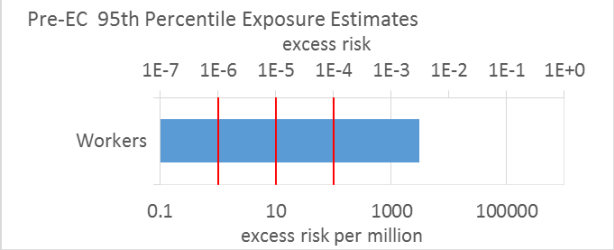


Figure 4-5 Cancer Risk Estimates for Occupational Uses of 1-BP in Spot Cleaning at Dry Cleaners Based on Modeling

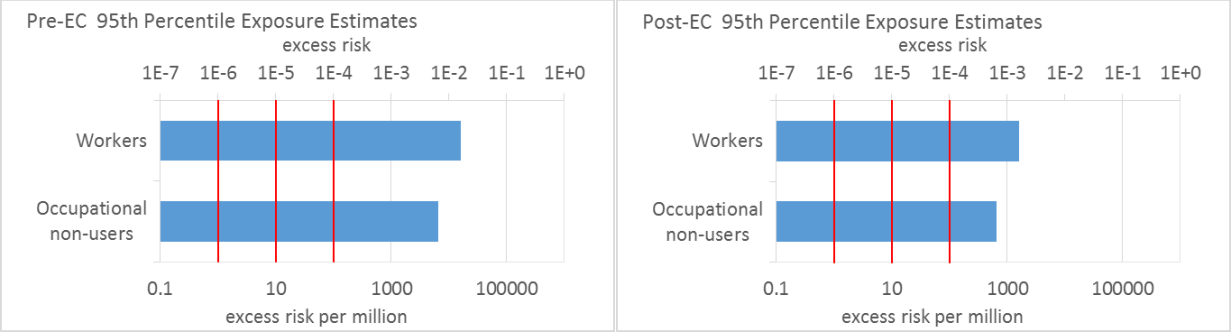


Figure 4-6 Cancer Risk Estimates for Occupational Use of 1-BP in Vapor Degreasing Based on Monitoring Data

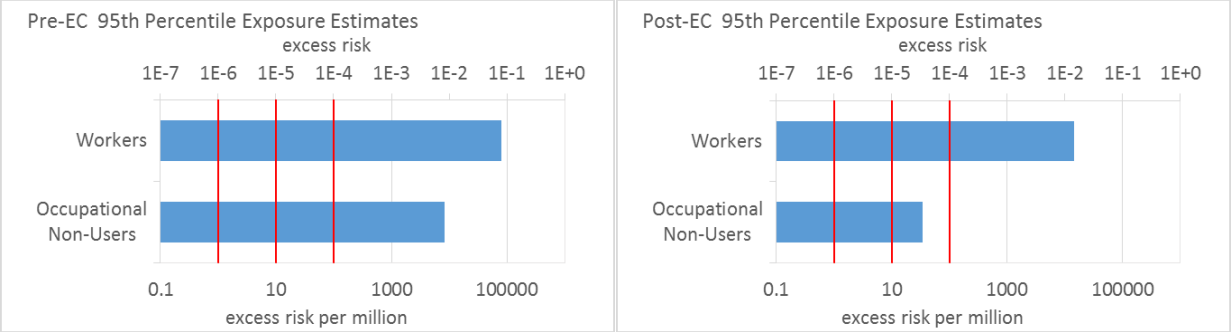


Figure 4-7 Cancer Risk Estimates for Occupational Use of 1-BP in Vapor Degreasing Based on Modeling

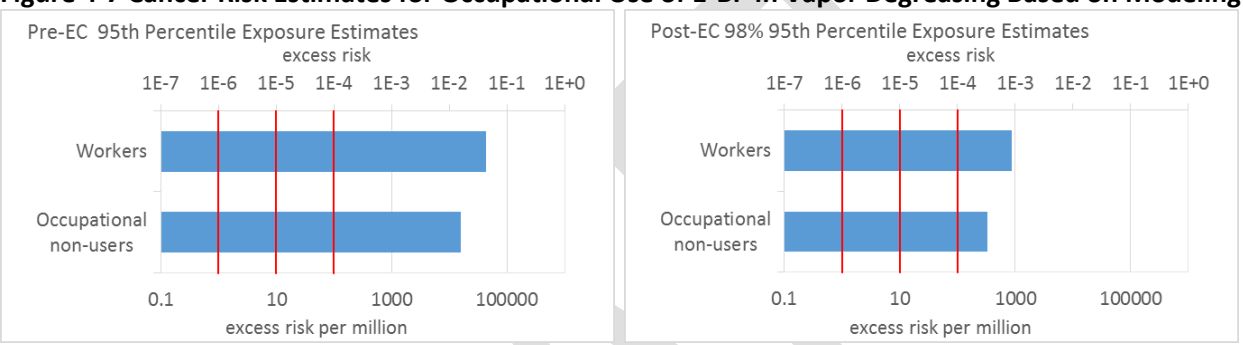


Figure 4-8 Cancer Risk Estimates for Occupational Use of 1-BP in Cold Cleaning Based on Monitoring Data

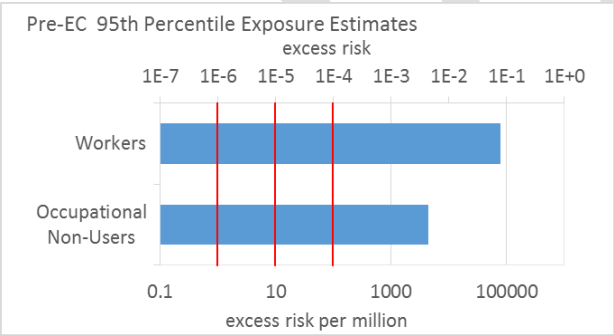


Figure 4-9 Cancer Risk Estimates for Occupational Use of 1-BP in Cold Cleaning Based on Modeling

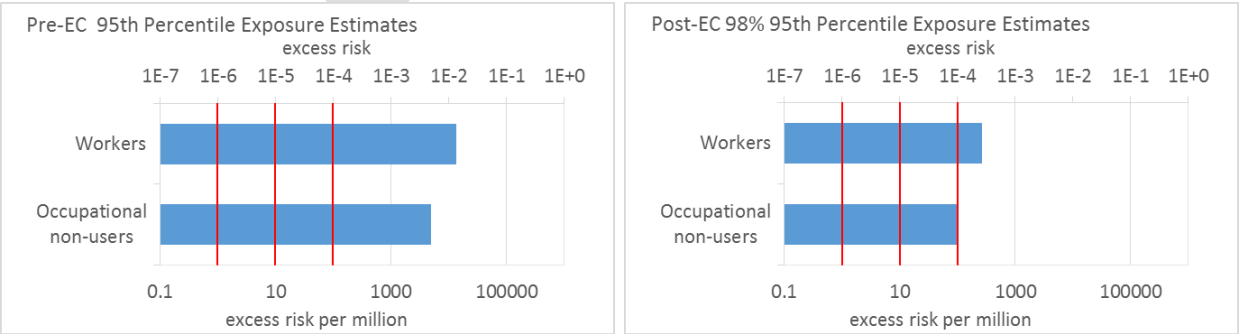


Figure 4-10 Cancer Risk Estimates for Occupational Uses of 1-BP in Aerosol Degreasing Based on Monitoring Data

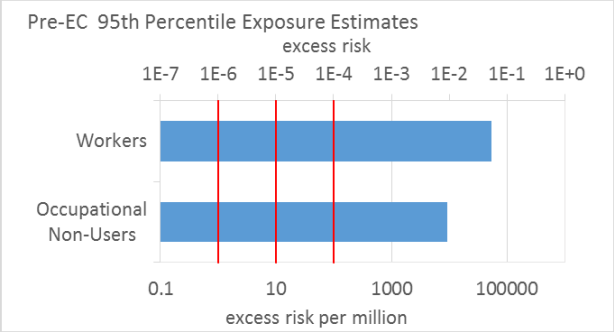
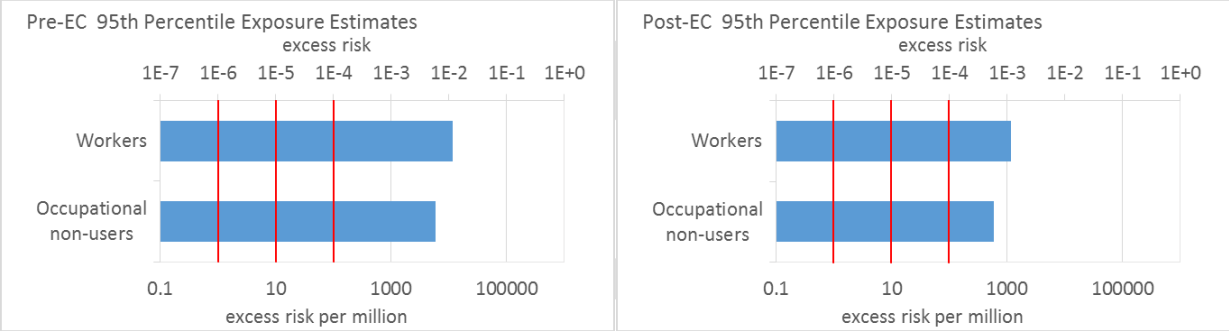


Figure 4-11 Cancer Risk Estimates for Occupational Uses of 1-BP in Aerosol Degreasing Based on Modeling



Added cancer risks calculated for workers and occupational non-users exposed at the 95th percentile exceeded all identified cancer benchmarks (i.e., 1x10^{-4} (1 in 10,000), 1x10^{-5} (1 in 100,000) and 1x10^{-6} (1 in 1,000,000)) in most of the use scenarios evaluated under the scope of this assessment. In most cases a 1,000-fold exceedance of the 1 in 1,000,000 cancer risk benchmark was observed (this corresponds to a cancer risk greater than 1x10^{-3} (or a probability of 1 in 1,000 that an exposed individual will develop cancer). It is important to note however, that this value reflects the added lifetime cancer risk estimated for high end (i.e., 95th percentile) exposures that occur over the assumed duration of an occupational life (i.e. 8 hours/day, 260 days/yr for 40 years of a 70 year lifespan). Although most occupational exposure concentrations at the 50th percentile are about an order of magnitude lower than those at the 95th percentile (Shown in section 2), the associated risk estimates exceeded the 1 in 10,000 cancer benchmark (calculations of cancer risks at the 50th percentile are shown in the supplemental excel file). The range of added cancer risks calculated for workers in each use category are described below. Risk estimates are based on occupational exposure values derived from monitoring and modeling data (with and without engineering controls).

Spray Adhesives Use in Foam Cushion Manufacturing:

For the occupational use of 1-BP in spray adhesives, the range of added cancer risks in workers (sprayers and non-sprayers) exposed at the 95th percentile was 5x10^{-2} to 4x10^{-1} (Figure 4-1). The estimated number of workers potentially exposed in spray adhesive use ranged from 551 to 4,384 (Table 2-1). If the number of workers is roughly in the middle of the estimated range, i.e., about 2,000, and of those workers, 5 percent (100 workers) are exposed at the 95th percentile

exposure concentration or higher for the assumed occupational duration (i.e. 8 hours/day, 260 days/yr for 40 years of a 70 year lifespan), then 5 to 40 workers may have an increased cancer incidence.

For the occupational use of 1-BP in spray adhesives, the 50th percentile estimated exposure concentrations in workers (sprayers and non-sprayers) were roughly 2-fold lower than the 95th percentile (Table 2-2). The range of added cancer risks in workers exposed at the 50th percentile was $3x10^{-2}$ to $2x10^{-1}$. The added cancer risks are lower in workers exposed at the 50th percentile however more workers are exposed at the 50th percentile concentration. If the estimated number of workers is about 2,000 (as described above), and of those workers, half are assumed to be exposed at the 50th percentile exposure concentration or higher for the assumed occupational duration (i.e. 8 hours/day, 260 days/yr for 40 years of a 70 year lifespan), then 30 to 200 workers may have an increased cancer incidence.

Degreasing Use (Vapor, Cold Cleaning and Aerosol):
The range of added cancer risks in workers with 1-BP exposure at the 95th percentile for vapor degreasing was $8x10^{-4}$ to $8x10^{-2}$ (Figure 4-6 and Figure 4-7), for cold cleaning was $3x10^{-4}$ to $8x10^{-2}$ (Figure 4-8 and Figure 4-9) and for aerosol degreasing was $1x10^{-3}$ to $1x10^{-2}$ (Figure 4-10 and Figure 4-11). The estimated number of workers potentially exposed in vapor degreasing ranged from 3,245 to 16,226 (Table 2-8), the number of workers potentially exposed in cold cleaning were not estimated and in aerosol degreasing ranged from 2,227 to 11,137 (Table 2-13). If the number of workers is roughly in the middle of the estimated ranges, i.e., about 10,000 for vapor degreasing and 6,000 for aerosol degreasing, of those workers, 5 percent (500 and 300 workers respectively) are exposed at the 95th percentile exposure concentration or higher for the assumed occupational duration (i.e. 8 hours/day, 260 days/yr for 40 years of a 70 year lifespan), then <1 to 40 workers for vapor degreasing and <1 to 3 workers for aerosol degreasing may have an increased cancer incidence.

For the occupational use of 1-BP in degreasing, the 50th percentile estimated exposure concentrations in workers were roughly one order of magnitude lower than the 95th percentile (Table 2-9 through Table 2-12, Table 2-14, and Table 2-15). The range of added cancer risks in workers with 1-BP exposure at the 50th percentile for vapor degreasing workers was $6x10^{-5}$ to $1x10^{-2}$, for cold cleaning was and for aerosol degreasing were $4x10^{-4}$ to $2x10^{-2}$. The added cancer risks are lower in workers exposed at the 50th percentile however more workers are exposed at the 50th percentile concentration. If the numbers of workers potentially exposed are about 10,000 for vapor degreasing and 6,000 (as described above), and of those workers, if half are exposed at the 50th percentile exposure concentration or higher for the assumed occupational duration (i.e. 8 hours/day, 260 days/yr for 40 years of a 70 year lifespan), then < 1 to 50 workers for vapor degreasing and cold cleaning and 1 to 60 workers for aerosol degreasing may have an increased cancer incidence.

Dry Cleaning and Spot Cleaning Uses:
For the occupational use of 1-BP in dry cleaning and spot cleaning, the range of added cancer risks in workers with 1-BP exposure at the 95th percentile was $1x10^{-3}$ to $1x10^{-1}$. The estimated

number of workers potentially exposed in dry cleaning shops is 821 (Table 2-3). If 5 percent (41 workers) are exposed at the 95th percentile exposure concentration or higher for the assumed occupational duration (i.e. 8 hours/day, 260 days/yr for 40 years of a 70 year lifespan), then <1 to 4 workers may have an increased cancer incidence.

For the occupational use of 1-BP in dry cleaning and spot cleaning, the 50th percentile estimated exposure concentrations in workers were roughly 10-fold lower than the 95th percentile (Table 2-4 through Table 2-7). The range of added cancer risks in workers exposed at the 50th percentile was $3x10^{-4}$ to $5x10^{-2}$. The added cancer risks are lower in workers exposed at the 50th percentile however more workers are exposed at the 50th percentile concentration. If the number of workers potentially exposed in dry cleaning shops is 821 (Table 2-3), and of those workers if half are exposed at the 50th percentile exposure concentration or higher for the assumed occupational duration (i.e. 8 hours/day, 260 days/yr for 40 years of a 70 year lifespan), then <1 to 21 workers may have an increased cancer incidence.

Overall, there are significant increased risks to developing cancer in workers if they are exposed to 1-BP for the assumed occupational duration (i.e. 8 hours/day, 260 days/yr for 40 years of a 70 year lifespan) at the concentrations estimated for the spray adhesive, dry cleaning and degreasing uses. While not included in the calculations above occupational non-users also have significant increased risks to developing cancer if they are exposed to 1-BP for the assumed occupational duration (i.e. 8 hours/day, 260 days/yr for 40 years of a 70 year lifespan) at the concentrations estimated as shown by the added cancer risks in Figure 4-1 through Figure 4-11. The cancer risk calculations are based on assumptions and have uncertainties such as the exposure frequency of 260 days/year and 40 years of exposure over a 70-year lifespan which may produce conservative cancer risk estimates. The assumptions and uncertainties are further explained in the following section.

4.4 ASSUMPTIONS AND KEY SOURCES OF UNCERTAINTY

The characterization of variability and uncertainty is fundamental to any risk assessment. Variability refers to “the true heterogeneity or diversity in characteristics among members of a population (i.e., inter-individual variability) or for one individual over time (intra-individual variability)” (U.S. EPA, 2001). The risk assessment was designed to reflect critical sources of variability to the extent allowed by available methods and data and given the resources and time available.

On the other hand, uncertainty is “the lack of knowledge about specific variables, parameters, models, or other factors” (U.S. EPA, 2001) and can be described qualitatively or quantitatively. Uncertainties in the risk assessment can raise or lower the confidence of the risk estimates. In this assessment, the uncertainty analysis also included a discussion of data gaps/limitations.

The next sections describe the uncertainties and data gaps in the exposure, hazard/dose-response and risk characterization.

4.4.1 Uncertainties and Limitations of the Occupational Exposure Assessment

4.4.1.1 Variability

In the 1-BP exposure assessment, EPA/OPPT addressed variability by applying a Monte Carlo simulation to the vapor degreasing, cold cleaning, aerosol degreasing, and spot cleaning scenarios. The Monte Carlo method is a stochastic technique for propagating variability through a model.

EPA/OPPT addressed variability in the exposure models by identifying key model parameters to apply a statistical distribution that mathematically defines the parameter's variability. EPA/OPPT defined statistical distributions for parameters using documented statistical variations where available.

4.4.1.2 Uncertainties and Limitations

Uncertainty is *"the lack of knowledge about specific variables, parameters, models, or other factors"* and can be described qualitatively or quantitatively (U.S. EPA, 2001). The following sections discuss uncertainties in each of the assessed 1-BP use scenarios.

4.4.1.2.1 Number of Workers

There are a number of uncertainties surrounding the estimated number of workers potentially exposed to 1-BP, as outlined below. Most are unlikely to result in a systematic underestimate or overestimate, but could result in an inaccurate estimate. The exception is for our inability to estimate the percentage of workers in the degreasing application group using 1-BP rather than other solvents, which results in an overestimate of exposed workers.

First, BLS' OES employment data for each industry/occupation combination are only available at the 3-, 4-, or 5-digit NAICS level, rather than the full 6-digit NAICS level. This lack of granularity could result in an overestimate of the number of exposed workers if some 6-digit NAICS are included in the less granular BLS estimates but are not, in reality, likely to use solvents for the assessed applications. EPA/OPPT addressed this issue by refining the OES estimates using total employment data from the U.S. Census' SUSB (2012) (see Appendix F). However, this approach assumes that the distribution of occupation types (SOC codes) in each 6-digit NAICS is equal to the distribution of occupation types at the parent 5-digit NAICS level. If the distribution of workers in occupations with solvent exposure differs from the overall distribution of workers in each NAICS, then this approach will result in inaccuracy, but would be unlikely to systematically either overestimate or underestimate the count of exposed workers.

Second, EPA/OPPT's judgments about which industries (represented by NAICS codes) and occupations (represented by SOC codes) are associated with degreasing, dry cleaning, and the use of spray adhesives are based on EPA/OPPT's understanding of how solvents are used in each industry. Designations of which industries and occupations have potential exposures is nevertheless subjective, and some industries/occupations with few exposures might

erroneously be included, or some industries/occupations with exposures might erroneously be excluded. This would result in inaccuracy, but would be unlikely to systematically either overestimate or underestimate the count of exposed workers.

Finally, the accuracy of estimates of the percentage of workers using 1-BP instead of other chemicals could fail to capture either the market penetration or any changes in market penetration over time. The estimates for dry cleaning and spray adhesive applications are based on the EPA market reports (U.S. EPA, 2013b, c), but these single point estimates might not fully or accurately capture 1-BP use.

For degreasing, EPA/OPPT referenced EPA's Work Plan Chemical Assessment for TCE to determine the NAICS industry sectors where solvent degreasing may occur. However, it should be noted that degreasing is not an industry-specific activity. Many of these industries do not perform degreasing as a primary part of their business; some facilities within the degreasing NAICS codes may not perform degreasing at all. Therefore, using a broad range of NAICS codes likely overestimate the number of workers and occupational non-users. Additionally, there is a lack of data on the prevalence of 1-BP use in solvent degreasing. Therefore, EPA/OPPT presented the total number of workers in the industry/occupation combinations using *any* solvents rather than just 1-BP. This likely results in an overestimate of the number of exposed workers (see Appendix F).

4.4.1.2.2 Analysis of Exposure Monitoring Data

This report uses existing worker exposure monitoring data to assess exposure to 1-BP during spray adhesive, vapor degreasing, aerosol degreasing, cold cleaning, dry cleaning, and spot cleaning applications. To analyze the exposure data, EPA/OPPT categorized each PBZ data point as either "worker" or "occupational non-user". In addition, EPA/OPPT categorized the data into "pre-EC" and "post-EC" scenarios. The categorizations are based on descriptions of worker job activity and engineering control as provided in literature and EPA's judgment. Some data sources, such as the OSHA IMIS, lack details on the worker activity and presence of ventilation. Where information is not available, EPA/OPPT assumed no specific engineering controls are implemented and categorized the data as a "pre-EC" scenario.

The analysis combines exposure data from multiple sources. The aggregated data show a distribution of exposure levels at multiple facilities. It should be noted that the environmental conditions and engineering controls likely differ from facility to facility. The representativeness of the exposure levels and the engineering controls used at these facilities has not been evaluated. For each 1-BP use, the facilities included in the pre-EC and post-EC scenario may also differ. Therefore, the aggregated exposure data should not be used to calculate the engineering control effectiveness; rather, any such calculation should be done on the facility-level. The post-EC exposure levels presented in this report represent a snapshot of possible exposure levels when engineering controls are implemented.

Exposures for occupational non-users can vary substantially. Most data sources do not sufficiently describe the proximity of these employees to the 1-BP exposure source. As such, exposure levels for the "occupational non-user" category will have high variability depending

on the specific work activity performed. It is possible that some employees categorized as "occupational non-user" have exposures similar to those in the "worker" category depending on their specific work activity pattern.

Some data sources may be inherently biased. For example, NIOSH HHEs for the spray adhesive use were conducted to address concerns regarding adverse human health effects reported following 1-BP exposure with spray adhesive use in furniture manufacturing. Two HHEs were requested by the North Carolina Department of Labor; one was conducted in response to a confidential request submitted by the facility's employees. OSHA IMIS data are obtained from OSHA inspections, which also may be the result of worker complaints, and may provide exposure results that are generally more conservative than the industry average.

There are limited exposure monitoring data in literature for cold cleaning and for spot-cleaning. Where there are few data points available, it is unlikely the results will be representative of worker exposure across the industry. Additionally, there is uncertainty as to whether the exposure monitoring data presented for cold cleaning are specific to a "cold cleaner" of interest, or whether they are associated with other types of degreasing equipment.

The 95th and 50th percentile exposure concentrations were calculated using available data. The 95th percentile exposure concentration is intended to represent a high-end exposure level, while the 50th percentile exposure concentration represents typical exposure level. The underlying distribution of the data, and the representativeness of the available data, are not known.

EPA/OPPT calculated ADC and LADC values assuming a high-end exposure duration of 260 days per year over 40 years. This assumes the workers and occupational non-users are regularly exposed during their entire working lifetime, which likely results in an overestimate. Individuals may change jobs during the course of their career such that they are no longer exposed to 1-BP, and that actual ADC and LADC values become lower than the estimates presented.

4.4.1.2.3 Near-Field / Far-Field Model Framework

Because the near-field / far-field approach applies to all of the workplaces modeled, the following describe uncertainties and simplifying assumptions generally associated with this modeling approach:

- There is some degree of uncertainty associated with each model input parameter. In general, the model inputs were determined based on review of available literature. Where the distribution of the input parameter is known, a distribution is assigned to capture uncertainty in the Monte Carlo analysis. Where the distribution is unknown, a uniform distribution is often used. The use of a uniform distribution will capture the low-end and high-end values, but may not accurately reflect actual distribution of the input parameters.
- The model assumes the near-field and far-field are each well mixed, such that each of these zones can be approximated by a single, average concentration.

- All of the emissions from the facility are assumed to enter the near-field zone. This assumption will overestimate exposures and risks in facilities where some of the emissions do not enter the airspaces relevant to the worker exposure modeling.
- The exposure models are actually modeling airborne concentrations. Exposures are calculated by assuming the workers spend the entire activity time in each of their respective exposure zones (i.e., the worker in the near field and the occupational non-user in the far field). Since vapor and cold degreasing involve automated processes, a worker may actually walk away from the near-field during part of the process and return when it is time to unload the degreaser. As such, assuming the worker is exposed at the near-field concentration for the entire worker activity duration may result in an overexposure.
- For certain 1-BP applications (e.g. vapor degreasing and spot cleaning), 1-BP vapor is assumed to be emitted continuously while the equipment operates, with a constant vapor generation rate. It is possible that actual vapor generation will vary with time. However, small time variability in vapor generation is unlikely to have a large impact in the exposure estimates as exposures are calculated as a time-weighted average.
- The exposure models represent model workplace settings for each 1-BP application (e.g. vapor degreasing, cold cleaning, dry cleaning, etc). While monitoring studies were used to determine appropriate model input values during model development, it should be noted that the models have not been regressed or fitted with monitoring data. Therefore, the model results do not represent specific facilities being monitored.
- The models represent a baseline scenario that do not have LEV. EPA/OPPT does not have adequate data to construct LEV systems into the exposure models. Additionally, there is no data on the fraction of U.S. facilities that use LEV. "What-if" values on engineering control effectiveness are applied to the model baseline to provide post-EC scenarios. These values were obtained by reviewing statements made in published literature regarding potential emission or exposure reductions after implementation of engineering control or equipment substitution.

Each subsequent section below discuss uncertainties associated with the individual model.

4.4.1.2.4 Vapor Degreasing and Cold Cleaning Model

The vapor degreasing and cold cleaning assessments use a near-field / far-field approach to model worker exposure. In addition to the uncertainties described above, the vapor degreasing and cold cleaning models have the following uncertainties:

- The indoor air speed is based on Baldwin and Maynard (1998) measurements at a variety of workplaces (e.g. industrial facilities, office, schools, etc.). The range of indoor wind speed at degreasing facilities may be more narrow than the range of values measured by Baldwin and Maynard.
- To estimate vapor generation rate for vapor degreasing, EPA/OPPT references a 1-BP emission factor developed by CARB for the California Solvent Cleaning Emissions Inventories (CARB, 2011). The emission factor is an average emission for the "vapor degreasing" category for the California facilities surveyed by CARB. The category

includes batch-loaded vapor degreaser, aerosol surface preparation process, and aerosol cleaning process. For the purpose of modeling, EPA/OPPT assumes the 1-BP emission factor is entirely attributed to vapor degreasing applications. The representativeness of the emission factor for vapor degreasing emissions in other geographic locations within the U.S. is uncertain.

- The CARB emission factor covers batch degreasing units. However, CARB does not further specify whether these are open-top vapor degreasers, enclosed, or other types of batch degreasers. EPA/OPPT assumes the emission factor is representative of open-top vapor degreaser, as it is the most common design for batch units. In addition, EPA/OPPT assumes that the surveyed facilities likely switched to using 1-BP, an alternative, non-HAP solvent, as a way of complying with Federal and State regulations for HAP halogenated solvents (i.e., chemical substitution, rather than equipment changes).
- The CARB emission factor, in the unit of pound per employee-year, was developed for the purpose of estimating annual emissions. These types of emission factor typically reflect the amount of solvent lost / emitted, some of which may not be relevant to worker exposure. For example, 1-BP emitted and captured through a stack may not result in worker exposure. Therefore, assuming all of the 1-BP is emitted into the workplace air may result in overestimating of exposure. In addition, the use of an annual emission factor does not capture time variability of emissions. The approach assumes a constant emission rate over a set number of operating hours, while actual emissions and worker exposures will vary as a function of time and worker activity.
- EPA/OPPT combines the CARB emission factor with nationwide Economic Census employment data across 78 NAICS industry sector codes. It should be noted that vapor degreasing is not an industry-specific operation. Only a subset of facilities within the 78 selected industry sectors are expected to operate vapor degreasers. Therefore, the industry-average employment data may not be representative of the actual number of employees at vapor degreasing facilities.
- To estimate worker exposure during cold cleaning, EPA/OPPT applied an emission reduction factor to the vapor degreasing model by comparing the AP-42 emission factors for the two applications. The AP-42 emission factors are dated. Furthermore, the cold cleaning model results have not been validated with actual monitoring data.
- Both models assume the equipment operates two hours per day. The value was derived from the 2001 CEB Generic Scenario for the Use of Vapor Degreasers (ERG, 2001). Actual worker exposure will increase as the hours of equipment operation increases.
- The exposure models assume that exposures are zero outside of the degreasing hours per day. However, even if a worker were to completely remove the source of 1-BP emissions at the conclusion of a task, residual 1-BP would remain in the air and decay to zero as the ventilation replaces the contaminated air with clean air. EPA/OPPT assumes the workers and occupational non-users remove themselves from the contaminated near- and far-field zones at the conclusion of the task, such that they are no longer exposed to the residual airborne concentrations. Note that this assumption does not apply to aerosol degreasing, where the task continues for seven hours of the eight-hour

work day. EPA/OPPT only assumes there are no exposures during the first hour as the workers prepare for the aerosol degreasing task.

- The model assumes an exposure reduction of 90 percent with engineering control and 98 percent with equipment substitution based on two studies. In reality, engineering controls and their effectiveness are site-specific, and the representativeness of these studies is not known.

4.4.1.2.5 Aerosol Degreasing Model

The aerosol degreasing assessment also uses a near-field/far-field approach to model worker exposure. Uncertainties and limitations with the near-field/far-field model have been described previously. Additional uncertainties associated with the aerosol degreasing scenario are presented below:

- The model references indoor air speed measurements from the Baldwin and Maynard (1998) study, which covers a variety of workplaces (e.g. industrial facilities, office, schools, etc.). The variability in wind speed contributes to a wide range of exposure levels; actual wind speed at aerosol degreasing facilities may be less variable than the data set presented in Baldwin and Maynard.
- The model assumes the worker applies the aerosol degreaser once per hour with seven applications in an eight-hour work day. In reality, the application frequency will vary depending on the workload at each facility.
- The model assumes an application amount of 27.5 grams of degreaser per application. This value is based on a 2014 literature study for general degreasing applications (oven cleaning); it is uncertain whether this value is representative of a typical aerosol degreasing facility. EPA/OPPT assumes the amount per application is not chemical-specific. The actual application amount will depend on the specific work practice and surface area to be cleaned.
- Information on engineering control effectiveness was not found for this workplace setting. The post-EC scenario references Wadden et al. (1989), which estimates 90 percent LEV effectiveness for an open-top vapor degreaser. The applicability of this value to the aerosol degreasing model has not been demonstrated.

4.4.1.2.6 Dry Cleaning Model

The multi-zone dry cleaning model also uses a near-field/far-field approach. Uncertainties and limitations with the near-field/far-field model have been described previously. Additional uncertainties associated with the dry cleaning scenario are presented below:

- The model references indoor air speed measurements from the Baldwin and Maynard (1998) study, which covers a variety of workplaces (e.g. industrial facilities, office, schools, etc.). The variability in wind speed contributes to a wide range of exposure levels; actual wind speed at dry cleaning facilities may be less variable than the data set presented in Baldwin and Maynard.

- The model assumes each facility only has one dry cleaning machine, cleaning one to fourteen loads of garments per day. While the dry cleaning facilities in Blando et al. (2010) and NIOSH (2010) appear to only have one machine, the representativeness of these two studies is not known. Larger facilities are likely to have more machines, which could result in additional 1-BP exposures.
- The model conservatively uses a hemispherical volume based on the dry cleaning machine door diameter as the near-field for machine unloading. The small near-field volume results in a large spike in concentration when the machine door is opened, where any residual 1-BP solvent is assumed to be instantaneously released into the near-field. In reality, the residual solvent will likely be released continuously over a period of time. In addition, the worker may move around while unloading the garments, such that the worker's breathing zone will not always be next to the machine door throughout the duration of this activity. Therefore, these assumptions may result in an overestimate of worker exposure during machine unloading.
- Many of the model input parameters were obtained from (von Grote et al., 2003), which is a German study. Aspects of the U.S. dry cleaning facilities may differ from German facilities. However, it is not known whether the use of German data will under- or over-estimate exposure.
- Information on engineering control effectiveness was not found for this workplace setting. The post-EC scenario references Wadden et al. (1989), which estimates 90 percent LEV effectiveness for an open-top vapor degreaser. This value may not be conservative, as it is uncertain whether engineering control at dry cleaning facilities could achieve 90 percent exposure reduction.
- EPA/OPPT assumed dry cleaning shops operate twelve hours a day, and individual employees work eight-hour shifts. The model exposures are therefore calculated as 8-hr TWA. In some cases, owners of small dry cleaning shops may be present at the shop longer than a typical eight-hour shift, and could have a longer exposure duration. Therefore, the use of 8-hr TWA values is not expected to present a "worst-case" or conservative exposure estimate.

4.4.1.2.7 Spot Cleaning Model

The spot cleaning assessment also uses a near-field/far-field approach to model worker exposure. Uncertainties and limitations with the near-field/far-field model have been described previously. Additional uncertainties associated with the spot cleaning scenario are presented below:

- The model references indoor air speed measurements from the Baldwin and Maynard (1998) study, which covers a variety of workplaces (e.g. industrial facilities, office, schools, etc.). The variability in wind speed contributes to a wide range of exposure levels; actual wind speed at dry cleaning facilities may be less variable than the data set presented in Baldwin and Maynard.
- The model estimates a use rate of 16 gallons per year spot cleaner. This value was derived using a MADEP case study for one specific dry cleaner in Massachusetts, handling 100 pieces of garments per day. MADEP noted that the size of each dry cleaner

can vary substantially. As such, the spot cleaner use rate will also vary by the individual facility work load.

Information on engineering control effectiveness was not found for this workplace setting. The post-EC scenario references Wadden et al. (1989), which estimates 90 percent LEV effectiveness for an open-top vapor degreaser. This value may not be conservative, as it is uncertain whether engineering control at dry cleaning facilities could achieve 90 percent exposure reduction.

4.4.2 Uncertainties of the Consumer Exposure Assessment

Due to the absence of indoor air monitoring data from consumer use of 1-BP, the EPA used modeling based on experimental data, survey information and a number of assumptions to estimate indoor air concentrations resulting from the use of consumer spray adhesives, aerosol spot removers and aerosol cleaners and degreasers. Use of a modeling approach to estimate indoor air concentration has a number of limitations, as detailed below.

4.4.2.1 Consumer Use Information

Although EPA/OPPT found some information about 1-BP products intended for consumer use, there is some general uncertainty regarding the nature and extent of the consumer use of 1-BP for the products within the scope of this assessment. The model input for the use profile was derived from an older products survey (Westat, 1987), thereby introducing uncertainty as to the relevance for current consumer settings where spray adhesives, spot removers or aerosol cleaners and degreasers containing 1-BP may be used. EPA/OPPT considers the assumptions used for the model exposure scenarios to be reasonable, but recognizes that these assumptions may not reflect actual current usage patterns or use conditions in consumer settings. Consequently, the limited data and variable results associated with different exposure scenarios, when used to extrapolate to consumer inhalation risk characterization, have associated uncertainty.

4.4.2.2 Model Assumptions and Input Parameters

There is a high degree of confidence in the consumer product weight fractions identified for the consumer products evaluated in this assessment. Also, there is a medium to high degree of confidence in certain modeling inputs to the CEM model, including vapor pressure, molecular weight, room volumes, whole house volume, air exchange rate, body weight, and inhalation rate. There are no chamber data available for the products modeled in the exposure assessment, thus CEM was used to calculate the mass of 1-BP entering the room of use by relying on data from a paper that studied the emission rates of solvents from a surface (DTIC DLA, 1981). The consumer uses described in this assessment with higher weight fraction 1-BP result in only 1-BP being on the surface so these uses fit well into the Chinn data set, however if the product has a significant fraction other components this may affect the evaporation rate of 1-BP. This introduces uncertainty and a further discussion of this issue is provided in Appendix L.

4.4.2.3 Conversion of Acute Dose Rates to Air Concentrations

Because the E-FAST2/CEM model outputs for exposure to the user and bystander scenarios are reported in mg/kg-bw/day, it was necessary to convert these values to air concentrations (ppm) in order to perform the non-cancer assessment. This conversion introduces some uncertainty, and therefore may over- or under-estimate exposures.

4.4.3 Uncertainties in the Hazard and Dose-Response Assessments

4.4.3.1 Uncertainties and Assumptions in the Non-Cancer Hazard/Dose-Response Assessments

EPA/OPPT's risk assessment relied on the hazard values (i.e., HECs) derived in this evaluation. These hazard values were used to estimate acute and chronic risks to various health effects following 1-BP exposure related to specific 1-BP uses.

There are several uncertainties inherent to the data and the assumptions used to support the derivation of the acute and chronic non-cancer PODs for different health effects domains. Below is a summary of the major uncertainties affecting the non-cancer hazard/dose response approach used for this assessment. However, the key endpoints identified in this assessement (liver toxicity, kidney toxicity, reproductive/developmental toxicity, neurotoxicity, and cancer) showed a strength of evidence among the studies in the database for consistency, sensitivity, and relevance.

The uncertainties in hazard and dose response assessment are predicated on assumptions of relevancy of cancer and non-cancer findings in rodents being relevant to humans.

Decreased live litter size was selected as an endpoint to evaluate risks associated with acute exposures to 1-BP. Although the developmental toxicity studies included repeated exposures, EPA/OPPT considered evidence that a single exposure to a toxic substance can result in adverse developmental effects, described by (Van Raaij et al., 2003), as relevant to 1-BP.
Although there is evidence of biological effects in both the fetus and neonate, there are uncertainties in extrapolating doses for these lifestages. It is not known if 1-BP or its metabolites are transferred to the pups via lactation. It is possible that the doses reaching the fetus and the neonate are similar and that these lifestages are equally sensitive; however, it is also possible that one lifestage is more sensitive than the other or that internal doses are different. Additional data would be needed to refine dose estimates for the fetus and pups and to determine if there are specific windows of sensitivity.

Neurotoxicity produced by 1-BP are based on rodent and human literature, with considerable similarities in both qualitative and quantitative outcomes. In the human and rodent literature, the most consistent responses are symptoms of frank neurotoxicity occurring at high exposures, with effects that are progressive at repeated exposures to low concentrations. In humans, the reports of effects in factory workers with lower exposures are limited by questions regarding exposure characterization as well as measurement techniques, sensitivity, and analysis: for

these reasons the data are not sufficiently robust for quantitative exposure-response function. On the other hand, the findings of decreased peripheral nerve function are supported by parallel measures in several rodent studies.

Protection of Different Lifestages and Subpopulations: EPA also is interested in the impact of 1-BP on other lifestages and subpopulations. Consideration of other lifestages, such as male and non-pregnant female workers in the occupational environment, children in the home environment would require using an alternative POD based on systemic toxicity, instead of using the POD based on developmental toxicity. Other endpoints associated with systemic toxicity generally had higher human equivalent concentrations than those associated with developmental toxicity. Therefore EPA assumed that margins of exposure for pregnant women would also be protective of other lifestages.

While it is anticipated that there may be differential 1-BP metabolism based on lifestage; currently there are no data available, therefore the impact of this cannot be quantified. Similarly, while it is known that there may be genetic differences that influence CYP2E1 metabolic capacity, there may also be other metabolizing enzymes that are functional and impact vulnerability. There is insufficient data to quantify these differences for risk assessment purposes.

Heterogeneity among humans is an uncertainty associated with extrapolating the derived PODs to a diverse human population. One component of human variability is toxicokinetic, such as variations in CYP2E1 and glutathione transferase activity in humans (Arakawa et al., 2012; Trafalis et al., 2010) which are involved in 1-BP metabolism in humans. EPA did not have the chemical specific information on susceptible human populations, or the distribution of susceptibility in the general population to decrease or increase the default intraspecies UF_H for toxicodynamic variability of 3. As such, EPA used an intraspecies UF_H of 10 for the risk assessment.

Uncertainties in the acute and chronic hazard values stem from the following sources:

Non-cancer hazard values (e.g., NOAELs, LOAELs, BMD): PODs were identified from the animal studies that were suitable for dose-response analysis. The process of identifying PODs for various health effects domains involved the evaluation of the strengths and limitations of the data and the weight of evidence for a particular health effects domain before supporting an association between 1-BP exposure and various human health effects. The selected PODs values (e.g., NOAEL, LOAEL or BMD) depend on the current available data and could change as additional studies are published.

Also, when selecting a BMD as a POD, the selection of the benchmark dose response (BMR) (e.g., 1%, 5% or 10% level) directly affects the calculation of the BMD. There are uncertainties related to the BMRs since their selection depends on scientific judgments on the statistical and biological characteristics of the dataset and how the BMDs will be finally used.

In addition, there are uncertainties about the appropriate dose-response model used to generate the BMDs. However, these uncertainties should be minimal if the chosen model fits well the observable range of the data, as discussed in EPA Benchmark Dose Technical Guidance.

1. **Duration adjustment to continuous exposure:** Most of the PODs used to derive HECs came from studies that did not expose animals or humans to 1-BP on a continuous basis. These PODs were then mathematically adjusted to reflect equivalent continuous exposures (daily doses) over the study exposure period under the assumption that the effects are related to concentration × time (C x t), independent of the daily (or weekly) exposure regimen (U.S. EPA, 2011). However, the validity of this assumption is generally unknown, and, if there are dose-rate effects, the assumption of C × t equivalence would tend to bias the POD downwards (U.S. EPA, 2011). A single exposure to 1-BP at a critical window of fetal development may produce adverse developmental effects (U.S. EPA, 2011). This was assumed to be a health protective approach and no duration adjustment was performed for adverse developmental outcomes.

2. **Extrapolation of repeated dose developmental effects to acute scenarios:** There are uncertainties related to whether developmental effects observed in developmental toxicity studies may result from a single exposure to 1-BP. In this assessment, the acute risk assessment used the hazard value for decreases in litter size from the (WIL Research, 2001) two-generation reproductive toxicity study. However, EPA policy is based on the presumption that a single exposure to a chemical during a critical window of development may be sufficient to produce adverse developmental toxicity.

4.4.3.2 Uncertainties and Assumptions in the Cancer Hazard/Dose-Response Assessments

For cancer hazard assessment, the major uncertainty is whether the mechanism/mode of action of 1-BP carcinogenesis should be considered mutagenic/genotoxic or nongenotoxic. The uncertainty arose mainly because of the equivocal results of the Ames tests complicated by the high volatility of 1-BP. Despite focusing solely on tests using desiccators or closed systems, the equivocality remains as both positive and negative data were reported. To circumvent the problem, EPA/OPPT used the weight of evidence approach using related test data: (a) Genotoxicity tests of mammalian cells: 1-BP caused mutations in cultured mammalian cells with or without metabolic activation and DNA damage in cultured human cells without metabolic activation. There was also limited evidence of DNA damage in leukocytes in 1-BP-exposed workers. (b) Metabolic activation to mutagenic intermediates: Rodent metabolic studies have indicated that 1-BP can be activated by CYP2E1 to at least five mutagenic intermediates, including two clearly mutagenic and carcinogenic chemicals, glycidol and propylene oxide. Glycidol has been shown to induce tumors in intestines, one of the carcinogenic targets of 1-BP. There is evidence that humans have CYP2E1 in lung and similar metabolic pathways for 1-BP as rodents (c) Multiplicity of cancer targets of 1-BP: In general, chemical carcinogens that induce cancer in more than one animal species and in multiple targets tend to act via mutagenic mechanism/mode of action. 1-BP has been shown to induce a variety of tumors in rats and

mice. (d) Structure-Activity Relationship (SAR) consideration: 1-BP is a low M.W. alkyl bromide that is generally known to be a good alkylating agent. In fact, 1-BP has been shown to bind to DNA in vitro. Bromoethane and 1-bromobutane, two of the closest analogs of 1-BP, were both reported to give positive results in the Ames test when tested in closed systems. (e) Other possible mechanism of action: Besides genotoxicity, at least three other possible mechanisms – oxidative stress, immunosuppression, and cell proliferation—have been suggested by the NTP (2013). These mechanisms can act synergistically to complete the multi-stage process of carcinogenesis. While there is residual uncertainty in the mechanism/mode of action for 1-BP carcinogenesis, overall, the totality of the available data/information support a justifiable basis to support a probable mutagenic mode of action for 1-BP carcinogenesis.

While a mutagenic mode of action of action may be assumed to be operative at least in part for the carcinogenicity of 1-BP the default linear extrapolation method for dose-response is used. For the cancer dose-response assessment uncertainties exist arising from the animal to human extrapolation in the derivation of the IUR. A source of uncertainty is the cancer model used to estimate the POD for the IUR derivation. The POD was based on a model averaging approach to fit the bioassay data for lung tumors. Although the model average fit the data alternate model selections can also fit the data. A sensitivity analysis comparing reasonable alternate model choices found similar PODs therefore the impact of selecting between alternative models results in similar IURs.

4.4.4 Uncertainties in the Risk Assessment

The non-cancer acute or chronic risks were expressed in terms of MOEs. MOEs are obtained by comparing the hazard values (i.e., HEC) for various 1-BP-related health effects with the exposure concentrations for the specific use scenarios. Given that the MOE is the ratio of the hazard value divided by the exposure, the confidence in the MOEs is directly dependent on the uncertainties in the hazard/dose-response and exposure assessments that supported the hazard and exposure estimates used in the MOE calculations.

Overall uncertainties in the exposure estimates used in the MOE calculations include uncertainties in the exposure monitoring and modeling. In the occupational exposure monitoring data for workers the sites used to collect 1-BP were not selected randomly; therefore, the reported data may not be representative of all occupational exposure scenarios. The exposure modeling approaches used for both occupational and consumer scenarios employed knowledge-based assumptions that may not apply to all occupational- and consumer-use scenarios.

The benchmark MOE used to evaluate risks for each use scenario represents the product of of all UFs used for each non-cancer POD. These UFs accounted for various uncertainties including:

1. **Animal-to-human extrapolation (UF_A):** The UF_A accounts for the uncertainties in extrapolating from rodents to humans. In the absence of data, the default UF_A of 10 is adopted which breaks down to a factor of 3 for toxicokinetic variability and a factor of 3 for pharmacodynamic variability. There is no PBPK model for 1-BP to account for the

interspecies extrapolation using rodent pharmacokinetic data in order to estimate internal doses for a particular dose metric.

2. **Inter-individual variation (UF_H):** The UF_H accounts for the variation in sensitivity within the human population. In the absence of data, the default UF_H of 10 is adopted which breaks down to a factor of 3 for toxicokinetic variability and a factor of 3 for pharmacodynamic variability. Since there is no PBPK model for 1-BP to reduce the human toxicokinetic/toxicodynamic variability, the total UF_H of 10 was retained. Qualitative evidence exists from mechanistic information and population evidence for burden of disease that metabolic disorders including diabetes, nutritional deficits and smoking will predispose some of the population to greater risk for adverse developmental exacerbated by concurrent 1-BP exposure.

3. **Extrapolation from subchronic to chronic (UF_S):** The UF_S accounts for the uncertainty in extrapolating from a subchronic to a chronic POD. Typically, a UF_S of 10 is used to extrapolate a POD from a less-than-chronic study to a chronic exposure. The same is true for a developmental toxicity study because the developmental period is recognized as a susceptible life stage where exposure during certain time windows is more relevant to the induction of developmental effects than lifetime exposure (U.S. EPA, 1991). Thus, a UF_S of 10 was retained for all of the HECs discussed in the OPPT's risk assessment.

4. **LOAEL-to-NOAEL extrapolation (UF_L):** The UF_L accounts for the uncertainty in extrapolating from a LOAEL to a NOAEL. A value of 10 is the standard default UF_L value, although lower values (e.g., 3) can be used if the effect is considered minimally adverse at the LOAEL or is an early marker for an adverse effect (U.S. EPA, 2002). Typically, UF_L ranging from 3 to 30 (i.e., 3, 10, or 30) are used in the HECs. For one of the reproductive PODs (Yamada et al., 2003), a UF_L value of 10 was used based on a minimally adverse effect, which resulted in a total UF of 1000.

The human populations considered in this risk assessment include individuals of both sexes ($\geq$ 16 and older, including pregnant females) for occupational and consumer settings. Although exposures to younger non-users may be possible, the margins of exposure calculated for women of childbearing age are expected to be protective of this sensitive subpopulation. Currently there is insufficient data regarding specific genetic and/or lifestage differences that could impact 1-BP metabolism and toxicity for further refinement of the risk assessment.

The chronic risks for the occupational scenarios assumed that the non-cancer human health effects are constant for a working lifetime based on the exposure assumptions used in the occupational exposure assessment. However, the risks could be under- or over-estimated depending on the variations to the exposure profile of the workers and occupational non-users using 1-BP-containing adhesives, dry cleaning and spot cleaners, vapor degreasing, cold cleaning, and aerosol degreasers.

Confidence in the PBPK model predictions for 1-BP concentrations in blood and tissues are limited by the lack of comparison of model predictions with measured data. The PBPK model

was further extended to simulate human exposures by scaling the physiological parameters to humans, assuming the partition coefficients are the same in rats and humans and scaling metabolic parameters by $BW^{3/4}$. Cross species and route to route extrapolations with the Garner et al. (2015) model are precluded by the lack of data to inform a model of a species other than rat and a route other than inhalation.

The impact of dermal exposures on human health risks was not assessed in this assessment for the consumer and occupational scenarios. Dermal exposure was not quantifiable and could not be aggregated with inhalation exposures. Although dermal exposures are possible, physical-chemical properties (e.g., volatility) in combination with data indicating dermal uptake to be orders of magnitude lower than uptake by inhalation, limited toxicological data for this route of exposure, and no available toxicokinetic information to develop physiologically-based pharmacokinetic models or route-to-route extrapolations, all lessen the concern for the dermal route of exposure. Exclusion of an exposure assessment of dermal and aggregate exposures would be expected to underestimate the overall risks of the selected 1-BP uses. However, this would only be an issue of concern in those exposure scenarios that resulted in a "no-risk" finding, especially those that reported MOEs close to the benchmark MOE, but still above the benchmark.

As discussed previously, the estimates for added cancer risk were based on the assumption of linearity in the relationship between 1-BP exposure and probability of cancer. Uncertainties are introduced in the cancer risks when there is limited information justifying the linear cancer dose-response model when compared to other available models. In the case of 1-BP, the cancer IUR was based on reliable data supporting a mutagenic mode of action for at least 1-BP-induced lung tumors (NTP, 2011).

4.5 RISK ASSESSMENT CONCLUSIONS

This risk assessment focused on the occupational uses of 1-BP-containing spray adhesives, dry cleaning, and degreasing activities; and consumer uses of aerosol spray adhesives and spot removers, and aerosol degreasers/cleaners. The population of interest consisted of workers and consumers with direct (users) or indirect (occupational non-users) exposure to 1-BP. Only the inhalation route of exposure was considered in this risk assessment. The occupational and consumer exposures were generated for all of these 1-BP scenarios to derive non-cancer and cancer risks.

MOEs were used to evaluate non-cancer risks for both acute and chronic exposures using the hazard values identified in this assessment. Hazard values based on the developmental toxicity endpoint (WIL Research, 2001) were used to estimate non-cancer risks for acute exposures in the occupational and consumer scenarios. Non-cancer risks for chronic occupational exposure scenarios were evaluated based on hazard values reported following long-term exposure to 1-BP (i.e., liver toxicity, kidney toxicity, reproductive toxicity, developmental toxicity, and neurotoxicity). Note that minimal variability (i.e., ≤ 3-fold) exists among the acute and chronic non-cancer hazard values (i.e., HEC) used in this assessment.

Most of the acute exposure scenarios for occupational and consumer uses presented risks based on concerns for adverse developmental effects that may occur as a result of a single exposure to 1-BP during a critical window of susceptibility. Particularly, inhalation risks were identified for all occupational and consumer acute exposure scenarios, with only a few MOE values above the benchmark MOE of 100. These included the 50th percentile estimates for dry cleaning (modeling post-EC worker and pre-EC occupational non-user), vapor degreasing (monitoring post-EC occupational non-user), and cold cleaning (modeling post–EC occupational non-user); and for the 95th percentile estimates for vapor degreasing (monitoring and modeling post-EC occupational non-user) and cold cleaning (modeling post-EC occupational non-user).

There is a concern for a range of adverse human health effects other than cancer that may appear after chronic exposures to 1-BP during the occupational use of 1-BP-containing spray adhesives, dry cleaning, and degreasing activities. The greatest concern is for nervous system effects, followed by developmental effects (i.e., decreased live litter size), and then reproductive toxicity, kidney toxicity, and liver toxicity, with an overall higher risk for the spray adhesive exposure scenarios. In general, risks were observed across all of the uses in workers and occupational non-users. High-end (95th percentile) exposures pre-EC had risks for workers and occupational non-users for all health effects in all the uses evaluated. Furthermore, there are risks for adverse effects on the nervous system and development regardless of the type of 1-BP exposure (50th percentile/central tendency or 95th percentile/high-end) pre-EC in all the uses evaluated. Occupational non-users had risks for adverse effects on the nervous system and development at high-end (95th percentile/high-end) exposures regardless of the availability of engineering controls for most uses.

Cancer risks were presented as added lifetime risks, meaning the the probability that an individual will develop cancer as a result of occupational exposure over a normal lifetime of 70 years. Added lifetime cancer risk estimates from 1-BP exposure were compared to benchmark cancer risk levels ranging from 10^{-6} to 10^{-4}. All of the spray adhesive exposure scenarios using monitoring data exceeded the benchmark cancer risks of 10^{-6}, 10^{-5} and 10^{-4} and in many cases exceeded the benchmark cancer risks by 2-3 orders of magnitude. This analysis resulted in higher modeled incidences of cancer in the commercial use of spray adhesives, vapor degreasing and cold cleaning, dry cleaning and aerosol degreasing in descending order. Thus, the greatest potential for added cancer risk came from the occupational exposures to commercial adhesive and vapor cold cleaning degreaser uses. Furthermore, higher added cancer risk estimates resulted from direct use of the adhesive and degreaser when there was a lack of local exhaust ventilation at the workplace.

Main Conclusions of this Risk Assessment

Most acute exposure scenarios for occupational and consumer uses presented risks based on concerns for adverse developmental effects that may occur as a result of a single exposure to 1-BP during a critical window of susceptibility. Particularly, inhalation risks were identified for all occupational and consumer acute exposure scenarios, with only a few MOE values above the benchmark MOE of 100 (acceptable risk range). These included the 50th percentile estimates for dry cleaning (modeling post-EC worker and pre-EC occupational non-user), vapor degreasing

(monitoring post-EC occupational non-user), and cold cleaning (modeling post–EC occupational non-user); and for the 95th percentile estimates for vapor degreasing (monitoring and modeling post-EC occupational non-user) and cold cleaning (modeling post-EC occupational non-user).

There is a concern for a range of adverse human health effects due to chronic inhalation exposures resulting from 1-BP use in spray adhesive, dry cleaning, and degreasing applications. Cancer and neurological effects represent the greatest human health concern for chronic exposure, with the highest risks expected for the spray adhesive occupational exposure scenario. In general, risks were observed across all uses in workers and occupational non-users. High-end (95th percentile/pre-EC) exposures (considered to represent exposure levels at the baseline exposure condition) showed risks to workers and occupational non-users for all health effects and all use scenarios evaluated. Risks for adverse neurological and developmental effects were apparent regardless of the type of 1-BP exposure (50th percentile/central tendency or 95th percentile/high-end) pre-EC for all the uses evaluated. Occupational non-users showed risks for adverse neurological and developmental effects with high-end exposures (95th percentile) regardless of the availability of engineering controls for most use scenarios.

Cancer risks were determined as added lifetime cancer risks, meaning the probability that an individual will develop cancer as a result of occupational exposure over a normal lifetime of 70 years. Added lifetime cancer risk estimates from 1-BP exposure were compared to benchmark cancer risk levels of 10^{-6}, 10^{-5} and 10^{-4} (i.e., 1 in 10,000, 1 in 100,000 and 1 in 1,000,000). All of the spray adhesive exposure scenarios evaluated using monitoring data exceeded the benchmark cancer risk levels by multiple orders of magnitude and were near or above the cancer risk of 10^{-2} (1 in 100). This analysis showed higher estimated cancer incidences for occupational exposures associated with commercial use of 1-BP in spray adhesives, vapor degreasing, cold cleaning, dry cleaning and aerosol degreasing in descending order. A greater cancer risk was observed with the spray adhesive and degreasing (vapor, cold cleaning) occupational exposure scenarios, with the highest risks resulting from direct use of 1-BP containing spray adhesive and degreasing formulations in the absence of engineering controls (e.g., local exhaust ventilation) in the workplace.

EPA/OPPT estimated the population size for workers and occupational non-users at risk as:

- *Spray Adhesives:* 1,503 to 11,952
- *Dry Cleaning and Spot Cleaning at Dry Cleaning:* 1,088
- *Vapor Degreasing:* 4,712 to 23,558
- *Aerosol Degreasing:* 2,466 to 12,329

At this time, there is not sufficient information to develop estimates of the number of workers and occupational non-users potentially exposed to 1-BP during cold-cleaning; however, the use of 1-BP in this sector is expected to be minimal.

Also, at this time, there is not sufficient information to develop estimates of the populations for consumers and non-users exposed to 1-BP during the use of aerosol spray adhesives, aerosol spot removers, and aerosol cleaners and degreasers.

In summary, the risk assessment showed the following risk findings:

There Are Non-Cancer Risks Identified for Consumers as a Result of Acute Exposure to 1-BP from Use in Spray Adhesives, Spot Removers, and Degreasers.

A concern for adverse developmental effects was identified for all acute consumer exposure scenarios (i.e., MOEs were below the benchmark MOE of 100), with 1-BP use in aerosol spray cleaners and degreasers showing the greatest risk. Risks for most acute consumer scenarios were 1-2 orders of magnitude below the benchmark MOE.

There Are Non-Cancer Risks Identified for Workers as a Result of Acute Exposure to 1-BP from Occupational Use in Spray Adhesives, Dry Cleaning, and Degreasing Operations.

A concern for non-cancer risks (including risks to workers and occupational non-users) was identified for all but three acute occupational exposure scenarios (i.e., MOEs were below the benchmark MOE of 100), with 1-BP use in spray adhesives showing the greatest risk. Risks for most acute occupational scenarios were 1-2 orders of magnitude below the benchmark MOE.

There are Non-Cancer Risks Identified for Workers as a Result of Chronic Exposure to 1-BP from Occupational Use as a Spray Adhesive, Dry Cleaning (including as a spot cleaner), and Degreasing Operations (vapor, cold cleaning, and aerosol)

A concern for non-cancer risks (including risks to workers and occupational non-users) was identified for all chronic occupational exposure scenarios evaluated based on a range of adverse human health effects. In general, higher risks were indicated for adverse neurological effects in association with 1-BP use in spray adhesives.

All chronic occupational exposure scenarios presented risks for adverse neurological or developmental effects in the absence of engineering controls (pre-EC).

In many instances, occupational non-users with chronic high-end exposures (95^{th} percentile) showed risks for adverse neurological effects regardless of the availability of engineering controls.

Risks for non-cancer effects following chronic occupational exposure (without engineering controls) were 2-3 orders of magnitude below the benchmark MOE.

There are Added Cancer Risks Identified for Workers as a Result of Chronic Exposure to 1-BP from Occupational Use as a Spray Adhesive, Dry Cleaning (including as a spot cleaner), and Degreasing Operations (vapor, cold cleaning, and aerosol)

Added cancer risks were identified for workers and occupational non-users who may be exposed as a result of 1-BP use in spray adhesive, dry cleaning (including spot cleaning), and degreasing operations (vapor, cold cleaning, and aerosol).

Cancer risk estimates exceeded 1 in 1,000 (exceeding all of the cancer risk benchmarks) for all occupational use scenarios evaluated (workers and occupational non-users) based on

monitoring and modeling estimates (regardless of the use of engineering controls), with relatively few exceptions. 1-BP use in spray adhesives presented the greatest cancer risk concern.

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Appendix A MARKET INFORMATION

1-BP is a high production volume chemical (over 15 million lb in 2011) used in numerous solvent applications including non-aerosol solvent cleaning, spray adhesives, and dry cleaning. In the past, 1-BP was used as a solvent for fats, waxes, or resins and as an intermediate in pharmaceutical, insecticide, quaternary ammonium compound, flavor, and fragrance synthesis (NTP, 2013).

A-1 Production Volume

There has been a tremendous change in production volume of 1-BP from 1986 to 2012[15]. The reported production volume of 1-BP has steadily increased since 1986 as seen in Table_Apx A-1. 1-BP's use may have recently increased in many industrial applications because the chemical is used as an alternative to ozone-depleting substances and chlorinated solvents. 1-BP was reported as used as a solvent for cleaning or degreasing for the 2012 CDR (summarized in EPA (2013b).

Table_Apx A-1 Production Volume Data from 1986 to 2012 (lbs)

Chemical	1986	1990	1994	1998	2002	2006	2012
1-BP	10K-<500K	10K-<500K	500K-<1M	1M-<10M	1M-<10M	1M-<10M	15,348,727

Source: EPA (2013b)

Import volumes for 1-BP reported to the 2012 CDR were claimed confidential and are therefore not publically available. Import data for the chemical from other sources indicate that 10.9 million pounds of brominated derivatives of acyclic hydrocarbons were imported into the U.S. in 2007 which dropped to 10.3 million pounds in 2011 (NTP, 2013). Import data for 1-BP alone were not located, and therefore the category "brominated derivatives of acyclic hydrocarbons" includes import volumes for chemicals other than 1-BP.

A-2 Manufacturers

The most recently-collected EPA production information, the 2012 CDR data, indicates two companies that manufacture and three that import 1-BP in the United States (U.S. EPA, 2013b). Table_Apx A-2 contains a list of U.S. 1-BP manufacturers and importers. For the 2012 CDR cycle, manufacturers (including importers) of substances on the TSCA inventory were required to report information about those substances manufactured (including imported) in amounts of 25,000 lb or more at a single site during calendar year 2011. Additional CDR information is included in Appendix B. An industry estimate of the price of 1-BP ranges from $40/gallon to $64/gallon (TURI, 2012).

[15] In CDR reporting periods prior to 2012, production volumes were reported in the public database in ranges instead of a single value.

Table_Apx A-2 CDR Manufacturers and Importers of 1-BP in 2011

Company	City	State	Manufacture	Import
Albemarle Corporation	Magnolia	AR	Yes	No
CBI	CBI	CBI	Yes	No
Dow Chemical Company	Midland	MI	No	Yes
ICL	St. Louis	MO	No	Yes
Special Materials Company	New York	NY	No	Yes

Source: EPA (2013b)

The Hazardous Substances Data Bank also lists Diaz Chemical Corporation as a possible manufacturer of the chemical (HSDB). Other companies that have or are marketing 1-BP solvent blends include:

- Petroferm;
- M.G. Chemicals;
- Albatross USA;
- Alpha Metals;
- Amity UK;
- Enviro Tech International;
- Poly Systems USA;
- Baker (NTP-CERHR, 2003).

A-3 Degreasers

1-BP is primarily used as a vapor degreaser for cleaning optics electronics, plastics, and metals (NTP, 2013) and (NCDOL, 2013). The prevalence of its use is partly due to its high quality, compatibility with many metals, low tendency to cause corrosion, and ability to be used in most modern vapor degreasing equipment (ICF Consulting, 2004; UNEP, 2001). The vapor degreasing sector is assumed to account for six to eight million pounds of 1-BP use per year (U.S. EPA, 2007c). The number of businesses in this use sector of 1-BP is estimated at 500 to 2,500 businesses (U.S. EPA, 2007c). Vapor degreasing products are estimated to contain between 80 and >95 percent 1-BP by weight.

The dominant solvents historically used for vapor degreasing are methyl chloroform, methylene chloride, and CFC-113 (TURI, 1996). However, both methyl chloroform and CFC-113 were phased-out in 1996 under the Montreal Protocol. Along with methylene chloride, other popular solvents currently used in the vapor degreasing industry are trichloroethylene and perchloroethylene. As part of EPA's Significant New Alternatives Policy (SNAP) Program, EPA issued a final rule in 2007 determining 1-BP to be an acceptable substitute to methyl chloroform and CFC-113 in the solvent cleaning sector in industrial equipment for metals cleaning, electronics cleaning, or precision cleaning (U.S. EPA, 2013c). The Brominated Solvents

Consortium (BSOC) estimated that 1-BP may take over a large portion of the methyl chloroform market because of the similar performance characteristics and prices of the chemicals (UNEP, 2001).

In addition to vapor degreasing, 1-BP is used in cold cleaning which covers a wide variety of machines or other cleaning processes. In vapor degreasing the solvent is heated to its boiling point and then the component to be cleaned passes through the vapor. With cold cleaning, even if the solvent is heated above room temperature, it never reaches the solvent's boiling point. Components are dipped, sprayed, wiped or run through the solvent on an inline, conveyor type machine. The current number of businesses using 1-BP in cold cleaning is unknown.

A-4 Spray Adhesives

1-BP adhesives are primarily used in foam cushion manufacturing and, to a lesser degree, for laminates (NTP, 2013) and (HSIA, 2010). Approximately one third of all foam cushion manufacturers use 1-BP based glues (Urbina, 2013). While 1-BP is used in this industry, it is not the primary chemical used in most spray adhesives due to cheaper solvents being able to fit the same need. Some companies use 1-BP instead of cheaper alternatives because it is less flammable, but larger companies in the foam cushion manufacturing industry will likely use a less expensive, flammable solvent and add fire-proofing. The adhesives sector is assumed to account for five to seven million pounds of 1-BP use per year (U.S. EPA, 2007b). The number of businesses in this use sector of 1-BP is estimated to be between 100 and 280 (U.S. EPA, 2007c). Spray adhesive products are estimated to contain between 35 and 85 percent 1-BP by weight.

Global demand volume for adhesives and sealants increased by 2.8 percent in 2012 and was expected to grow at a rate of 3.5 to 4 percent through 2013 (FEICA, 2013). Note that these estimates do not necessarily pertain to solely spray adhesives. Methyl chloroform had been the dominant adhesive before being phased out by the Montreal Protocol in 1990 (Adams, 2008). Alternatives to methyl chloroform include water-based adhesives and methylene chloride. However, water-based adhesives perform poorly and methylene chloride is subject to strict OSHA TWA exposure limits (Adams, 2008). 1-BP gained popularity as an alternative to both of these options because it is non-flammable, fast-drying and works well in foam-fabricating formulations (Adams, 2008).

In 2007, EPA proposed to list 1-BP as an unacceptable alternative to CFC-113 and methyl chloroform for adhesive solvents (U.S. EPA, 2013c). Many in the industry have voluntarily halted use of 1-BP, including Protonique, Great Lakes, and Atofina (Urbina, 2013). Current production and use data for 1-BP spray adhesives could not be found, most likely due to effects of EPA's proposed rule.

A-5 Aerosol Solvents

1-BP aerosol solvents are often used to spot clean electrical or electronic equipment, aircraft maintenance or synthetic fiber production (FR, 2007 as cited in (NTP, 2013). It may also be used in asphalt production (OSHA, 2013). An estimated 1,000 to 5,000 businesses used 1-BP-based aerosol solvents in 2002 (U.S. EPA, 2007c). Aerosol solvent products are estimated to contain between 10 and 100 percent 1-BP by weight.

The Consumer Specialty Products Association (CSPA) conducted a survey of 29 member businesses that use 1-BP-based aerosol solvent products and estimated that 690,900 pounds of aerosol solvents were sold by 8 companies per year (CSPA, 2007). CSPA acknowledged that although this figure did not represent the entire market, it did capture a significant portion of 1-BP industrial aerosol products (CSPA, 2007). This figure was consistent with EPA estimates of 0.5-2 million pounds of 1-BP aerosols sold per year (U.S. EPA, 2007b, c). The Halogenated Solvents Industry Association estimated in 2010 that 1-BP solvents in the U.S. were growing at a rate of 15 to 20 percent per year (HSIA, 2010). Note that it is unclear whether this estimate refers to just aerosol solvents, or all cleaning solvents (which would include vapor degreasing).

A-6 Dry Cleaning

One of the most commonly used 1-BP products in dry cleaning is DrySolv®. DrySolv® is a mixture of 1-BP (>87 percent by weight) and nitromethane and 1,2-butylene oxide (<5 percent) (Enviro Tech International, 2013). The product is manufactured by Enviro Tech International, Inc., a small company with an estimated 10-49 employees and annual sales of $5 to $9.9 million (IdeVw, 2013; Thomasnet.com, 2013). DrySolv® evolved from EnSolv®, a 1-BP degreasing and cleaning solvent used in various industries including aerospace, precision engineering, medical equipment, and electronics (Childers, 2008). Fabrisolv™ XL, manufactured by Poly Systems USA, is another 1-BP-based dry cleaning solvent (Poly Systems USA, 2013). Poly Systems USA is also a small business, with estimated annual revenue of $1.7 million (Manta Media, 2015).

At the end of 2007, the California Air Resources Board (CARB) passed the Airborne Toxic Control Measure for Emissions of Perchloroethylene from Dry Cleaning Operations (Dry Cleaning ATCM) into law. The Dry Cleaning ATCM requires all perchloroethylene dry cleaning facilities in California with machines at co-residential facilities to be removed by January 1, 2023 (CARB, 2009). The law also requires perchloroethylene dry cleaning machines that are 15 years or older to be removed by 2023. Literature provided to affected dry cleaning facilities by CARB listed 1-BP as one of the seven available perchloroethylene alternatives (CARB, 2009).

It is estimated that only a small fraction of the 36,000 dry cleaning establishments in the U.S. (NIOSH, 2012) use 1-BP solvents. According to figures from the Dry Cleaning and Laundry Institute (DLI) cited in 2009, only about 50 dry cleaning systems in the U.S. are using DrySolv® compared to 70 percent of the market that still uses perchloroethylene, 27 percent using hydrocarbon, and 2 percent using GreenEarth (Vince, 2009). Findings from a survey conducted about dry cleaning solvent systems in 2009 by AmerianDrycleaner.com revealed that 2.0 percent of respondents use DrySolv® (Murphy, 2009). Respondents reported using other

solvents such as perchloroethylene (50.5 percent), high-flash point hydrocarbon (33.3 percent), GreenEarth (11.1 percent), liquid CO_2 (2.0 percent), Solvair (1.0 percent), petroleum (14.1 percent), and GreenJet (2.0 percent) (Murphy, 2009). The survey also polled respondents on which solvent system they plan to use in the next dry cleaning machine they purchase. Only 4.1 percent of respondents indicated that the next solvent system they plan to use is DrySolv® compared to 27.6 percent for high-flash point hydrocarbons, 16.3 percent for perchloroethylene , 14.3 percent for GreenEarth, 11.2 percent for Solvair, 5.1 percent for low-flash petroleum, and 4.1 percent for liquid CO_2 (Murphy, 2009).

Overall, growth of the 1-BP market is forecasted to be small according to a five-year projection by DLI (Vince, 2009). The Institute also predicted that use of perchloroethylene and liquid CO_2 systems will decrease and that there will be moderate growth in the use of hydrocarbon systems, Solvair, and GreenEarth. Use of wet cleaning was forecasted to grow from 2009 to 2014 (Vince, 2009).

1-BP is considered a drop-in replacement for perchloroethylene in existing dry cleaning machinery (TURI, 2012). Perchloroethylene has historically been the standard dry cleaning solvent due to its effectiveness, ease of use, and relatively low cost (TURI, 2012). However, due to human health and environmental concerns associated with perchloroethylene, many states have taken action to manage perchloroethylene's use in dry cleaning (U.S. EPA, 2012b).

A-7 Spot Cleaners

1-BP is used in some spot cleaner formulations in commercial dry cleaning businesses. Commercial dry cleaners may spot clean garments both before and after the items are run through the dry cleaning machine. While 1-BP is in known formulations and currently used to a certain degree within the dry cleaning industry, potential regulatory action on perchloroethylene could increase the presence of 1-BP in this sector.

A-8 Consumer Uses

EPA/OPPT searched the NIH Household Products Database, various government and trade association sources (including Halogenated Solvents Industry Association, Association of the European Adhesive and Sealant Industry, and the National Toxicology Program reports) for products containing 1-BP, company websites for SDSs, *Kirk-Othmer Encyclopedia of Chemical Technology*, and general internet searches. The NIH Household Products Database and *Kirk-Othmer Encyclopedia of Chemical Technology* contained no relevant information on consumer products containing 1-BP. Through the other search means, EPA/OPPT identified a number of products available to consumers which contain 1-BP. There may be other consumer products containing 1-BP which are available to consumers since not all SDSs display a complete list of chemical ingredients, therefore, some products may contain 1-BP but this cannot be confirmed by EPA. However, the availability of the products found with percent 1-BP by weight ranging from 1 to 100 raised sufficient concern within the Agency to include these uses in the Risk Assessment.

Table_Apx A-3 1-BP Consumer Use Products

Use	Company	Product	% 1-BP (wt%)	Source
Aerosol Spray Adhesive	Maple Leaf Sales II	K-Grip 503	35-60	(Maple Leaf Sales II Inc., 2013)
	ITW TACC	STA'-PUT SP4H Canister Adhesive	35-60	(ITW Inc., 2014)
	Choice Brand Adhesives	751G	40-60	(Choice Brand Adhesives, 2010)
	Blair Rubber Company	Endurabond™ Normac 900R-NPB	60-85	(Blair Rubber Co., 2011)
	Satellite City [a]	NCF Accelerator	98-99	(Satellite City Instant Glues, 2015)
Aerosol Spot Remover	Albatross USA	Everblum Gold Cleaning Fluid	20-30	(Albatross USA Inc., 2015)
	EnviroTech	DrySolv Spray Testing & Spotter	>93	(Enviro Tech International, 2013)
	PettyJohn's Solutions	Homerun Cleaning Fluid	>96	(Pettyjohn's Solutions, 2012)
	The Sherwin-Williams Company [b]	SPRAYON LIQUI-SOL® Food Grade ULTRA-FORCE™ Safety Solvent & Degreaser	100	(Sherwin Williams, 2014)
Aerosol Spray Cleaner or Degreaser	ITW Pro Brands	LPS Instant Super Degreaser	60-70	(ITW Pro Brands, 2015)
	ITW Pro Brands	LPS NoFlash Nu	60-70	(ITW Pro Brands, 2014)
	ZEP, Inc	Power Solv 5000	60-100	(ZEP, 2015)
	ACL, Inc	Precision Rinse NS	65-75	(ACL Inc., 2014)
	CRC Industries, Inc	Super Degreaser/Cleaner	90-100	(CRC Industries Inc., 2014)
	CRC Industries, Inc	Cable Clean RD	1-3	(CRC Industries Inc., 2015)
	MRO Solutions	525 Contact Cleaner	47-84	(MRO Solutions, 2015)
	Osborn	76334 High Tech Electronic Cleaner	50	(Osborn, 2015),
	ITW Chemtronics [b]	Electro-Wash NR	65-75	(ITW Chemtronics, 2008)
	ITW Chemtronics [b]	Kontact Restorer	65-75	(ITW Chemtronics, 2012)
	Sprayon	EL 2846 Non-Chlorinated Flash Free Electronic Solvent	96	(Sprayon Products, 2014)
Mold Release	Flexbar Machine Corporation	Epoxy Parfilm Paintable Mold Release	35-65	(Flexbar Machine Corporation, 2010)
Coin Cleaner	Amity International	Koinsolv	>93	(Amity International, 2006)
Refrigerant Flush	Technical Chemical Company	Johnsen's Premium AC Flush Non-flammable	>90	(TCC, 2014)
Lubricant	Slide Products, Inc	Cutting Oil – aerosol	10-20	(Slide Products Inc., 2012b)
	Slide Products, Inc	Cutting Oil – bulk	11	(Slide Products Inc., 2012a)

Notes:

[a] Technically, the NCF Accelerator is added to another spray adhesive to make it dry more quickly.

[b] Not currently made by the manufacturer, but available on the secondary market.

Appendix B CHEMICAL DATA REPORTING RULE DATA FOR 1-BP

EPA's 2012 Chemical Data Reporting (CDR) reported a 1-BP production volume of 15.4 million pounds. Albemarle Corporation and a CBI company reported domestic manufacturing of 1-BP (U.S. EPA, 2012c). Dow Chemical Company, Special Materials Company, and ICL reported imports of 1-BP (U.S. EPA, 2012c). Data in Table_Apx B-1 through Table_Apx B-3 were extracted from the 2012 CDR records (U.S. EPA, 2012c).

Table_Apx B-1 National Chemical Information for 1-BP from 2012 CDR

Production Volume (aggregate)	15.4 million pounds
Maximum Concentration (at manufacture or import site)	>90%
Physical form(s)	Liquid
Number of reasonably likely to be exposed industrial manufacturing, processing, and use workers (aggregated)	>1,000
Was industrial processing or use information reported?	Yes
Was commercial or consumer use information reported?	Yes

Table_Apx B-2 Summary of Industrial 1-BP Uses from 2012 CDR

Industrial Sector (Based on NAICS)	Industrial Function	Type of Processing
Soap, Cleaning Compound, and Toilet Preparation Manufacturing	Solvents (for cleaning or degreasing)	Processing-repackaging
Soap, Cleaning Compound, and Toilet Preparation Manufacturing	Solvents (for cleaning or degreasing)	Processing-incorporation

Abbreviations: NAICS=North American Industry Classification System

Table_Apx B-3 Commercial/Consumer Use Category Summary of 1-BP

Commercial/Consumer Product Category	Intended for Commercial and/or Consumer Uses or Both	Intended for Use in Children's Products in Related Product Category
Cleaning and Furnishing Care Products	Commercial	No
Electrical and Electronic Products	Commercial	No

Appendix C STATE REGULATIONS OF 1-BP

Table_Apx C-1 State 1-BP Regulations

State	Regulation	Link or Reference
California	California's Proposition 65 list for developmental, female and male reproductive toxicity (Intent to list for cancer 7/10/15)	State of California Environmental Protection Agency Office of Environmental Health Hazard Assessment (OEHHA) (2015). OEHHA Proposition 65 Notice of Intent to List: 1-Bromopropane. http://oehha.ca.gov/prop65/CRNR_notices/admin_listing/intent_to_list/NOIL0710151bromopropane.html
California	Proposed a permissible exposure limit (PEL) at 5 ppm as an 8-hr time-weighted average (TWA)	Division of Occupational Safety and Health, Department of Industrial Relations, State of California (2009a). Permission Exposure Limits for Chemical Contaminants. http://www.dir.ca.gov/oshsb/airborne_contaminants09.html
California	Biomonitoring California Designated Chemicals	State of California Environmental Protection Agency Office of Environmental Health Hazard Assessment (CA EPA OEHHA) (2015) Biomonitoring California Designated Chemicals. http://oehha.ca.gov/prop65/CRNR_notices/admin_listing/intent_to_list/NOIL0710151bromopropane.html
Massachusetts	Toxic or hazardous substances list	Massachusetts Executive Office of Energy and Environmental Affairs (2013) Massachusetts 301 CMR 41.00: Toxic or Hazardous Substances List. http://www.mass.gov/eea/docs/eea/ota/tur-prog/clean-tdi-301-cmr-41.pdf
Massachusetts	Higher hazard substances	Massachusetts Executive Office of Energy and Environmental Affairs (2015) Designation of TURA Higher & Lower Hazard Substances in Massachusetts, February 2015 http://www.mass.gov/eea/docs/eea/ota/programs/hhs-lhs-fact-sheet-final-2015.pdf
Minnesota	Listed chemical of high concern (Development, Reproduction)	Minnesota Department of Health (2013) Chemicals of High Concern list, July 1, 2013. http://www.health.state.mn.us/divs/eh/hazardous/topics/toxfreekids/chclist/mdhchc2013.pdf
New Hampshire	Class III Regulated Toxic Air Pollutants	New Hampshire Department of Environmental Service (2013) Regulated Toxic Air Pollutants, New Hampshire Code of Administrative Rules, CHAPTER Env-A 1400, Table-1450-1,

	Ambient Air Level (AAL) 2,096 μg/m^3 (24 hours), 499 μg/m^3 (Annual)	adopted May 26, 2006 http://des.nh.gov/organization/divisions/air/pehb/ehs/atp/documents/toxlistann.pdf
New Jersey	Right to Know Hazardous Substance List, Special Health Hazard Substance List (F3 – Flammable - Third Degree)	State of New Jersey Department Health (2010) Right To Know Hazardous Subtances List http://www.nj.gov/health/eoh/rtkweb/documents/hsl_alpha.pdf
Pennsylvania	Hazardous Substance Lists	Pennsylvania Department of Labor and Industry (1982) Pennsylvania Worker and Community Right-to-Know Act http://www.portal.state.pa.us/portal/server.pt?open=514&objID=552975&mode=2
Rhode Island	Toxic Air Contaminants Acceptable Ambiente Levels 5,000 μg/m^3 (24 hour), 1,000 μg/m^3 (annual)	State of Rhode Island Department of Environmental Management (2008) Air Pollution Control Regulation No. 22 Air Toxics http://www.dem.ri.gov/pubs/regs/regs/air/air22_08.pdf

Appendix D ENVIRONMENTAL EFFECTS SUMMARY

The ecological hazard summary of 1-BP is based on available hazard data. In addition, an updated literature survey was conducted to identify articles on ecological toxicity. The search terms included freshwater and saltwater fish, aquatic invertebrates, and aquatic plants; pelagic and benthic organisms; acute and chronic sediment toxicity in freshwater and saltwater and terrestrial toxicity to soil organisms, birds, and mammals. The test species, test conditions, toxicity endpoints, statistical significance, and strengths/limitations of the study were evaluated for data quality.

Table_Apx D-1 contains all data considered for the ecological hazard characterization of 1-BP. 1-BP has been tested for acute aquatic toxicity. With the exception of algae, no chronic aquatic or terrestrial data were found. In order to characterize the effects of 1-BP to the environment, a hazard rating was assigned based on EPA methodology for existing chemical classification (U.S. EPA, 2013a). Included in this assessment are five acute aquatic toxicity studies which includes both algae and micro-organism studies. There are no available sediment, soil, avian, chronic fish, or chronic aquatic invertebrate toxicity studies found in literature for 1-BP.

The data show that there is a low acute ecotoxicity for fish, aquatic invertebrates, aquatic plants and micro-organisms. Hazard to sediment and terrestrial organisms as well as chronic aquatic toxicity is expected to be low since 1-BP does not bioaccumulate, does not persist in the environment, highly volatile, and photodegrades quickly.

Table_Apx D-1 Ecological Hazard Characterization of 1-Bromopropane

Test Species	Test System	Duration	End-point	Conc. (mg/L)	Test Analysis	Effect	References
Fish							
Rainbow trout (*Oncorhynchus mykiss*)	Freshwater, semi-static	96 hours	EC_{50}	24.3	Measured	Not Reported	(ECHA, 2015) 2008 study
			NOEC	1.77			
Fathead minnow (*Pimphales promelas*)	Freshwater, flow-through	96 hours	LC_{50}	67.3	Measured	Mortality	Geiger (1988)
Aquatic Invertebrates							
Water flea (*Daphnia magna*)	Fresh	48 hours	EC_{50}	99.3	Measured	Immobility	(ECHA, 2015) 2008 study
			NOEC	29.6			
Algae							
Green algae (*Pseudokirchnerella subcapitata*)	Freshwater, static	96 hours	EC_{50}	52.4		Biomass	(ECHA, 2015) 2008 study
			EC_{50}	72.3		Growth Rate	
			NOEC	12.4		Biomass and Growth Rate	
Micro-organism							
n/a	Freshwater, static	5 min	EC_{50}	270		Mortality	(ECHA, 2015) 2008 study

D-1 Acute Toxicity to Aquatic Organisms

Acute Toxicity to Fish

The 96-hour LC_{50} value for 1-BP with rainbow trout was 24.3 mg/L. Conditions were in a sealed environment to prevent the volatile test substance from escaping.

The 96-hr LC_{50} for 1-BP with fathead minnow was 67.3 mg/L. Affected fish lost schooling behavior and swam near the tank surface. They were hypoactive, underreactive to external stimuli, had increased respiration, were darkly colored and lost equilibrium prior to death.

Acute Toxicity to Aquatic Invertebrates

The EC_{50} and NOEC for aquatic invertebrate were 99.3 mg/L and 29.6 mg/L, respectively.

Toxicity to Aquatic Plants

There were no available acute or chronic toxicity studies that characterize the hazard of 1-BP to aquatic plants.

Toxicity to Micro-organisms

The EC_{50} and NOEC for micro-organisms toxicity study for a 5 minute time period was 270 mg/L and 100 mg/L, respectively. Testing protocols require the test duration to be 3 hours and rigorous aeration of the test vessels. The submitter reduced the test duration from 3 hours to 5 minutes due to the volatile nature of 1-BP. To minimize any 1-BP losses, the submitter kept 1-BP test preparations in suspension by stirring via magnetic stirrers and sealed all vessels with film instead of vigorously aerating the test vessels.

D-2 Chronic Toxicity to Aquatic Organisms

With the exception of algae, no chronic aquatic toxicity data were found. The EC_{50} for the algae toxicity test was 52.4 mg/L (biomass) and 72.3 mg/L (growth rate). The NOEC for the algae toxicity test was 12.4 mg/L. The LOEC was not defined in the study; thus, a chronic value (ChV) was not calculated.

D-3 Toxicity to Sediment and Soil Dwelling Organisms

There were no available acute or chronic toxicity studies that characterize the hazard of 1-BP to sediment- or soil-dwelling organisms.

D-4 Toxicity to Wildlife

There were no available acute or chronic toxicity studies that characterize the hazard of 1-BP to wildlife.

D-5 Summary of Environmental Hazard Assessment

Table_Apx D-1 provides a summary of the toxicity data available for 1-BP. The acute hazard of 1-BP to aquatic organisms is considered low based on available data. The hazard of 1-BP is expected to be low for chronic aquatic organisms, sediment, and terrestrial organisms based on physical and chemical properties of 1-BP.

Appendix E ENVIRONMENTAL FATE

E-1 Fate in Air

If released to the atmosphere, 1-BP is expected to exist solely in the vapor-phase based on its vapor pressure. In the vapor phase, it is degraded by reaction with photochemically produced hydroxyl radicals. The half-life of this reaction is approximately 9 - 12 days assuming a hydroxyl radical concentration over a 12 hour day of 1.5×10^{6} hydroxyl radicals per cubic centimeter of air (Version 4.10 EPISuite). Its atmospheric degradation and its photooxidation products were investigated for their ozone depletion potential (Burkholder et al., 2002). It was shown that the hydroxyl radical initiated degradation does not lead to long-lived bromine containing species that can migrate to the stratosphere. The major photodegradation products were bromoacetone, propanal and 3-bromopropanal. Bromoacetone was rapidly photolyzed releasing bromine which was removed from the atmosphere by wet deposition. 1-BP does not absorb light greater than 290 nm; therefore, degradation of this substance by direct photolysis is not expected to be an important fate process. The bromoacetone and propanal constitute about 90% of 1-BP that is degraded in the atmosphere, and they, as well as 3-bromopropanal, are expected to be rapidly degraded. Apparently, the major atmospheric degradative fate of 1-BP is the rapid and irreversible release of Br atoms. Based on the 1-BP estimated half-life of 9-12 days in air, it is possible that it can undergo long range transport via the atmosphere.

E-2 Fate in Water

When released to water, 1-BP is not expected to adsorb to suspended solids and sediment in the water column based upon its Koc value of about 40 (U.S. EPA, 2013a). The rate of volatilization is expected to be rapid based on a Henry's Law constant of 7.3×10^{-3} atm-m^3/mole. 1-BP was reported to achieve 70% of its theoretical biochemical oxygen demand (BOD) in the MITI (OECD 301C) test (Sakuratani et al., 2005) which is considered readily biodegradable. However, an OECD 301D (closed bottle) test showed 19.2% degradation after 28 days which is not considered readily biodegradable (European Chemicals (ECHA) registry substances data base). Bacterial strains isolated from organobromide-rich industrial wastewater were shown to degrade it (HSDB). Arthrobacter HA1 debrominated 1-BP under aerobic conditions yielding 1-propanol as a degradation product and Acinetobacter strain GJ70, isolated from activated sludge was able to utilize it as a carbon source (HSDB). These results suggest that 1-BP will undergo biodegradation in the environment under aerobic conditions. Hydrolysis of 1-BP is expected based on studies of (Mabey and Mill, 1978) and it cited in the Hazardous Substances Databank (HSDB). A hydrolysis half-life of about 26 days was calculated at pH 7 and 25 degrees Celsius from its first-order neutral rate constant of 3.01×10^{-7} sec^{-1}. The expected hydrolysis product is propanol and the hydrodebromination product propene is also possible. Photooxidation in water has not been reported to be an important environmental fate process. 1-BP is not expected to be persistent in water.

E-3 Fate in Sediment and Soil

1-BP is expected to have high mobility in soil based on an estimated log Koc of 1.6. Volatilization is expected to be an important fate process given its relatively high Henry's law constant of 7.3×10^{-3} atm m^3/mole and it is expected to volatilize from dry soil surfaces based upon its high vapor pressure. Its biodegradation is considered to be moderate in sediment and soil. 1-BP is not persistent in sediment or soil.

Appendix F APPROACH FOR ESTIMATING NUMBER OF WORKERS

This appendix summarizes the methods that EPA/OPPT used to estimate number of workers who are potentially exposed to 1-BP during degreasing, dry cleaning and spot cleaning, and spray adhesive use. The method consists of the following steps:

1. Identify the North American Industry Classification System (NAICS) codes for the industry sectors associated with these uses.
2. Estimate total employment by industry/occupation combination using the Bureau of Labor Statistics' Occupational Employment Statistics (OES) data (2015).
3. Refine the OES estimates where they are not sufficiently granular by using the U.S. Census' Statistics of US Businesses (SUSB) (2012) data on total employment by 6-digit NAICS.
4. Estimate the percentage of employees likely to be using 1-BP instead of other chemicals.
5. Combine the data generated in Steps 1 through 4 to produce an estimate of the number of establishments and employees using 1-BP in each industry/occupation combination, and sum these to arrive at a total estimate of the number of employees with exposure.

Step 1: Identify Affected NAICS Codes

As a first step, EPA/OPPT identified NAICS industry codes associated with the uses in the scope. For vapor degreasing, EPA/OPPT referenced EPA's Trichloroethylene (TCE) risk assessment, in which EPA/OPPT has identified a list of all possible NAICS industry sectors that may have degreasing operations (U.S. EPA, 2014c). It should be noted that degreasing encompasses a large number of industry sectors, and not all facilities in the identified NAICS code will have a degreasing operation. Additionally, EPA/OPPT identified NAICS codes for repair and maintenance shops that are likely to perform aerosol degreasing.

For dry cleaning and spray adhesive uses, EPA/OPPT evaluated all NAICS codes and identified those that are applicable to dry cleaning and foam cushion manufacturing. Table_Apx F-1 lists the proposed 6-digit NAICS codes for the uses. In addition, the table lists the corresponding BLS NAICS code at the 4-digit or 5-digit level. Note BLS employment data for certain sectors are only available at the 4-digit or 5-digit NAICS level (see Step 3 for refinement of BLS data).

Table_Apx F-1 NAICS Codes for Degreasing, Dry Cleaning, and Spray Adhesive Uses

NAICS	BLS NAICS	Industry	Application
337121	337120	Upholstered Household Furniture Manufacturing	Foam Cushions
337125	337120	Household Furniture (except Wood and Metal) Manufacturing	Foam Cushions
337127	337120	Institutional Furniture Manufacturing	Foam Cushions
337214	337200	Office Furniture (except Wood) Manufacturing	Foam Cushions
812320	812300	Drycleaning and Laundry Services (except Coin-Operated)	Dry Cleaning
314999	314900	All Other Miscellaneous Textile Product Mills	Degreasing
321113	321100	Sawmills	Degreasing
323111	323100	Commercial Printing (except Screen and Books)	Degreasing
325180	325100	Other Basic Inorganic Chemical Manufacturing	Degreasing

Table_Apx F-1 NAICS Codes for Degreasing, Dry Cleaning, and Spray Adhesive Uses

NAICS	BLS NAICS	Industry	Application
325998	325900	All Other Miscellaneous Chemical Product and Preparation Manufacturing	Degreasing
326299	326200	All Other Rubber Product Manufacturing	Degreasing
331110	331100	Iron and Steel Mills and Ferroalloy Manufacturing	Degreasing
331210	331200	Iron and Steel Pipe and Tube Manufacturing from Purchased Steel	Degreasing
331410	331400	Nonferrous Metal (except Aluminum) Smelting and Refining	Degreasing
331420	331400	Copper Rolling, Drawing, Extruding, and Alloying	Degreasing
332111	332100	Iron and Steel Forging	Degreasing
332112	332100	Nonferrous Forging	Degreasing
332119	332100	Metal Crown, Closure, and Other Metal Stamping (except Automotive)	Degreasing
332117	332100	Powder Metallurgy Part Manufacturing	Degreasing
332215	332200	Metal Kitchen Cookware, Utensil, Cutlery, and Flatware (except Precious) Manufacturing	Degreasing
332216	332200	Saw Blade and Handtool Manufacturing	Degreasing
332311	332300	Prefabricated Metal Building and Component Manufacturing	Degreasing
332313	332300	Plate Work Manufacturing	Degreasing
332431	332400	Metal Can Manufacturing	Degreasing
332510	332500	Hardware Manufacturing	Degreasing
332618	332600	Other Fabricated Wire Product Manufacturing	Degreasing
332721	332720	Precision Turned Product Manufacturing	Degreasing
332722	332720	Bolt, Nut, Screw, Rivet, and Washer Manufacturing	Degreasing
332811	332800	Metal Heat Treating	Degreasing
332812	332800	Metal Coating, Engraving (except Jewelry and Silverware), and Allied Services to Manufacturers	Degreasing
332813	332800	Electroplating, Plating, Polishing, Anodizing, and Coloring	Degreasing
332912	332900	Fluid Power Valve and Hose Fitting Manufacturing	Degreasing
332913	332900	Plumbing Fixture Fitting and Trim Manufacturing	Degreasing
332919	332900	Other Metal Valve and Pipe Fitting Manufacturing	Degreasing
332994	332900	Small Arms, Ordnance, and Ordnance Accessories Manufacturing	Degreasing
332996	332900	Fabricated Pipe and Pipe Fitting Manufacturing	Degreasing
332999	332900	All Other Miscellaneous Fabricated Metal Product Manufacturing	Degreasing
333132	333100	Oil and Gas Field Machinery and Equipment Manufacturing	Degreasing
333249	333200	Other Industrial Machinery Manufacturing	Degreasing
333318	333300	Other Commercial and Service Industry Machinery Manufacturing	Degreasing
333410	333400	Ventilation, Heating, Air-Conditioning, and Commercial Refrigeration Equipment Manufacturing	Degreasing
333415	333400	Air-Conditioning and Warm Air Heating Equipment and Commercial and Industrial Refrigeration Equipment Manufacturing	Degreasing
333921	333900	Elevator and Moving Stairway Manufacturing	Degreasing
333994	333900	Industrial Process Furnace and Oven Manufacturing	Degreasing
333999	333900	All Other Miscellaneous General Purpose Machinery Manufacturing	Degreasing

Table_Apx F-1 NAICS Codes for Degreasing, Dry Cleaning, and Spray Adhesive Uses

NAICS	BLS NAICS	Industry	Application
334220	334200	Radio and Television Broadcasting and Wireless Communications Equipment Manufacturing	Degreasing
334413	334400	Semiconductor and Related Device Manufacturing	Degreasing
334416	334400	Capacitor, Resistor, Coil, Transformer, and Other Inductor Manufacturing	Degreasing
334417	334400	Electronic Connector Manufacturing	Degreasing
334419	334400	Other Electronic Component Manufacturing	Degreasing
334513	334500	Instruments and Related Products Manufacturing for Measuring, Displaying, and Controlling Industrial Process Variables	Degreasing
334515	334500	Instrument Manufacturing for Measuring and Testing Electricity and Electrical Signals	Degreasing
335120	335100	Lighting Fixture Manufacturing	Degreasing
335121	335100	Residential Electric Lighting Fixture Manufacturing	Degreasing
335210	335200	Small Electrical Appliance Manufacturing	Degreasing
335310	335300	Electrical Equipment Manufacturing	Degreasing
335312	335300	Motor and Generator Manufacturing	Degreasing
335313	335300	Switchgear and Switchboard Apparatus Manufacturing	Degreasing
335911	335900	Storage Battery Manufacturing	Degreasing
335921	335900	Fiber Optic Cable Manufacturing	Degreasing
335929	335900	Other Communication and Energy Wire Manufacturing	Degreasing
335999	335900	All Other Miscellaneous Electrical Equipment and Component Manufacturing	Degreasing
336320	336300	Motor Vehicle Electrical and Electronic Equipment Manufacturing	Degreasing
336340	336300	Motor Vehicle Brake System Manufacturing	Degreasing
336410	336400	Aerospace Product and Parts Manufacturing	Degreasing
336411	336400	Aircraft Manufacturing	Degreasing
336413	336400	Other Aircraft Parts and Auxiliary Equipment Manufacturing	Degreasing
336414	336400	Guided Missile and Space Vehicle Manufacturing	Degreasing
336510	336500	Railroad Rolling Stock Manufacturing	Degreasing
337125	337120	Household Furniture (except Wood and Metal) Manufacturing	Degreasing
337127	337120	Institutional Furniture Manufacturing	Degreasing
339114	339100	Dental Equipment and Supplies Manufacturing	Degreasing
339990	339900	All Other Miscellaneous Manufacturing	Degreasing
339992	339900	Musical Instrument Manufacturing	Degreasing
339995	339900	Burial Casket Manufacturing	Degreasing
339999	339900	All Other Miscellaneous Manufacturing	Degreasing
488111	488100	Air Traffic Control	Degreasing
493110	493100	General Warehousing and Storage	Degreasing
811310	811300	Commercial and Industrial Machinery and Equipment (except Automotive and Electronic) Repair and Maintenance	Degreasing
811111	811110	General Automotive Repair	Aerosol degreasing
811112	811110	Automotive Exhaust System Repair	Aerosol degreasing
811113	811110	Automotive Transmission Repair	Aerosol degreasing
811118	811110	Other Automotive Mechanical and Electrical Repair and Maintenance	Aerosol degreasing

Table_Apx F-1 NAICS Codes for Degreasing, Dry Cleaning, and Spray Adhesive Uses

NAICS	BLS NAICS	Industry	Application
811121	811120	Automotive Body, Paint, and Interior Repair and Maintenance	Aerosol degreasing
811122	811120	Automotive Glass Replacement Shops	Aerosol degreasing
811191	811190	Automotive Oil Change and Lubrication Shops	Aerosol degreasing
811192	811190	Car Washes	Aerosol degreasing
811198	811190	All Other Automotive Repair and Maintenance	Aerosol degreasing
811211	811200	Consumer Electronics Repair and Maintenance	Aerosol degreasing
811212	811200	Computer and Office Machine Repair and Maintenance	Aerosol degreasing
811213	811200	Communication Equipment Repair and Maintenance	Aerosol degreasing
811219	811200	Other Electronic and Precision Equipment Repair and Maintenance	Aerosol degreasing
811310	811300	Commercial and Industrial Machinery and Equipment (except Automotive and Electronic) Repair and Maintenance	Aerosol degreasing
811411	811400	Home and Garden Equipment Repair and Maintenance	Aerosol degreasing
811490	811400	Other Personal and Household Goods Repair and Maintenance	Aerosol degreasing
451110	451110	Sporting Goods Stores	Aerosol degreasing

Step 2: Estimating Total Employment by Industry and Occupation

BLS's OES data (2015) provide employment data for workers in specific industries and occupations. The industries are classified by NAICS codes (identified previously), and occupations are classified by Standard Occupational Classification (SOC) codes.

Among the relevant NAICS codes (identified previously), EPA/OPPT reviewed the occupation description and identified those occupations (SOC codes) where workers will potentially come in contact with 1-BP.

Table_Apx F-2 shows example SOC codes where workers and occupational non-users are likely exposed to 1-BP at dry cleaning facilities. EPA/OPPT classified the SOC codes into "workers (W)" (near-field exposure) and "occupational non-users (N)" (far-field exposure), where possible.

Table_Apx F-2 SOC Codes with 1-BP Exposure at Dry Cleaning Facilities

Application	SOC	Occupation	Designation
Dry cleaning	41-2000	Retail Sales Workers	N
	49-9040	Industrial Machinery Installation, Repair, and Maintenance Workers	W
	49-9070	Maintenance and Repair Workers, General	W
	49-9090	Miscellaneous Installation, Maintenance, and Repair Workers	W
	51-6010	Laundry and Dry-Cleaning Workers	W
	51-6020	Pressers, Textile, Garment, and Related Materials	W
	51-6030	Sewing Machine Operators	N
	51-6040	Shoe and Leather Workers	N
	51-6050	Tailors, Dressmakers, and Sewers	N
	51-6090	Miscellaneous Textile, Apparel, and Furnishings Workers	N

After identifying relevant NAICS and SOC codes, EPA/OPPT used BLS data to determine total employment by industry and by occupation based on the NAICS and SOC combinations. For

example, there are 106,440 employees associated with 4-digit NAICS 812300 (*Drycleaning and Laundry Services*) and SOC 51-6010 (*Laundry and Dry-Cleaning Workers*).

Using a combination of NAICS and SOC codes to estimate total employment provides more accurate estimates for the number of workers than using NAICS codes alone. Using only NAICS codes to estimate number of workers typically result in a gross overestimate, because not all workers employed in that industry sector will be exposed. However, note in some cases, BLS only provide employment data at the 4-digit or 5-digit NAICS level; therefore, further refinement of this approach may be needed (see next step).

Step 3: Refining Employment Estimates to Account for Lack of NAICS Granularity
The third step in EPA/OPPT's methodology was to further refine the employment estimates by using total employment data in the U.S. Census' SUSB (2012). In some cases, BLS OES's occupation-specific data are only available at the 4-digit or 5-digit NAICS level, whereas the SUSB data are available at the 6-digit level (but are not occupation-specific). Identifying specific 6-digit NAICS will ensure that only industries with potential 1-BP exposure are included. For instance, OES data are available for the 5-digit NAICS 81230 *Drycleaning and Laundry Services*, which includes the following 6-digit NAICS:

- NAICS 812310 Coin-Operated Laundries and Drycleaners;
- NAICS 812320 Drycleaning and Laundry Services (except Coin-Operated);
- NAICS 812331 Linen Supply; and
- NAICS 812332 Industrial Launderers.

Only NAICS 812320 is of interest, while the remaining 6-digit NAICS are unlikely to cover dry cleaning facilities that use 1-BP. The Census data allow us to calculate employment in the specific 6-digit NAICS of interest as a percentage of employment in the BLS 5-digit NAICS.

Table_Apx F-3 and Table_Apx F-4 provide example calculations. NAICS 812320 make up 48 percent of total employment under NAICS 81230. This percentage can be multiplied by the occupation-specific employment estimates given in the BLS OES data to further refine our estimates of the number of employees with potential 1-BP exposure.

For example, the number of workers under NAICS 812320 is calculated as:

206,250 (*Employment in NAICS/SOC*) x 48% (*Granularity Adjustment Percentage) = 98,920 workers* and *occupational non-users* under 6-digit NAICS 812320.

Table_Apx F-3 Sample Granularity Calculation

NAICS	Industry	Total Employment	Percent of Total Employment
5-Digit Parent NAICS			
81230	Drycleaning and Laundry Services	290,868	100%
6-Digit NAICS Relevant to 1-BP Use			
812320	Drycleaning and Laundry Services (except Coin-Operated)	139,504	48%

Source: U.S. Census Bureau (2012)

Table_Apx F-4 Estimated 1-BP Employment under NAICS 812320

NAICS	SOC CODE	SOC Description	Employment by SOC at 4-digit NAICS level	% of Total Employment	Estimated Employment by SOC at 6-digit NAICS level
812300	41-2000	Retail Sales Workers	45,570	48.0%	21,856
812300	49-9040	Industrial Machinery Installation, Repair, and Maintenance Workers	1,640	48.0%	787
812300	49-9070	Maintenance and Repair Workers, General	3,410	48.0%	1,635
812300	49-9090	Miscellaneous Installation, Maintenance, and Repair Workers	930	48.0%	446
812300	51-6010	Laundry and Dry-Cleaning Workers	106,440	48.0%	51,050
812300	51-6020	Pressers, Textile, Garment, and Related Materials	43,160	48.0%	20,700
812300	51-6030	Sewing Machine Operators	1,810	48.0%	868
812300	51-6040	Shoe and Leather Workers	0	48.0%	0
812300	51-6050	Tailors, Dressmakers, and Sewers	3,160	48.0%	1,516
812300	51-6090	Miscellaneous Textile, Apparel, and Furnishings Workers	130	48.0%	62
812300	41-2000	Retail Sales Workers	45,570	48.0%	21,856
Total			**206,250**		**98,920**

Sources: U.S. Census Bureau (2012) and U.S. BLS (2015).

Step 4: Estimating the Percentage of Workers Using 1-BP instead of Other Chemicals

In the final step, EPA/OPPT accounted for the market share by applying a factor to the number of workers determined in Step 3. This accounts for the fact that 1-BP is only one of many chemicals used for the applications of interest. EPA/OPPT determined the "factor", or 1-BP market penetration, using information provided in EPA's 1-BP market reports, *Use and Market Profiles* (U.S. EPA, 2013c) and *Use and Market Profile for 1-Bromopropane in Dry Cleaning* (U.S. EPA, 2013b). For dry cleaning, the market penetration is estimated to be 1.1 percent based on a 2012 survey conducted by AmericanDrycleaner.com.

Step 5: Final Worker Estimates

For the final estimates, EPA/OPPT calculated the number of workers and occupational non-users in each industry/occupation combination potentially exposed to 1-BP, using the formula below (note granularity adjustment is only applicable where SOC data are not available at the 6-digit NAICS level):

Employment in NAICS/SOC (Step 2) × Granularity Adjustment Percentage (Step 3) × Percentage of Workers Using 1-BP (Step 4) = Employees using 1-BP

For example, the estimated number of workers and occupational non-users under NAICS 812320 from Step 3, after granularity adjustment, is 98,920. Assuming a 1-BP market penetration of 1.1 percent, the estimated number of workers and occupational non-users using 1-BP under this NAICS code is:

98,920 x 1.1% = 1,088 workers and occupational non-users using 1-BP under NAICS 812320

The number of establishments is calculated by multiplying the total establishments under 6-digit NAICS 812320 by the market penetration.

22,359 establishments under NAICS 812320 x 1.1% = 246 establishments using 1-BP

The number of workers and occupational non-users can then be divided by the number of establishments to calculate the average number of workers and occupational non-users per site.

F-1 Estimates for Number of Workers Using Spray Adhesives

EPA/OPPT estimated the number of workers potentially exposed to 1-BP in spray adhesives using Bureau of Labor Statistics' Occupational Employment Statistics (OES) data (2015) and U.S. Census' Statistics of US Businesses (SUSB) (2012). The method for estimating number of workers is detailed above in Appendix F. The worker estimates were derived using industry- and occupation-specific employment data from these sources. The industry sectors and occupations that EPA/OPPT determined to be relevant to spray adhesive use are presented below.

Table_Apx F-5 presents the NAICS industry sectors relevant to spray adhesive use, while Table_Apx F-6 presents BLS occupation codes where workers are potentially exposed to 1-BP. EPA/OPPT designated each occupation code as either "Worker (W)" or "Occupational non-user (N)" to separately estimate the number of potentially exposed workers and occupational non-users. There are no occupation codes described as adhesive "sprayers". EPA/OPPT assumed SOC 51-9121 "Coating, Painting, and Spraying Machine Setters, Operators, and Tenders" and SOC 51-9191 "Adhesive Bonding Machine Operators and Tenders" could involve manual or automated spraying of 1-BP adhesives. EPA/OPPT also assumed that assemblers and fabricators work in areas where the spraying occurs, and are directly exposed. EPA/OPPT assumed production supervisors and other production workers are "occupational non-users".

Table_Apx F-5 NAICS Codes for Spray Adhesive Uses in Foam Cushion Manufacturing

NAICS	BLS NAICS	Industry
337121	337120	Upholstered Household Furniture Manufacturing
337125	337120	Household Furniture (except Wood and Metal) Manufacturing
337127	337120	Institutional Furniture Manufacturing
337214	337200	Office Furniture (except Wood) Manufacturing

Table_Apx F-6 SOC Codes for Worker Exposure in the Spray Adhesive Sector

SOC	Occupation	Exposure Designation
51-1000	Supervisors of Production Workers	N
51-2090	Miscellaneous Assemblers and Fabricators	W
51-6000	Textile, Apparel, and Furnishings Workers	N
51-9121	Coating, Painting, and Spraying Machine Setters, Operators, and Tenders	W
51-9191	Adhesive Bonding Machine Operators and Tenders	W
51-9198	Helpers--Production Workers	N
51-9199	Production Workers, All Other	N

Source: U.S. BLS (2015) W – worker, N – occupational non-user

The number of businesses in this use sector of 1-BP is estimated to be between 100 and 280 (U.S. EPA, 2007b). Based on a total of 2,386 establishments in the industry sectors shown in Table_Apx F-5, the 1-BP market penetration is 4.2 percent to 11.7 percent. Alternatively, an article published in The New York Times estimated that 33 percent of the foam cushion industry uses 1-BP based adhesives (NY Times, as cited in (U.S. EPA, 2013c)). Table_Apx F-7 presents the estimated number of workers and occupational non-users using the low-end market penetration of 4.2 percent and the high-end market penetration of 33 percent. The total number of potentially exposed workers and occupational non-users ranges from 1,503 to 11,952.

Table_Apx F-7 Estimated Number of Workers Potentially Exposed to 1-BP in Spray Adhesive Use in Foam Cushion Manufacturing

Exposed Workers	Exposed Occupational Non-Users	Total Exposed	Estimated Number of Establishments	Workers per Site	Occupational Non-Users per Site
Low-end					
551	952	1,503	100	6	10
High-end					
4,384	7,568	11,952	795	6	10

Note: Number of workers and occupational non-users per site are calculated by dividing the exposed number of workers or occupational non-users by the number of establishments. Values are rounded to the nearest integer.

F-2 Estimates for Number of Workers at Dry Cleaners

EPA/OPPT estimated the number of workers and occupational non-users potentially exposed to 1-BP at dry cleaners using Bureau of Labor Statistics' OES data (2015) and the U.S. Census' SUSB (2012). The method for estimating number of workers is detailed above in Appendix F. These

estimates were derived using industry- and occupation-specific employment data from the BLS and U.S. Census.

Table_Apx F-8 presents the NAICS industry sector relevant to dry cleaning, while Table_Apx F-9 presents BLS occupation codes where workers are potentially exposed to dry cleaning solvents. EPA/OPPT designated each occupation code as either "Worker (W)" or "Occupational non-user (N)" to separately estimate the number of potentially exposed workers and occupational non-users. EPA/OPPT classified laundry and dry cleaning workers, pressers, and machine repairers as "Workers" because they are likely to have direct exposure to the dry cleaning solvents. EPA/OPPT classified retail sales workers (e.g., cashiers), sewers, tailors, and other textile workers as "occupational non-users" because they perform work at the dry cleaning shop, but do not directly handle dry cleaning solvents.

Table_Apx F-8 NAICS Code for Dry Cleaning

NAICS	BLS NAICS	Industry
812320	812300	Drycleaning and Laundry Services (except Coin-Operated)

Table_Apx F-9 SOC Codes for Worker Exposure in Dry Cleaning

SOC	Occupation	Exposure Designation
41-2000	Retail Sales Workers	N
49-9040	Industrial Machinery Installation, Repair, and Maintenance Workers	W
49-9070	Maintenance and Repair Workers, General	W
49-9090	Miscellaneous Installation, Maintenance, and Repair Workers	W
51-6010	Laundry and Dry-Cleaning Workers	W
51-6020	Pressers, Textile, Garment, and Related Materials	W
51-6030	Sewing Machine Operators	N
51-6040	Shoe and Leather Workers	N
51-6050	Tailors, Dressmakers, and Sewers	N
51-6090	Miscellaneous Textile, Apparel, and Furnishings Workers	N

Source: U.S. BLS (2015) W – worker, N – occupational non-user

There are 22,359 dry cleaning establishments in the United States under NAICS 812320 (U.S. Census Bureau, 2012). Among these establishments, only a small subset use 1-BP as a dry cleaning solvent. In 2009, the Drycleaning and Laundry Institute (DLI) estimated only about 50 dry cleaning systems used DrySolv® (U.S. EPA, 2013b). A more recent survey conducted by AmericanDrycleaner.com in 2012 indicated that 1.1% of respondents used DrySolv, but did not specify the number of respondents participating in the survey (Beggs, 2012, as cited in (U.S. EPA, 2013b)). EPA/OPPT conservatively assumed a 1-BP market penetration of 1.1 percent. Using this factor, EPA/OPPT estimated that approximately 246 dry cleaning establishments and 1,088 workers and occupational non-users are exposed to 1-BP; see Table_Apx F-10.

Table_Apx F-10 Estimated Number of Workers Potentially Exposed to 1-BP in Dry Cleaning Shops

Exposed Workers	Exposed Occupational non-users	Total Exposed	Estimated Number of Establishments	Workers per Site	Occupational non-users per Site
821	267	1,088	246	3	1

Note: Number of workers and occupational non-users per site are calculated by dividing the exposed number of workers or occupational non-users by the number of establishments. Values are rounded to the nearest integer.

F-3 Estimates for Number of Workers in Vapor Degreasing

EPA/OPPT estimated the number of workers potentially exposed to 1-BP in vapor degreasing using Bureau of Labor Statistics' OES data (2015) and (2012) U.S. Census SUBS. The method for estimating number of workers is detailed above in Appendix F. The worker estimates were derived using industry- and occupation-specific employment data from these sources. The industry sectors and occupations that EPA/OPPT determined to be relevant to degreasing uses are presented below. EPA/OPPT was unable to determine which industry sectors and occupations perform specific degreasing types (e.g., vapor degreasing versus cold cleaning). It is possible that establishments under the same NAICS code perform a combination of vapor degreasing and cold cleaning.

Table_Apx F-11 presents the NAICS industry sectors relevant to degreasing applications. These NAICS codes were obtained from the list of degreasing NAICS codes in EPA's Work Plan Chemical Assessment of Trichloroethylene (TCE) (U.S. EPA, 2014c). These codes cover a wide range of workplaces where degreasing activities could be performed; however, note degreasing is unlikely to be a primary operation for many of these industries. Therefore, using such a broad range of NAICS codes likely result in an overestimate.

Table_Apx F-12 presents BLS occupation codes among the relevant NAICS sectors where workers are potentially exposed to degreasing solvents. EPA/OPPT designated repairers, mechanics, production workers and assemblers as "Worker (W)" because they are likely to work directly with the degreasing equipment. In addition, EPA/OPPT assumed engineers, technicians, and production supervisors could be "Occupational non-user (N)". There are general uncertainties in how the job duties in these sectors relate to degreasing; it is possible that employees within a single occupation code perform work both as a "worker" and as an "occupational non-user".

Table_Apx F-11 NAICS Codes for All Degreasing Types

NAICS	BLS NAICS	Industry
314999	314900	All Other Miscellaneous Textile Product Mills
321113	321100	Sawmills
323111	323100	Commercial Printing (except Screen and Books)
325180	325100	Other Basic Inorganic Chemical Manufacturing
325998	325900	All Other Miscellaneous Chemical Product and Preparation Manufacturing
326299	326200	All Other Rubber Product Manufacturing
331110	331100	Iron and Steel Mills and Ferroalloy Manufacturing
331210	331200	Iron and Steel Pipe and Tube Manufacturing from Purchased Steel
331410	331400	Nonferrous Metal (except Aluminum) Smelting and Refining

Table_Apx F-11 NAICS Codes for All Degreasing Types

NAICS	BLS NAICS	Industry
331420	331400	Copper Rolling, Drawing, Extruding, and Alloying
332111	332100	Iron and Steel Forging
332112	332100	Nonferrous Forging
332119	332100	Metal Crown, Closure, and Other Metal Stamping (except Automotive)
332117	332100	Powder Metallurgy Part Manufacturing
332215	332200	Metal Kitchen Cookware, Utensil, Cutlery, and Flatware (except Precious) Manufacturing
332216	332200	Saw Blade and Handtool Manufacturing
332311	332300	Prefabricated Metal Building and Component Manufacturing
332313	332300	Plate Work Manufacturing
332431	332400	Metal Can Manufacturing
332510	332500	Hardware Manufacturing
332618	332600	Other Fabricated Wire Product Manufacturing
332721	332720	Precision Turned Product Manufacturing
332722	332720	Bolt, Nut, Screw, Rivet, and Washer Manufacturing
332811	332800	Metal Heat Treating
332812	332800	Metal Coating, Engraving (except Jewelry and Silverware), and Allied Services to Manufacturers
332813	332800	Electroplating, Plating, Polishing, Anodizing, and Coloring
332912	332900	Fluid Power Valve and Hose Fitting Manufacturing
332913	332900	Plumbing Fixture Fitting and Trim Manufacturing
332919	332900	Other Metal Valve and Pipe Fitting Manufacturing
332994	332900	Small Arms, Ordnance, and Ordnance Accessories Manufacturing
332996	332900	Fabricated Pipe and Pipe Fitting Manufacturing
332999	332900	All Other Miscellaneous Fabricated Metal Product Manufacturing
333132	333100	Oil and Gas Field Machinery and Equipment Manufacturing
333249	333200	Other Industrial Machinery Manufacturing
333318	333300	Other Commercial and Service Industry Machinery Manufacturing
333410	333400	Ventilation, Heating, Air-Conditioning, and Commercial Refrigeration Equipment Manufacturing
333415	333400	Air-Conditioning and Warm Air Heating Equipment and Commercial and Industrial Refrigeration Equipment Manufacturing
333921	333900	Elevator and Moving Stairway Manufacturing
333994	333900	Industrial Process Furnace and Oven Manufacturing
333999	333900	All Other Miscellaneous General Purpose Machinery Manufacturing
334220	334200	Radio and Television Broadcasting and Wireless Communications Equipment Manufacturing
334413	334400	Semiconductor and Related Device Manufacturing
334416	334400	Capacitor, Resistor, Coil, Transformer, and Other Inductor Manufacturing
334417	334400	Electronic Connector Manufacturing
334419	334400	Other Electronic Component Manufacturing
334513	334500	Instruments and Related Products Manufacturing for Measuring, Displaying, and Controlling Industrial Process Variables
334515	334500	Instrument Manufacturing for Measuring and Testing Electricity and Electrical Signals
335120	335100	Lighting Fixture Manufacturing
335121	335100	Residential Electric Lighting Fixture Manufacturing

Table_Apx F-11 NAICS Codes for All Degreasing Types

NAICS	BLS NAICS	Industry
335210	335200	Small Electrical Appliance Manufacturing
335310	335300	Electrical Equipment Manufacturing
335312	335300	Motor and Generator Manufacturing
335313	335300	Switchgear and Switchboard Apparatus Manufacturing
335911	335900	Storage Battery Manufacturing
335921	335900	Fiber Optic Cable Manufacturing
335929	335900	Other Communication and Energy Wire Manufacturing
335999	335900	All Other Miscellaneous Electrical Equipment and Component Manufacturing
336320	336300	Motor Vehicle Electrical and Electronic Equipment Manufacturing
336340	336300	Motor Vehicle Brake System Manufacturing
336410	336400	Aerospace Product and Parts Manufacturing
336411	336400	Aircraft Manufacturing
336413	336400	Other Aircraft Parts and Auxiliary Equipment Manufacturing
336414	336400	Guided Missile and Space Vehicle Manufacturing
336510	336500	Railroad Rolling Stock Manufacturing
337125	337120	Household Furniture (except Wood and Metal) Manufacturing
337127	337120	Institutional Furniture Manufacturing
339114	339100	Dental Equipment and Supplies Manufacturing
339990	339900	All Other Miscellaneous Manufacturing
339992	339900	Musical Instrument Manufacturing
339995	339900	Burial Casket Manufacturing
339999	339900	All Other Miscellaneous Manufacturing
488111	488100	Air Traffic Control
493110	493100	General Warehousing and Storage
811310	811300	Commercial and Industrial Machinery and Equipment (except Automotive and Electronic) Repair and Maintenance

Table_Apx F-12 SOC Codes for Worker Exposure in the Degreasing Sector

SOC	Occupation	Exposure Designation
17-2000	Engineers	N
17-3000	Drafters, Engineering Technicians, and Mapping Technicians	N
19-4000	Life, Physical, and Social Science Technicians	N
49-1000	Supervisors of Installation, Maintenance, and Repair Workers	N
49-2000	Electrical and Electronic Equipment Mechanics, Installers, and Repairers	W
49-3000	Vehicle and Mobile Equipment Mechanics, Installers, and Repairers	W
49-9010	Control and Valve Installers and Repairers	W
49-9020	Heating, Air Conditioning, and Refrigeration Mechanics and Installers	W
49-9040	Industrial Machinery Installation, Repair, and Maintenance Workers	W
49-9060	Precision Instrument and Equipment Repairers	W
49-9070	Maintenance and Repair Workers, General	W
49-9090	Miscellaneous Installation, Maintenance, and Repair Workers	W
51-2000	Assemblers and Fabricators	W
51-9192	Cleaning, Washing, and Metal Pickling Equipment Operators and Tenders	W

Source: (U.S. BLS, 2015) W – worker, N – occupational non-user

There are 109,966 establishments among the industry sectors presented in Table_Apx F-11. The number of businesses that use 1-BP for vapor degreasing is estimated at 500 to 2,500 businesses (U.S. EPA, 2007c). This translates to a 1-BP market penetration of 0.5 percent to 2.3 percent.

Table_Apx F-13 presents the estimated number of workers and occupational non-users based on industry- and occupational-specific employment data. The low-end estimates correspond to a 0.5 percent market penetration, while the high-end estimates correspond to a 2.3 percent market penetration. The total number of potentially exposed workers and occupational non-users range from 4,712 to 23,558.

Table_Apx F-13 Estimated Number of Workers Potentially Exposed to 1-BP in Degreasing Uses

Exposed Workers	Exposed Occupational non-users	Total Exposed	Estimated Number of Establishments	Workers per Site	Occupational non-users per Site
Low-end					
3,245	1,466	4,712	500	6	3
High-end					
16,226	7,332	23,558	2,500	6	3

Note: Number of workers and occupational non-users per site are calculated by dividing the exposed number of workers or occupational non-users by the number of establishments. Values are rounded to the nearest integer.

F-4 Estimates for Number of Workers Potentially Using Aerosol Degreasing

Table_Apx F-14 presents the NAICS industry sectors relevant to aerosol degreasing. These NAICS codes cover repair and maintenance shops where aerosol degreasing is likely to occur. Table_Apx F-12 of Section F-3 presents BLS occupation codes where workers are potentially exposed to degreasing solvents. EPA/OPPT assumed the types of occupation with potential solvent exposure are similar between vapor degreasing and aerosol degreasing.

Table_Apx F-14 NAICS Codes for Aerosol Degreasing

NAICS	BLS NAICS	Industry
811111	811110	General Automotive Repair
811112	811110	Automotive Exhaust System Repair
811113	811110	Automotive Transmission Repair
811118	811110	Other Automotive Mechanical and Electrical Repair and Maintenance
811121	811120	Automotive Body, Paint, and Interior Repair and Maintenance
811122	811120	Automotive Glass Replacement Shops
811191	811190	Automotive Oil Change and Lubrication Shops
811192	811190	Car Washes
811198	811190	All Other Automotive Repair and Maintenance
811211	811200	Consumer Electronics Repair and Maintenance
811212	811200	Computer and Office Machine Repair and Maintenance
811213	811200	Communication Equipment Repair and Maintenance
811219	811200	Other Electronic and Precision Equipment Repair and Maintenance

Table_Apx F-14 NAICS Codes for Aerosol Degreasing

NAICS	BLS NAICS	Industry
811310	811300	Commercial and Industrial Machinery and Equipment (except Automotive and Electronic) Repair and Maintenance
811411	811400	Home and Garden Equipment Repair and Maintenance
811490	811400	Other Personal and Household Goods Repair and Maintenance
451110	451110	Sporting Goods Stores

There are 222,940 establishments among the industry sectors presented in Table_Apx F-14. The EPA market report on 1-BP estimated that "*1,000 to 5,000 businesses used 1-BP-based aerosol solvents in 2002* (U.S. EPA, 2007c), as cited in (U.S. EPA, 2013c)". This translates to a market penetration of approximately 0.4 percent to 2.2 percent. Based on these estimates, approximately 2,466 to 12,329 workers and occupational non-users are potentially exposed to 1-BP as an aerosol degreasing solvent. It is unclear whether the number of establishments using 1-BP-based aerosol solvents has increased since 2002.

Table_Apx F-15 Estimated Number of Workers Potentially Exposed to 1-BP in Aerosol Degreasing

Exposed Workers	Exposed Occupational non-users	Total Exposed	Estimated Number of Establishments	Workers per Site	Occupational non-users per Site
Low-end					
2,227	238	2,466	1,000	2	0.2
High-end					
11,137	1,192	12,329	5,000	2	0.2

Note: Number of workers and occupational non-users per site are calculated by dividing the exposed number of workers or occupational non-users by the number of establishments. The number of workers per site is rounded to the nearest integer. The number of occupational non-users per site is shown as 0.2, as it rounds down to zero.

Appendix G APPROACH USED TO COLLECT MONITORING DATA AND INFORMATION ON MODEL PARAMETERS

EPA/OPPT conducted a comprehensive literature search to identify worker exposure monitoring data relevant to 1-BP use in degreasing, dry cleaning, and spot cleaning applications. In addition, EPA/OPPT searched for information on model parameters for the purpose of 1-BP exposure modeling. Some of these model parameters include, but are not limited to, 1-BP use rate, use volume, and vapor generation rate.

For each 1-BP use scenario, EPA/OPPT developed scenario-specific primary and secondary keywords to be used for the literature search. EPA/OPPT searched the following data sources:

- Standard engineering sources used by OPPT/RAD for occupational exposure assessments.
- Internet literature search (e.g. ScienceDirect.com)

All search results were reviewed, compared to the data quality criteria, and documented. Table_Apx G-1 presents the data quality criteria and corresponding acceptance specifications for the literature review.

Table_Apx G-1 Data Quality Criteria and Acceptance Specifications for 1-BP Literature Review for Monitoring Data and Information on Model Parameters

Quality Criterion	Description/Definition	Acceptance Specification
Currency (up to date)	The information reflects present conditions.	Data from all years are acceptable.
Geographic Scope	The information reported reflects an area relevant to the assessment.	Data for the modeling input parameters for the commercial scenarios in scope in the United States and the rest of world are acceptable.
Reliability	The information reported is reliable. For example, this criterion may include the following acceptance specifications: The information or data are from a peer-reviewed, government, or industry-specific source. The source is published. The author is engaged in a relevant field such that competent knowledge is expected (i.e., the author writes for an industry trade association publication versus a general newspaper). The information was presented in a technical conference where it is subject to review by other industry experts.	Data are reliable if they are from one of the following sources: U.S. or other government publication. Sources by an academic researcher where: • Publication is in peer-reviewed journal; or • Presented at a technical conference; or • Source has documented qualifications or credentials to discuss particular topic. Sources by an industry expert or trade group where: • Presented at a technical conference where the information is subject to review by other industry experts; or • Source has documented qualifications or credentials to discuss particular topic; or • Source represents a large portion of the industry of interest.

Table_Apx G-1 Data Quality Criteria and Acceptance Specifications for 1-BP Literature Review for Monitoring Data and Information on Model Parameters

Unbiased	The information is not biased towards a particular product or outcome.	• Objective of the information is clear. • Methodology is designed to answer a specific question.
Comparability	The data are comparable to other sources that have been identified.	Data sources will not be accepted or rejected based on their comparison to data from other sources.
Representativeness	The data reflect the typical industry practices. The data are based on a large industry survey or study, as opposed to a case study or sample from a limited number of sites.	Literature sources are not rejected based on the sample size of sites. Large industry surveys as well as case studies and limited sample sizes are acceptable.
Applicability	For surrogate data, the data are expected to be similar for the industry or property of interest.	Surrogate data deemed applicable only if approved by EPA.

Appendix H EQUATIONS FOR CALCULATING ACUTE AND CHRONIC EXPOSURES FOR NON-CANCER AND CANCER

This report assesses 1-BP exposures to workers in occupational settings, presented as 8-hr time weighted average (TWA) exposure. The 8-hr TWA exposures are then used to calculate acute exposure, average daily concentration (ADC) for chronic, non-cancer risks, and lifetime average daily concentration (LADC) for chronic, cancer risks.

Acute workplace exposures are assumed to be equal to the contaminant concentration in air (8-hr TWA).

ADC and LADC are used to estimate workplace exposures for non-cancer and cancer risks, respectively. These exposures are estimated as follows:

Equation_Apx H-1 ADC and LADC

$$\text{ADC or LADC} = \frac{\text{C} \times \text{ED} \times \text{EF} \times \text{WY}}{\text{AT}}$$

where:

ADC = average daily concentration (8-hr TWA) used for chronic non-cancer risk calculations
LADC = lifetime average daily concentration (8-hr TWA) used for chronic cancer risk calculations
C = contaminant concentration in air (8-hr TWA)
ED = exposure duration (8 hr/day)
EF = exposure frequency (260 days/yr)
WY = working years per lifetime (40 yr)
AT = averaging time (LT × 260 days/yr × 8 hrs/day; where LT = lifetime; LT = 40 yr for non-cancer risks; LT=70 yr for cancer risks)

The parameter values in Table_Apx H-1 are used to calculate each of the above exposure estimates with the exception that the multi-zone dry cleaning model varies the exposure frequency from 250 to 312 days per year. The AC, ADC, and LADC calculations are integrated into the Monte Carlo simulation for dry cleaning.

Table_Apx H-1 Parameter Values for Calculating Exposure Estimates

Parameter Name	Symbol	Value	Unit
Exposure Duration (acute)	ED_{Acute}	8	hr/day
Averaging Time (acute)	AT_{Acute}	24	hr/day
Exposure Duration (chronic)	$ED_{Chronic}$	8	hr/day
Exposure Frequency (chronic)	$EF_{Chronic}$	260	day/yr
Working Years per Lifetime (chronic)	$WY_{Chronic}$	40	yr
Lifetime (chronic, non-cancer)	$LT_{Chronic, Non-Cancer}$	40	yr
Lifetime (chronic, cancer)	$LT_{Chronic, Cancer}$	70	yr
Averaging Time (chronic, non-cancer)	$AT_{Chronic, Non-Cancer}$	83,200	hr
Averaging Time (chronic, cancer)	$AT_{Chronic, Cancer}$	145,600	hr

Example AC, ADC and LADC calculations for 1-BP use in spray adhesives:

1-BP pre-EC 8-hr TWA exposure for sprayers, 95th percentile: 253.26 ppm (see Appendix I below for explanation of this estimate)

$$\mathrm{AC} = \frac{\mathrm{C} \times \mathrm{ED}}{\mathrm{AT}} = \frac{253.26\ \mathrm{ppm} \times 8\ \mathrm{hr}}{8\ \mathrm{hr}} = 253.26\ \mathrm{ppm}$$

$$\mathrm{ADC} = \frac{\mathrm{C} \times \mathrm{ED} \times \mathrm{EF} \times \mathrm{WY}}{\mathrm{AT}} = \frac{253.26\ \mathrm{ppm} \times 8\frac{\mathrm{hr}}{\mathrm{day}} \times 260\frac{\mathrm{day}}{\mathrm{yr}} \times 40\ \mathrm{yr}}{83{,}200\ \mathrm{hr}} = 253.26\ \mathrm{ppm}$$

$$\mathrm{LADC} = \frac{\mathrm{C} \times \mathrm{ED} \times \mathrm{EF} \times \mathrm{WY}}{\mathrm{AT}} = \frac{253.26\ \mathrm{ppm} \times 8\frac{\mathrm{hr}}{\mathrm{day}} \times 260\frac{\mathrm{day}}{\mathrm{yr}} \times 40\ \mathrm{yr}}{145{,}600\ \mathrm{hr}} = 144.72\ \mathrm{ppm}$$

Appendix I EXAMPLE OF MONITORING DATA ANALYSIS FOR SPRAY ADHESIVE USE

This appendix describes how EPA/OPPT analyzed the exposure monitoring data for the spray adhesive use scenario. The following data sources were included in EPA/OPPT's analysis:

- A 1998 NIOSH Health Hazard Evaluation (HHE) of Custom Products, Inc. in Mooresville, North Carolina (NIOSH, 2002a);
- A 2002 NIOSH HHE of STN Cushion Company in Thomasville, North Carolina (NIOSH, 2002b);
- A 2003 NIOSH HHE of Marx Industries, Inc. in Sawmills, North Carolina (NIOSH, 2003);
- OSHA IMIS data from OSHA inspection of Foamex International, Franklin Corp, Royale Comfort Seating, Inc., Starr Aircraft Products Inc., and Willard Packaging Company Inc. (OSHA, 2013).

Table_Apx I-1 shows how EPA/OPPT categorized each employee as either sprayer, non-sprayer, or occupational non-user. EPA/OPPT defined "sprayers" as employees who perform manual spraying of the 1-BP adhesive as a regular part of the job. EPA/OPPT defined "non-sprayers" as employees who are not sprayers, but either handle the adhesive or spend the majority of their shift working in an area where spraying occurs (e.g. employees who work in the Assembly department where spraying regularly occurs). EPA/OPPT defined "occupational non-users" as employees who do not regularly work in a department/area where spraying occurs (e.g. employees in the Saw and Sew departments).

Table_Apx I-1 Categorization of Employees as Sprayers, Non-Sprayers, or Occupational Non-Users

Data Source	Category		
	Sprayer	Non-sprayer	Occupational Non-user
NIOSH (2002a)	Sprayer (Assembly and Covers department)	Assembler and Supervisor in Assembly department	Operator and Supervisor in Saw department
NIOSH (2002b)	Sprayer (Fabrication department)	Floater (Fabrication department)	No data
NIOSH (2003)	Sprayer (Glue line and Spring line)	Doffer, supervisor, baler, and foam set-up worker (Glue line and Spring line)	Accounting, blowing, customer service, fiber cutting, foam cutting, maintenance, and supervisor worker (work areas other than Glue line and Spring line)
OSHA (2013): Foamex International	Sprayer (Gluing area)	No data	No data
OSHA (2013): Franklin Corp	Gluer	No data	No data
OSHA (2013): Royale comfort Seating Inc.	Sprayer	No data	No data
OSHA (2013): Starr Aircraft Products Inc.	Sprayer (Bonding and Blocking area)	No data	No data
OSHA (2013): Willard Packaging Company Inc.	Sprayer (Spray booth)	No data	No data

Table_Apx I-2 shows how EPA/OPPT categorized the exposure monitoring data into either "pre-EC" or "post-EC" scenarios. EPA/OPPT categorized the data into "pre-EC" scenario if the facility had little to no engineering control to reduce 1-BP vapor at the time of monitoring. EPA/OPPT categorized the data as "post-EC" if specific engineering controls were implemented to reduce 1-BP exposure.

Table_Apx I-2 Categorization of Exposure Data into Pre-EC and Post-EC Scenarios

Data Source	Scenario	
	Pre-EC	Post-EC
NIOSH (2002a)	Initial worker exposure assessment in 1998 is categorized as "pre-EC" due to ineffective control	Follow-up assessment in 2000 is categorized as "post-EC" after the facility improved spray booths with hoods and filters and removed excess adhesive from exhaust system
NIOSH (2002b)	Initial worker exposure assessment in 2000 is categorized as "pre-EC" due to ineffective control	Follow-up assessment in 2001 2000 is categorized as "post-EC" after facility improved ventilation and enclosed all spray stations to create spray booths
NIOSH (2003)	All data categorized as "pre-EC" due to ineffective control. Facility only had exhaust fans located on outside walls of spray rooms.	No data. Facility did not implement engineering controls in between the two studies.
OSHA (2013): Foamex International	All data categorized as "pre-EC". Facility had overhead canopy hood with two exhaust fans above the work stations, but it was unclear whether these fans were effective in controlling 1-BP vapor.	No data.
OSHA (2013): Franklin Corp	All data categorized as "pre-EC". Facility had no local exhaust ventilation.	No data
OSHA (2013): Royale comfort Seating Inc.	All data categorized as "pre-EC". Facility had poor to no ventilation. There were three wall fans that exhaust air to outside.	No data
OSHA (2013): Starr Aircraft Products Inc.	All data categorized as "pre-EC". Workers conducted spraying either in spray booths or at table top. No additional engineering controls were described.	No data
OSHA (2013): Willard Packaging Company Inc.	All data categorized as "pre-EC". Facility had a spray booth. No additional engineering controls were described.	No data

For example, EPA/OPPT determined the initial assessment in NIOSH (2002a) to be representative of a "pre-EC" scenario, where there is insufficient engineering control to prevent worker exposure to 1-BP. Data from the initial assessment are presented in Table_Apx I-3. The sample duration of the personal breathing zone measurements are approximately 8 hours; therefore, we assume these data are representative of 8-hr TWA values.

Subsequent to NIOSH's initial assessment, the facility installed new spray booths with local exhaust ventilation for all adhesive spraying operations (Assembly and Covers departments) based on NIOSH recommendations. EPA/OPPT determined exposure data in the follow-up assessment to be representative of a "post-EC" scenario. These data are presented in Table_Apx I-4.

Table_Apx I-3 Personal Breathing Zone Monitoring Data for Sprayers, Initial NIOSH Assessment (Pre-EC Scenario)

Department	Worker Job Description	Sample Date	Sample Duration	Exposure Concentration (ppm)
Assembly	Sprayer	11/11/1998	8hr (0710-1518)	115.3
Covers	Sprayer	11/11/1998	8.25hr(0720-1533)	117.3
Covers	Sprayer	11/11/1998	8.25hr(0716-1533)	126.8
Assembly	Sprayer	11/11/1998	8hr(0732-1527)	132.8
Covers	Sprayer	11/11/1998	8.25hr(0719-1533)	140.5
Covers	Sprayer	11/11/1998	8.25hr(0724-1533)	142.8
Covers	Sprayer	11/11/1998	8.5hr(0713-1533)	142.9
Covers	Sprayer	11/11/1998	8.5hr(0708-1533)	147.3
Assembly	Sprayer	11/11/1998	8hr(0715-1521)	150.3
Assembly	Sprayer	11/11/1998	2hr(0722-0928)	156.5
Covers	Sprayer	11/11/1998	8.5hr(0700-1533)	157
Covers	Sprayer	11/11/1998	8.5hr(0710-1533)	161
Assembly	Sprayer	11/11/1998	8hr(0735-1533)	171.4
Covers	Sprayer	11/11/1998	8.5hr(0711-1533)	176.3
Covers	Sprayer	11/11/1998	8.5hr(0713-1533)	180.7
Covers	Sprayer	11/11/1998	8.5hr(0709-1533)	181.4
Assembly	Sprayer	11/11/1998	8hr(0732-1529)	184.8
Assembly	Sprayer	11/11/1998	8hr(0730-1529)	188
Assembly	Sprayer	11/11/1998	8hr(0730-1532)	190.8
Covers	Sprayer	11/11/1998	8.5hr(0712-1533)	194.5
Assembly	Sprayer	11/11/1998	5.75hr(0730-1310)	198.9
Covers	Sprayer	11/11/1998	8.25hr(0715-1533)	203.3
Covers	Sprayer	11/11/1998	8.5hr(0700-1533)	211.1
Assembly	Sprayer	11/11/1998	6.75hr(0730-1410)	211.7
Covers	Sprayer	11/11/1998	8.25hr(0716-1533)	221
Assembly	Sprayer	11/11/1998	6hr(0729-1333)	225.8
Assembly	Sprayer	11/11/1998	8hr(0735-1521)	227.1
Covers	Sprayer	11/11/1998	8.5hr(0700-1533)	232.7
Covers	Sprayer	11/11/1998	8.5hr(0701-1533)	235
Covers	Sprayer	11/11/1998	8.5hr(0705-1533)	241.1
Assembly	Sprayer	11/11/1998	3.75hr(1100-1443)	242
Assembly	Sprayer	11/11/1998	8hr(0729-1522)	249.1
Assembly	Sprayer	11/11/1998	8hr(0732-1526)	250.7
Covers	Sprayer	11/11/1998	8.5hr(0710-1533)	264.8
Covers	Sprayer	11/11/1998	8.5hr(0701-1533)	278.5
Covers	Sprayer	11/11/1998	8.5hr(0700-1533)	381.2

Source: (NIOSH, 2002a), (Appendix 2)

Table_Apx I-4 Personal Breathing Zone Monitoring Data for Sprayers, Follow-up NIOSH Assessment (Post-EC Scenario)

Department	Worker Job Description	Sample Date	Sample Duration	Exposure Concentration (ppm)
Covers-2	Sprayer	11/16/2000	8hr (0723-1520)	5.4
Covers-6	Sprayer	11/16/2000	8hr (0730-1520)	13.9
Assembly-1	Sprayer	11/16/2000	8hr (0710-1517)	14.9
Assembly-3	Sprayer	11/16/2000	8hr (0715-1520)	18.1
Covers-6	Sprayer	11/16/2000	8hr (0730-1521)	23.2
Covers-3	Sprayer	11/16/2000	8hr (0722-1522)	25.3
Covers-1	Sprayer	11/16/2000	8hr (0720-1521)	26.5
Covers-4	Sprayer	11/16/2000	6.25hr (0904-1519)	28.2
Assembly-2	Sprayer	11/16/2000	8.25hr (0708-1519)	32
Covers-2	Sprayer	11/16/2000	8hr (0723-1522)	33.7
Covers-5	Sprayer	11/16/2000	8hr (0727-1521)	36.8
Covers-5	Sprayer	11/16/2000	8hr (0730-1520)	45.3
Covers-3	Sprayer	11/16/2000	8hr (0725-1523)	51.6
Covers-1	Sprayer	11/16/2000	8hr (0719-1520)	58

Source: (NIOSH, 2002a), (Appendix 3)

For each employee category (sprayer, non-sprayer, and occupational non-user) and exposure scenario (pre-EC or post-EC), EPA/OPPT calculated the 95th and 50th percentile exposure levels[16] from the observed data set. The 95th percentile exposure concentration represents high-end exposure to 1-BP across the distribution of exposure data. The 50th percentile exposure concentration represents a typical exposure level. Table_Apx I-5 presents the analysis results.

Table_Apx I-5 Summary of Inhalation Exposure Monitoring Data for Spray Adhesives

Category	Acute and Chronic, Non-Cancer Exposures (8-Hour TWAs in ppm) $AC_{1\text{-BP, 8-hr TWA}}$ and $ADC_{1\text{-BP, 8-hr TWA}}$		Chronic, Cancer Exposures (ppm) $LADC_{1\text{-BP, 8-hr TWA}}$		Data Points
	95th Percentile	50th Percentile	95th Percentile	50th Percentile	
Sprayers					
Pre EC	253.26	131.40	144.72	75.09	85
Post EC[a]	41.90	17.81	23.94	10.18	49
Non-sprayers [b]					
Pre EC	210.85	127.20	120.49	72.69	31
Post EC[a]	28.84	18.00	16.48	10.29	9
Occupational non-users [c]					
Pre EC	128.66	3.00	73.52	1.71	39
Post EC[a]	5.48	2.00	3.13	1.14	17

Notes: AC = Acute Concentration; ADC = Average Daily Concentration and LADC = Lifetime Average Daily Concentration. EC = Engineering controls.

Sources: (OSHA, 2013; NIOSH, 2003, 2002a, b)

[a] Engineering controls implemented: Enclosing spray tables to create "spray booths" and/or improve ventilation.

[b] Non-Sprayer refers to those employees who are not sprayers, but either handle the adhesive or spend the majority of their shift working in an area where spraying occurs.

[c] Occupational non-user refers to those employees who do not regularly work in a department/area where spraying occurs (e.g., employees in Saw and Sew departments.

[16] Using Microsoft Excel

Appendix J OCCUPATIONAL EXPOSURE MODELING (NEAR-FIELD/FAR-FIELD) APPROACH

This appendix presents the modeling approach and model equations used in the 1-BP assessment. All of the models in this assessment use a near-field / far-field approach (Keil et al., 2009), where a vapor generation source located inside the near-field diffuses into the surrounding environment. Workers are assumed to be exposed to 1-BP vapor concentrations in the near-field, while occupational non-users are exposed at concentrations in the far-field.

In general, the ventilation rate, indoor air speed, near-field size, and other environmental conditions (e.g. temperature, pressure) are assumed to be the same across all use scenarios. However, a targeted literature search was conducted to identify chemical- and industry-specific use rate information to calculate vapor generation rates for each scenario. Where information is available, the far-field room size and number of working hours per day are also varied to provide more realistic results for that given scenario. The specific values used for each scenario are presented in the body of the report.

An individual model input parameter could either have a discrete value or a distribution of values. EPA/OPPT assigned statistical distributions based on available literature data.

A Monte Carlo simulation (a type of stochastic simulation) was conducted to capture variability in the model input parameters. The simulation was conducted using the Latin hypercube sampling method in @Risk Professional Edition, Version 6.2.0. The Latin hypercube sampling method is a statistical method for generating a sample of possible values from a multi-dimensional distribution. Latin hypercube sampling is a stratified method, meaning it guarantees that its generated samples are representative of the probability density function (variability) defined in the model. With the exception of the multi-zone model, the number of iterations was arbitrarily selected to be one million to capture the range of possible input values (i.e., including values with low probability of occurrence). For the multi-zone dry cleaning model, the number of iterations was selected to be 5,000 such that the simulation can be completed within a reasonable time period.

Model results from the Monte Carlo simulation are presented as 95th and 50th percentile values. The statistics were calculated directly in @Risk. The 95th percentile value was selected to represent high-end exposure level, whereas the 50th percentile value was selected to represent typical exposure level.

Vapor Degreasing, Cold Cleaning, and Spot Cleaning Exposure Modeling Equations

Near-Field Mass Balance

Equation_Apx J-1 Near-Field Mass Balance for Vapor Degreasing, Cold Cleaning and Spot Cleaning

$$V_{NF}\frac{dC_{NF}}{dt} = C_{FF}Q_{NF} - C_{NF}Q_{NF} + G$$

Far-Field Mass Balance

Equation_Apx J-2 Far-Field Mass Balance for Vapor Degreasing, Cold Cleaning and Spot Cleaning

$$V_{FF}\frac{dC_{FF}}{dt} = C_{NF}Q_{NF} - C_{FF}Q_{NF} - C_{FF}Q_{FF}$$

Where:

- V_{NF} is the near-field volume;
- V_{FF} is the far-field volume;
- Q_{NF} is the near-field ventilation rate;
- Q_{FF} is the far-field ventilation rate;
- C_{NF} is the average near-field concentration;
- C_{FF} is the average far-field concentration;
- G is the average vapor generation rate; and
- t is the elapsed time.

Both of the previous equations can be solved for the time-varying concentrations in the near-field and far-field as follows (Keil et al., 2009):

Equation_Apx J-3 Instantaneous Near-Field Concentration as a Function of Time

$$C_{NF} = G\left(k_1 + k_2 e^{\lambda_1 t} - k_3 e^{\lambda_2 t}\right)$$

Equation_Apx J-4 Instantaneous Far-Field Concentration as a Function of Time

$$C_{FF} = G\left(\frac{1}{Q_{FF}} + k_4 e^{\lambda_1 t} - k_5 e^{\lambda_2 t}\right)$$

Where:

Equation_Apx J-5 Regrouping of Parameters into Parameter k_1

$$k_1 = \frac{1}{\left(\frac{Q_{NF}}{Q_{NF}+Q_{FF}}\right)Q_{FF}}$$

Equation_Apx J-6 Regrouping of Parameters into Parameter k_2

$$k_2 = \frac{Q_{NF}Q_{FF} + \lambda_2 V_{NF}(Q_{NF}+Q_{FF})}{Q_{NF}Q_{FF}V_{NF}(\lambda_1 - \lambda_2)}$$

Equation_Apx J-7 Regrouping of Parameters into Parameter k_3

$$k_3 = \frac{Q_{NF}Q_{FF} + \lambda_1 V_{NF}(Q_{NF}+Q_{FF})}{Q_{NF}Q_{FF}V_{NF}(\lambda_1 - \lambda_2)}$$

Equation_Apx J-8 Regrouping of Parameters into Parameter k_4

$$k_4 = \left(\frac{\lambda_1 V_{NF} + Q_{NF}}{Q_{NF}}\right)k_2$$

Equation_Apx J-9 Regrouping of Parameters into Parameter k_5

$$k_5 = \left(\frac{\lambda_2 V_{NF} + Q_{NF}}{Q_{NF}}\right) k_3$$

Equation_Apx J-10 Eigenvalue λ_1

$$\lambda_1 = 0.5\left[-\left(\frac{Q_{NF}V_{FF} + V_{NF}(Q_{NF} + Q_{FF})}{V_{NF}V_{FF}}\right) + \sqrt{\left(\frac{Q_{NF}V_{FF} + V_{NF}(Q_{NF} + Q_{FF})}{V_{NF}V_{FF}}\right)^2 - 4\left(\frac{Q_{NF}Q_{FF}}{V_{NF}V_{FF}}\right)}\right]$$

Equation_Apx J-11 Eigenvalue λ_2

$$\lambda_2 = 0.5\left[-\left(\frac{Q_{NF}V_{FF} + V_{NF}(Q_{NF} + Q_{FF})}{V_{NF}V_{FF}}\right) - \sqrt{\left(\frac{Q_{NF}V_{FF} + V_{NF}(Q_{NF} + Q_{FF})}{V_{NF}V_{FF}}\right)^2 - 4\left(\frac{Q_{NF}Q_{FF}}{V_{NF}V_{FF}}\right)}\right]$$

EPA/OPPT calculated the hourly TWA concentrations in the near-field and far-field using the following equations. Note that the numerator and denominator of Equations E-12 and E-13 use two different sets of time parameters. The numerator is based on operating times for the scenario (e.g., 2 hours for vapor degreasing, see Table_Apx K-2) while the denominator is fixed to an average time span, t_{avg}, of 8 hours. Mathematically, the numerator and denominator must reflect the same amount of time. This is indeed the case since the numerator assumes exposures are zero for any hours not within the operating time. Therefore, mathematically speaking, both the numerator and the denominator reflect 8 hours regardless of the values selected for t_1 and t_2.

Equation_Apx J-12 Near-field Hourly TWA Concentration

$$C_{NF,TWA} = \frac{\int_{t_1}^{t_2} C_{NF}\,dt}{\int_0^{t_{avg}} dt} = \frac{\int_{t_1}^{t_2} G\left(k_1 + k_2 e^{\lambda_1 t} - k_3 e^{\lambda_2 t}\right)dt}{t_{avg}} =$$

$$\frac{\left(G\left(k_1 t_2 + \frac{k_2 e^{\lambda_1 t_2}}{\lambda_1} - \frac{k_3 e^{\lambda_2 t_2}}{\lambda_2}\right) - G\left(k_1 t_1 + \frac{k_2 e^{\lambda_1 t_1}}{\lambda_1} - \frac{k_3 e^{\lambda_2 t_1}}{\lambda_2}\right)\right)}{t_{avg}}$$

Equation_Apx J-13 Far-field Hourly TWA Concentration

$$C_{FF,TWA} = \frac{\int_{t_1}^{t_2} C_{FF}\,dt}{\int_0^{t_{avg}} dt} = \frac{\int_{t_1}^{t_2} G\left(\frac{1}{Q_{FF}} + k_4 e^{\lambda_1 t} - k_5 e^{\lambda_2 t}\right)dt}{t_{avg}} =$$

$$\frac{\left(G\left(\frac{t_2}{Q_{FF}} + \frac{k_4 e^{\lambda_1 t_2}}{\lambda_1} - \frac{k_5 e^{\lambda_2 t_2}}{\lambda_2}\right) - G\left(\frac{t_1}{Q_{FF}} + \frac{k_4 e^{\lambda_1 t_1}}{\lambda_1} - \frac{k_5 e^{\lambda_2 t_1}}{\lambda_2}\right)\right)}{t_{avg}}$$

To calculate the mass transfer to and from the near-field, the Free Surface Area, FSA, is defined to be the surface area through which mass transfer can occur. Note that the FSA is not equal to the surface area of the entire near-field. EPA/OPPT defined the near-field zone to be a rectangular box resting on the floor; therefore, no mass transfer can occur through the near-field box's floor. FSA is calculated as:

Equation_Apx J-14 Free Surface Area

$$FSA = 2(L_{NF}H_{NF}) + 2(W_{NF}H_{NF}) + (L_{NF}W_{NF})$$

Where: $L_{NF}, W_{NF}, and\ H_{NF}$ are the length, width, and height of the near-field, respectively. The near-field ventilation rate, Q_{NF}, is calculated from the near-field indoor wind speed, v_{NF}, and FSA, assuming half of FSA is available for mass transfer into the near-field and half of FSA is available for mass transfer out of the near-field:

Equation_Apx J-15 Near-Field Ventilation Rate

$$Q_{NF} = \frac{1}{2} v_{NF} FSA$$

The far-field volume, V_{FF}, and the air exchange rate, AER, is used to calculate the far-field ventilation rate, Q_{FF}, as given by:

Equation_Apx J-16 Far-Field Ventilation Rate

$$Q_{FF} = V_{FF} AER$$

Aerosol Degreasing Exposure Modeling Equations

Near-Field Mass Balance

Equation_Apx J-17 Near-Field Mass Balance for Aerosol Degreasing

$$V_{NF}\frac{dC_{NF}}{dt} = C_{FF}Q_{NF} - C_{NF}Q_{NF}$$

Far-Field Mass Balance

Equation_Apx J-18 Far-Field Mass Balance for Aerosol Degreasing

$$V_{FF}\frac{dC_{FF}}{dt} = C_{NF}Q_{NF} - C_{FF}Q_{NF} - C_{FF}Q_{FF}$$

Where:

- V_{NF} is the near-field volume;
- V_{FF} is the far-field volume;
- Q_{NF} is the near-field ventilation rate;
- Q_{FF} is the far-field ventilation rate;

- C_{NF} is the average near-field concentration at a given point in time; and
- C_{FF} is the average far-field concentration at a given point in time.

The aerosol degreasing model assumes a spontaneous "burst" in the near-field concentration, C_{NF}, at the time of each 1-BP application. Solving Equation_Apx J-17 and

Far-Field Mass Balance

Equation_Apx J-18 in terms of the time-varying concentrations in the near-field and far-field yields Equation_Apx J-19 and Equation_Apx J-20, which EPA/OPPT applied to each of the eight 1-hour increments. For each 1-hour increment, EPA/OPPT calculated the initial near-field concentration at the top of the hour (t_n), accounting for both the burst of 1-BP from the degreaser application and the residual near-field concentration remaining after the previous 1-hour increment (t_{n-1}; except for n = 1, in which case there would be no residual 1-BP from a previous application). The initial far-field concentration is equal to the residual far-field concentration remaining after the previous 1-hour increment. EPA/OPPT then calculated the decayed concentration in the near-field and far-field at the bottom of the hour, just before the degreaser application at the top of the next hour (t_{n+1}). EPA/OPPT also calculated a 1-hour TWA exposure for the near-field and far-field, representative of the worker's and occupational non-users' exposures to the airborne concentrations during each 1-hour increment. Note that the *k* coefficients (Equation_Apx J-21 through Equation_Apx J-24) are a function of the initial near-field and far-field concentrations, and therefore are re-calculated at the top of each hour.

Equation_Apx J-19 Instantaneous Near-Field Concentration as a Function of Time

$$C_{NF,t_{n+1}} = k_{1,t_n} e^{\lambda_1 t_2} + k_{2,t_n} e^{\lambda_2 t_2}$$

Equation_Apx J-20 Instantaneous Far-Field Concentration as a Function of Time

$$C_{FF,t_{n+1}} = k_{3,t_n} e^{\lambda_1 t_2} + k_{4,t_n} e^{\lambda_2 t_2}$$

Where:

Equation_Apx J-21 Regrouping of Parameters into Parameter k_1

$$k_{1,t_n} = \begin{cases} 0, & n = 0 \\ \dfrac{Q_{NF}\left(C_{FF,0}(t_n) - C_{NF,0}(t_n)\right) - \lambda_2 V_{NF} C_{NF,0}(t_n)}{V_{NF}(\lambda_1 - \lambda_2)}, & n = 1, 2, 3, 4, 5, 6, \text{or } 7 \end{cases}$$

Equation_Apx J-22 Regrouping of Parameters into Parameter k_2

$$k_{2,t_n} = \begin{cases} 0, & n = 0 \\ \dfrac{Q_{NF}\left(C_{NF,0}(t_n) - C_{FF,0}(t_n)\right) + \lambda_1 V_{NF} C_{NF,0}(t_n)}{V_{NF}(\lambda_1 - \lambda_2)}, & n = 1, 2, 3, 4, 5, 6, or\ 7 \end{cases}$$

Equation_Apx J-23 Regrouping of Parameters into Parameter k_3

$$k_{3,t_n} = \begin{cases} 0\,, & n = 0 \\ \frac{(Q_{NF}+\lambda_1 V_{NF})[Q_{NF}(C_{FF,0}(t_n)-C_{NF,0}(t_n))-\lambda_2 V_{NF}C_{NF,0}(t_n)]}{Q_{NF}V_{NF}(\lambda_1-\lambda_2)}, & n = 1,2,3,4,5,6,\text{or } 7 \end{cases}$$

Equation_Apx J-24 Regrouping of Parameters into Parameter k_4

$$k_{4,t_n} = \begin{cases} 0\,, & n = 0 \\ \frac{(Q_{NF}+\lambda_2 V_{NF})[Q_{NF}(C_{NF,0}(t_n)-C_{FF,0}(t_n))+\lambda_1 V_{NF}C_{NF,0}(t_n)]}{Q_{NF}V_{NF}(\lambda_1-\lambda_2)}, & n = 1,2,3,4,5,6,\text{or } 7 \end{cases}$$

Equation_Apx J-25 Near-field Concentration at the Moment of Aerosol Degreaser Application for each of the Seven Applications

$$\boldsymbol{C_{NF,0}(t_n)} = \begin{cases} \mathbf{0}\,, & n = 0 \\ \frac{Amt}{V_{NF}}\left(\frac{1{,}000\ mg}{g}\right), & n = 1 \\ \frac{Amt}{V_{NF}}\left(\frac{1{,}000\ mg}{g}\right) + \boldsymbol{k_{1,t_{n-1}}e^{\lambda_1 t_2}} + \boldsymbol{k_{2,t_{n-1}}e^{\lambda_2 t_2}}, & n = 2,3,4,5,6,or\ 7 \end{cases}$$

Equation_Apx J-26 Far-field Concentration at the Moment of Aerosol Degreaser Application for each of the Seven Applications

$$C_{FF,0}(t_n) = \begin{cases} 0\,, & n = 0\ or\ 1 \\ k_{3,t_{n-1}}e^{\lambda_1 t_2} + k_{4,t_{n-1}}e^{\lambda_2 t_2}, & n = 2,3,4,5,6,or\ 7 \end{cases}$$

Equation_Apx J-27 Eigenvalue λ_1

$$\boldsymbol{\lambda_1 = 0.5\left[-\left(\frac{Q_{NF}V_{FF}+V_{NF}(Q_{NF}+Q_{FF})}{V_{NF}V_{FF}}\right)+\sqrt{\left(\frac{Q_{NF}V_{FF}+V_{NF}(Q_{NF}+Q_{FF})}{V_{NF}V_{FF}}\right)^2-4\left(\frac{Q_{NF}Q_{FF}}{V_{NF}V_{FF}}\right)}\right]}$$

Equation_Apx J-28 Eigenvalue λ_2

$$\boldsymbol{\lambda_2 = 0.5\left[-\left(\frac{Q_{NF}V_{FF}+V_{NF}(Q_{NF}+Q_{FF})}{V_{NF}V_{FF}}\right)-\sqrt{\left(\frac{Q_{NF}V_{FF}+V_{NF}(Q_{NF}+Q_{FF})}{V_{NF}V_{FF}}\right)^2-4\left(\frac{Q_{NF}Q_{FF}}{V_{NF}V_{FF}}\right)}\right]}$$

Equation_Apx J-29 Near-Field Concentration, 1-hr TWA

$$\boldsymbol{C_{NF,1\text{-}hr\ TWA,t_n} = \frac{\left(\frac{k_{1,t_{n-1}}}{\lambda_1}e^{\lambda_1 t_2}+\frac{k_{2,t_{n-1}}}{\lambda_2}e^{\lambda_2 t_2}\right)-\left(\frac{k_{1,t_{n-1}}}{\lambda_1}e^{\lambda_1 t_1}+\frac{k_{2,t_{n-1}}}{\lambda_2}e^{\lambda_2 t_1}\right)}{t_2-t_1}}$$

Equation_Apx J-30 Far-Field Concentration, 1-hr TWA

$$\boldsymbol{C_{FF,1\text{-}hr\ TWA,t_n} = \frac{\left(\frac{k_{3,t_{n-1}}}{\lambda_1}e^{\lambda_1 t_2}+\frac{k_{3,t_{n-1}}}{\lambda_2}e^{\lambda_2 t_2}\right)-\left(\frac{k_{4,t_{n-1}}}{\lambda_1}e^{\lambda_1 t_1}+\frac{k_{4,t_{n-1}}}{\lambda_2}e^{\lambda_2 t_1}\right)}{t_2-t_1}}$$

After calculating all near-field/far-field 1-hour TWA exposures (i.e., $C_{NF,1\text{-}hr\ TWA,t_n}$ and $C_{FF,1\text{-}hr\ TWA,t_n}$ for each hour from t_n = 1 to t_n =8), EPA/OPPT calculated the near-field/far-field 8-hour TWA concentration by summing the 1-hour TWA exposures and dividing the respective totals by t_{avg} (i.e., 8 hours for an 8-hour TWA), as denoted by the equations below:

Equation_Apx J-31 Near-Field Concentration, 8-hr TWA

$$C_{NF,8\text{-}hr\ TWA} = \frac{\sum_{n=1}^{8} C_{NF,1\text{-}hr\ TWA,t_n}}{t_{avg}}$$

Equation_Apx J-32 Far-Field Concentration, 8-hr TWA

$$C_{FF,8\text{-}hr\ TWA} = \frac{\sum_{n=1}^{8} C_{FF,1\text{-}hr\ TWA,t_n}}{t_{avg}}$$

EPA/OPPT used the acute and chronic exposure equations presented in Equation_Apx J-1 and Equation_Apx J-2 for aerosol degreasing to obtain the final exposure results.

Dry Cleaning Exposure Modeling Equations

Near-Field Mass Balance

Equation_Apx J-33 Near-Field Mass Balance for Spot Cleaning (Multi-Zone)

$$V_S \frac{dC_S}{dt} = C_{FF}Q_S - C_S Q_S + G_S$$

Equation_Apx J-34 Near-Field Mass Balance for Finishing (Multi-Zone)

$$V_F \frac{dC_F}{dt} = C_{FF}Q_F - C_F Q_F + G_F$$

Equation_Apx J-35 Near-Field Mass Balance for Dry Cleaning Machine (Multi-Zone)

$$V_D \frac{dC_D}{dt} = C_{FF}Q_D - C_D Q_D$$

Far-Field Mass Balance

Equation_Apx J-36 Far-Field Mass Balance for Dry Cleaning Facility (Multi-Zone)

$$V_{FF} \frac{dC_{FF}}{dt} = C_S Q_S + C_F Q_F + C_D Q_D - C_{FF} Q_S - C_{FF} Q_F - C_{FF} Q_D - C_{FF} Q_{FF}$$

Where:

- V_S is the near-field volume for spot cleaning;
- V_F is the near-field volume for finishing;
- V_D is the near-field volume for unloading dry cleaning machine;
- V_{FF} is the far-field volume;
- Q_S is the near-field ventilation rate for spot cleaning;
- Q_F is the near-field ventilation rate for finishing;
- Q_D is the near-field ventilation rate for dry cleaning machine;

- Q_{FF} is the far-field ventilation rate;
- C_S is the average near-field concentration for spot cleaning;
- C_F is the average near-field concentration for finishing;
- C_D is the average near-field concentration for dry cleaning machine;
- C_{FF} is the average far-field concentration;
- G_S is the average vapor generation rate for spot cleaning;
- G_F is the average vapor generation rate for finishing; and
- t is the elapsed time.

To calculate the mass transfer to and from the near-field, the Free Surface Area, FSA, is defined to be the surface area through which mass transfer can occur. Note that the FSA may not be equal to the surface area of the entire near-field.

For spot-cleaning, EPA/OPPT defined the near-field zone to be a rectangular box resting on the floor; therefore, no mass transfer can occur through the near-field box's floor. FSA is calculated as:

Equation_Apx J-37 Free Surface Area for Spot Cleaning

$$\mathbf{FSA_S = 2(L_S H_S) + 2(W_S H_S) + (L_S W_S)}$$

For finishing, EPA/OPPT defined the near-field zone to be a rectangular box covering the upper body of a worker:

Equation_Apx J-38 Free Surface Area for Finishing

$$\mathbf{FSA_F = 2(L_{NF} H_{NF}) + 2(W_{NF} H_{NF}) + 2(L_{NF} W_{NF})}$$

For dry cleaning, EPA/OPPT defined the near-field zone to be a hemispheric area projecting from the door of the dry cleaning machine:

Equation_Apx J-39 Free Surface Area for Dry Cleaning Machine

$$\mathbf{FSA_D = 2\pi r_D^2}$$

Where:

- FSA_S is the free surface area for spot-cleaning;
- FSA_F is the free surface area for finishing;
- FSA_D is the free surface area for dry cleaning machine;
- L_S is the near-field length for spot-cleaning;
- H_S is the near-field height for spot-cleaning;
- W_S is the near-field width for spot-cleaning;
- L_F is the near-field length for finishing;
- H_F is the near-field height for finishing;
- W_F is the near-field width for finishing; and

- r_D is the radius of the dry cleaning machine door opening.

The near-field ventilation rates, Q_S, Q_D, and Q_F are calculated from the near-field indoor wind speed, v_{NF}, and FSA, assuming half of FSA is available for mass transfer into the near-field and half of FSA is available for mass transfer out of the near-field. The near-field indoor wind speed is assumed to be the same across all three near fields:

Equation_Apx J-40 Near-Field Ventilation Rate for Spot Cleaning

$$\mathbf{Q_S = \frac{1}{2} v_{NF} FSA_S}$$

Equation_Apx J-41 Near-Field Ventilation Rate for Finishing

$$\mathbf{Q_F = \frac{1}{2} v_{NF} FSA_F}$$

Equation_Apx J-42 Near-Field Ventilation Rate for Dry Cleaning Machine

$$\mathbf{Q_D = \frac{1}{2} v_{NF} FSA_D}$$

The far-field volume, V_{FF}, and the air exchange rate, AER, is used to calculate the far-field ventilation rate, Q_{FF}, as given by:

Equation_Apx J-43 Far-Field Ventilation Rate for Dry Cleaning Facility

$$\mathbf{Q_{FF} = V_{FF} AER}$$

The model results in the following four, coupled ordinary differential equations (ODEs):

Equation_Apx J-44 Differential Equation for Spot Cleaning Near-Field Concentration

$$\mathbf{\frac{dC_S}{dt} = -\frac{Q_S}{V_S} C_S + \frac{Q_S}{V_S} C_{FF} + \frac{G_S}{V_S}}$$

Equation_Apx J-45 Differential Equation for Finishing Near-Field Concentration

$$\mathbf{\frac{dC_F}{dt} = -\frac{Q_F}{V_F} C_F + \frac{Q_F}{V_F} C_{FF} + \frac{G_F}{V_F}}$$

Equation_Apx J-46 Differential Equation for Dry Cleaning Machine Near-Field Concentration

$$\mathbf{\frac{dC_D}{dt} = -\frac{Q_D}{V_D} C_D + \frac{Q_D}{V_D} C_{FF}}$$

Equation_Apx J-47 Differential Equation for Far-Field Concentration at Dry Cleaning Facility

$$\mathbf{\frac{dC_{FF}}{dt} = \frac{Q_S}{V_{FF}} C_S + \frac{Q_F}{V_{FF}} C_F + \frac{Q_D}{V_{FF}} C_D - \frac{(Q_S+Q_F+Q_D+Q_{FF})}{V_{FF}} C_{FF}}$$

When solving coupled ODEs, it is common to transform the equations into a standard mathematical format. This standard mathematical format allows one to more easily identify appropriate solution methodologies from standard mathematical references. EPA/OPPT transformed these four ODEs into the following format:

Equation_Apx J-48 Alternative Representation for the Spot Cleaning Near-Field Concentration Differential Equation

$$\mathbf{y_1' = a_{11}y_1 + a_{14}y_4 + g_1}$$

Equation_Apx J-49 Alternative Representation for the Finishing Near-Field Concentration Differential Equation

$$\mathbf{y_2' = a_{22}y_2 + a_{24}y_4 + g_2}$$

Equation_Apx J-50 Alternative Representation for the Dry Cleaning Machine Near-Field Concentration Differential Equation

$$\mathbf{y_3' = a_{33}y_3 + a_{34}y_4}$$

Equation_Apx J-51 Alternative Representation for the Far-Field Concentration Differential Equation

$$\mathbf{y_4' = a_{41}y_1 + a_{42}y_2 + a_{43}y_3 + a_{44}y_4}$$

Where:

$$\frac{\mathbf{dC_S}}{\mathbf{dt}} = {y_1}'$$

$$\frac{\mathbf{dC_F}}{\mathbf{dt}} = {y_2}'$$

$$\frac{\mathbf{dC_D}}{\mathbf{dt}} = {y_3}'$$

$$\frac{\mathbf{dC_{FF}}}{\mathbf{dt}} = {y_4}'$$

And:

$$\mathbf{C_S} = y_1 \qquad \mathbf{C_F} = y_2 \qquad \mathbf{C_D} = y_3 \qquad \mathbf{C_{FF}} = y_4$$

$$a_{11} = -\frac{Q_S}{V_S} \qquad a_{14} = \frac{Q_S}{V_S}$$

$$a_{22} = -\frac{Q_F}{V_F} \qquad a_{24} = \frac{Q_F}{V_F}$$

$$a_{33} = -\frac{Q_D}{V_D} \qquad a_{34} = \frac{Q_D}{V_D}$$

$$a_{41} = \frac{Q_S}{V_{FF}} \qquad a_{42} = \frac{Q_F}{V_{FF}} \qquad a_{43} = \frac{Q_D}{V_{FF}} \qquad a_{44} = -\frac{(Q_S+Q_F+Q_D+Q_{FF})}{V_{FF}}$$

$$g_1 = \frac{G_S}{V_S} \qquad g_2 = \frac{G_F}{V_F}$$

These ordinary differential equations can be solved using a numerical integration method. EPA/OPPT used the fourth-order Runge-Kutta method (RK4). RK4 numerically integrates a system of coupled ordinary differential equations from time step *n* to *n+1* with a constant time step size of *h* using the following equations (shown for generic variables y_1, y_2, y_3, and y_4 as a function of *t*).

Equation_Apx J-52 Redefinition of Time Derivative as Function of Independent and Dependent Variables (y_1')

$$\frac{dy_1}{dt} = f_1(t, y_1, y_2, y_3, y_4)$$

Equation_Apx J-53 Redefinition of Time Derivative as Function of Independent and Dependent Variables (y_2')

$$\frac{dy_2}{dt} = f_2(t, y_1, y_2, y_3, y_4)$$

Equation_Apx J-54 Redefinition of Time Derivative as Function of Independent and Dependent Variables (y_3')

$$\frac{dy_3}{dt} = f_3(t, y_1, y_2, y_3, y_4)$$

Equation_Apx J-55 Redefinition of Time Derivative as Function of Independent and Dependent Variables (y_4')

$$\frac{dy_4}{dt} = f_4(t, y_1, y_2, y_3, y_4)$$

Where, for each ODE *j* = 1, 2, 3, 4 (where 1 = spot cleaning, 2 = finishing, 3 = dry cleaning machine, and 4 = far field):

Equation_Apx J-56 RK4 Beginning-of-Interval Slope

$$k_1^j = f_j(t, y_1, y_2, y_3, y_4)$$

Equation_Apx J-57 RK4 First-Midpoint Slope

$$k_2^j = f_j\left(t + \tfrac{1}{2}h, y_1 + \tfrac{1}{2}k_1^1 h, y_2 + \tfrac{1}{2}k_1^2 h, y_3 + \tfrac{1}{2}k_1^3 h, y_4 + \tfrac{1}{2}k_1^4 h\right)$$

Equation_Apx J-58 RK4 Second-Midpoint Slope

$$k_3^j = f_j\left(t + \tfrac{1}{2}h, y_1 + \tfrac{1}{2}k_2^1 h, y_2 + \tfrac{1}{2}k_2^2 h, y_3 + \tfrac{1}{2}k_2^3 h, y_4 + \tfrac{1}{2}k_2^4 h\right)$$

Equation_Apx J-59 RK4 End-of-Interval Slope

$$k_4^j = f_j(t + h, y_1 + k_3^1 h, y_2 + k_3^2 h, y_3 + k_3^3 h, y_4 + k_3^4 h)$$

Equation_Apx J-60 RK4 Calculation of the Dependent Variable, *y*, at the Next Time Step

$$y_j^{n+1} = y_j^n + \frac{1}{6}h\left(k_1^j + 2k_2^j + 2k_3^j + k_4^j\right)$$

RK4 is an *explicit* integration method, meaning it solves for the dependent variables at step *n+1* explicitly using the dependent variables at step *n*. RK4 is a fourth-order method, which means the local truncation error at a single integration step is on the order of h^5, while the total global error is on the order of h^4.

The choice of step size *h* is such to allow a successful integration of the system of differential equations. If parameter values are chosen such that the differential equation coefficients (the *a* terms in Equations J-48 through J-51) are sufficiently large, the differential equations may become *stiff*. Stiff differential equations would require sufficiently small time step sizes to allow their integration. Stiffness can be difficult to predict. If stiffness is encountered, meaning if the solution diverges to unrealistic values, such as infinity, the step size should be reduced to see if that allows for successful integration.

Exposure Estimate Equations

Dry cleaning facilities are often small business that may operate up to twelve hours a day. For the purpose of modeling worker exposure, dry cleaning employees are assumed to work 8-hr shifts. EPA/OPPT assumed the first work shift covers hour 0 through hour 8, and the second work shift covers hour 4 through hour 12, such that there is a 4-hr period overlap between the two shifts. For each shift, one worker is assumed to perform each category of work bulleted below. Specific assumptions on each worker category are as follow:

- Spot cleaning is performed from hour 2 through hour 10 of the operating day, such that the first shift worker is exposed for six hours and the second shift worker is exposed for two hours. For example, the first-shift spot cleaning worker is exposed at concentration C_{FF} from hour 0 to hour 2, and is exposed at concentration C_S from hour 2 through hour 8;
- Machine unloading, garment finishing and pressing are performed at regular intervals throughout the operating day, and the frequency of this activity varies depending on the number of loads dry cleaned each day. Each machine and finishing worker is exposed to concentrations C_D and C_F for the duration of these activities, and is exposed at concentration C_{FF} for the remainder of the 8-hr shift. During the 4-hr overlap where both shifts are present, loads are assigned to the first shift if the load can be completed before first shift leaves at hour 8. EPA/OPPT defines a load as being “completed” when that load of garment is completely unloaded, finished and pressed. If the load cannot be completed during the first shift, it is assigned to the second shift.
- Occupational non-user who only spends time in the far-field is exposed at concentration C_{FF} for the entirety of the 8-hour shift.

Acute workplace exposures are estimated as follows:

Equation_Apx J-61 Acute Concentration for Dry Cleaning Model (Multi-Zone)

$$\mathrm{AC} = \frac{\mathrm{C} \times \mathrm{ED}}{\mathrm{AT}}$$

where:

AC = acute concentration (8-hr TWA)
C = contaminant concentration in air (8-hr TWA)
ED = exposure duration (8 hr/day)
AT = averaging time (8 hr/day)

The average daily concentration (ADC) and lifetime average daily concentration (LADC) are used to estimate workplace exposures for non-cancer and cancer risks, respectively. These exposures are estimated as follows:

Equation_Apx J-62 ADC and LADC for Dry Cleaning Model (Multi-Zone)

$$\mathrm{ADC\ or\ LADC} = \frac{\mathrm{C} \times \mathrm{ED} \times \mathrm{EF} \times \mathrm{WY}}{\mathrm{AT}}$$

where:

ADC = average daily concentration (8-hr TWA) used for chronic non-cancer risk calculations
LADC = lifetime average daily concentration (8-hr TWA) used for chronic cancer risk calculations
C = contaminant concentration in air (8-hr TWA)
ED = exposure duration (8 hr/day)
EF = exposure frequency (250 to 312 days/yr)
WY = working years per lifetime (40 yr)
AT = averaging time (LT × 365 days/yr × 12 hr/day; where LT = lifetime; LT = 40 yr for non-cancer risks; LT=70 yr for cancer risks)

Appendix K OCCUPATIONAL EXPOSURE MODELING PARAMETERS

This appendix presents the modeling input parameters. Table_Apx K-1 summarizes the input parameters and their assumptions common to all degreasing scenarios. Table_Apx K-2 summarizes input parameters specific to the vapor degreasing near-field/far-field model, while Table_Apx K-3 summarizes input parameters specific to the aerosol degreasing near-field/far-field model.

Table_Apx K-4 summarizes input parameters and their assumptions used to model all scenarios at dry cleaning facilities. Table_Apx K-5 through Table_Apx K-7 summarizes parameters for the multi-zone dry cleaning model, while Table_Apx K-8 summarizes parameters for the stand-alone spot cleaning model.

Table_Apx K-1 Summary of Environmental Parameters for Degreasing Facilities

Input Parameter	Symbol	Unit	Model Parameter Values		Uncertainty Analysis Assumptions			Distribution Type	Comments
			Value	Basis	Lower Bound	Upper Bound	Mode		
Near-field indoor wind speed	v_{NF}	cm/s (ft/s)	10 (1,181)	50th percentile	0	∞	—	Lognormal, μ= 17.5 cm/s σ= 25.3 cm/s	Baldwin and Maynard (1998) surveyed the wind speeds in 55 work areas covering a wide range of workplaces. The study states that the pooled distribution of all surveys and the distributions of each survey, in general, could be approximated by a lognormal distribution. EPA/OPPT fitted the data set, and the fitted mean and standard deviation are 17.5 cm/s and 25.3 cm/s, respectively.
Operating days per year	OD	day/yr	260	—	—	—	—	—	The 2001 EPA Generic Scenario on the Use of Vapor Degreasers estimates that degreasers of all sizes operate 260 days per year (ERG, 2001).
Near-field volume	V_{NF}	ft^3	600	—	—	—	—	—	EPA applied the same dimensions used in the final TCE risk assessment (i.e., 10 ft for L_{NF} and W_{NF} and 6 ft for H_{NF}) (U.S. EPA, 2014c). Value supported by Demou et al. (2009).
Engineering controls effectiveness	EC	%	90	—	—	—	—	—	Value supported by Wadden et al. (1989). The study indicates local exhaust ventilation can reduce workplace emissions by 90 percent. The estimate is based on an LEV system for an open-top vapor degreaser (lateral exhaust hoods installed on two sides of the tank).

Table_Apx K-2 Input Near-Field/Far-Field Model Parameters and Monte Carlo Simulation Assumptions for Vapor Degreasing

Input Parameter	Symbol	Unit	Model Parameter Values		Uncertainty Analysis Assumptions			Distribution Type	Comments
			Value	Basis	Lower Bound	Upper Bound	Mode		
Far-field volume	V_{FF}	ft^3	10,594	Minimum	10,594	70,629	17,657	Triangular	Per von Grote et al. (2003), volumes at European metal degreasing facilities can vary from 300 to several thousand cubic meters. They noted smaller volumes are more typical, and assumed 400 and 600 m^3 in their models (von Grote et al., 2003). EPA/OPPT assumed a triangular distribution bound from 300 m^3 (10,594 ft^3) to 2,000 m^3 (70,629 ft^3) with a mode of 500 m^3 (the midpoint of 400 and 600 m^3, or 17,657 ft^3)
Air exchange rate	AER	hr^{-1}	2	Minimum	2	20	3.5	Triangular	Hellweg et al. (2009) identifies average AER for occupational settings utilizing mechanical ventilation systems to be between 3 and 20 hr^{-1}. The EPA TCE RA peer review comments indicate values around 2 to 5 hr^{-1} may be more likely (SCG, 2013). A triangular distribution is used with the mode equal to the midpoint of the range provided by the RA peer reviewers.
Starting time	t_1	hr	0	—	—	—	—	—	Constant value.
Exposure Duration	t_2	hr	—	—	—	—	—	—	Equal to operating hours per day.
Averaging time	t_{avg}	hr	8	—	—	—	—	—	Constant value.
Emission factor	EF	lb/employee-yr	—	—	0	∞	—	Lognormal, μ= 10.4 σ= 17.2	To develop the California Solvent Cleaning Emissions Inventories, CARB surveyed solvent cleaning facilities and gathered site-specific information for 213 facilities. CARB estimated a 1-BP emission factor of 10.43 lb/employee-yr with a standard deviation of 17.24 lb/employee-yr (CARB, 2011). CARB

Input Parameter	Symbol	Unit	Model Parameter Values		Uncertainty Analysis Assumptions			Distribution Type	Comments
			Value	Basis	Lower Bound	Upper Bound	Mode		
									estimated that more than 98 percent of 1-BP emissions were attributed to vapor degreasing for the solvent cleaning facilities surveyed. EPA/OPPT applied a lognormal distribution to account for uncertainty in the CARB emission factor.
Number of employees per site	EMP	employee/ site	—	—	0	∞	—	Weibull α = 1.1165 β= 34.175	Data based on 2007 Economic Census for the vapor degreasing NAICS codes identified in the TCE RA (U.S. EPA, 2014c). EPA/OPPT fitted a Weibull distribution to the Census data set.
Units per site	U	unit/site	—	—	1	1.2	—	Discrete	The EPA TCE RA (2014c) estimated 1 unit/site for small vapor degreasing facilities, and 1.2 unit/site for large facilities based on analysis of the National Emissions Inventory (NEI). Because NEI data are not available for 1-BP, EPA/OPPT assumes equal probability of small versus large facilities.
Vapor generation rate	G	kg/unit-hr	—	—	—	—	—	N/A	Calculated as the following: G = EF x EMP / (2.2 x OH x OD x U)
Operating hours per day	OH	hr/day	2	—	—	—	—	Discrete	The 2001 Generic Scenario on the Use of Vapor Degreasers assumes degreasers operate 2 hours per day, regardless of unit size (ERG, 2001).
Equipment substitution effectiveness	ES	%	98	—	—	—	—	—	Value supported by NEWMOA (2001), as used in the EPA TCE RA (2014c). The study states that "air emissions can be reduced 98 percent or more when [a closed-loop degreaser is] compared with an open-top vapor degreaser".

Table_Apx K-3 Input Near-Field/Far-Field Model Parameters and Monte Carlo Simulation Assumptions for Aerosol Degreasing

Input Parameter	Symbol	Unit	Model Parameter Values		Uncertainty Analysis Assumptions			Distribution Type	Comments
			Value	Basis	Lower Bound	Upper Bound	Mode		
Far-field volume	V_{FF}	ft^3	10,594	Midpoint	10,594	37,328	—	Uniform	Golsteijn et al. (2014) indicates a characteristic volume of 300 m^3 (10,594 ft^3). Demou et al. (2009) indicates a characteristic volume of 1,057 m^3 (37,328 ft^3) for aerosol degreasing at automotive repair shops.
Air exchange rate	AER	hr^{-1}	1	Minimum	1	20	3.5	Triangular	Demou et al. (2009) identifies typical AERs of 1 hr^{-1} and 3 to 20 hr^{-1} for occupational settings with and without mechanical ventilation systems, respectively. Golsteijn, et al. (2014) indicates a characteristic AER of 4 hr^{-1}. RA peer review comments indicate values around 2 to 5 hr^{-1} may be more likely (SCG, 2013), in agreement with Golsteijn, et al. (2014). A triangular distribution is used with the mode equal to the midpoint of the range provided by the RA peer reviewer (3.5 is the midpoint of the range 2 to 5 hr^{-1})
Starting time	t_1	hr	0	—	—	—	—	—	Constant value.
Exposure Duration	t_2	hr	1	—	—	—	—	—	EPA assumed aerosol degreasers are applied in hourly increments.
Averaging time	t_{avg}	hr	8	—	—	—	—	—	Value supported by Golsteijn, et al. (2014).
Applications per day	APD	applications/ day	7	—	—	—	—	—	EPA assumed aerosol degreasers are applied once per hour, and that no applications occur during the first hour of the 8-hour work day.
Amount per application	AMT	g/ application	27.5	—	—	—	—	—	Aerosol degreasing facilities use 192.2 g degreaser/day Golsteijn, et al. (2014). Assuming an APD of 7 and 100% 1-BP in the degreaser yields an AMT of 27.5 g 1-BP/application.

Table_Apx K-4 Summary of Environmental Parameters at Dry Cleaning Facilities

Input Parameter	Symbol	Unit	Model Parameter Values		Uncertainty Analysis Assumptions			Distribution Type	Comments
			Value	Basis	Lower Bound	Upper Bound	Mode		
Far-field volume	V_{FF}	ft^3	2,472	Minimum	2,472	105,944	26,600	Triangular	Cal/EPA (2007) indicated a mean volume of 26,600 ft^3 for dry cleaning facilities in California. von Grote et al. (2006) indicated volumes at German dry cleaning facilities ranging from 70 to 3,000 m^3 (2,472 to 105,944 ft^3) with a mean of 618 m^3 (21,825 ft^3). Klein and Kurz (1994) indicated volumes at German dry cleaning facilities ranging from 200 to 630 m^3 (7,063 to 22,248 ft^3) with a mean of 362 m^3 (12,784 ft^3) (as cited in von Grote et al. (2006)). EPA/OPPT assumes a triangular distribution bound from 70 to 3,000 m3 (2,472 to 105,944 ft^3) with a mode of 26,600 ft^3, the mean reported by Cal/EPA (2007).
Near-field indoor wind speed	v_{NF}	cm/s (ft/s)	10 (1,181)	50th percentile	0	∞	—	Lognormal, μ= 17.5 cm/s σ= 25.3 cm/s	Baldwin and Maynard (1998) surveyed the wind speeds in 55 work areas covering a wide range of workplaces. The study states that the pooled distribution of all surveys and the distributions of each survey, in general, could be approximated by a lognormal distribution. EPA/OPPT fitted the data set, and the fitted mean and standard deviation are 17.5 cm/s and 25.3 cm/s, respectively. For model input, the distribution is capped at 202 cm/s, the maximum average wind speed observed in the study.
Air exchange rate	AER	hr^{-1}	1	Minimum	1	19	3.5	Triangular	von Grote et al. (2006) indicated typical AERs of 5 to 19 hr^{-1} for German dry cleaning facilities. Klein and Kurz (1994) indicated AERs of 1 to 19 h^{-1}, with a mean of 8 h^{-1} for German dry cleaning facilities (as cited in von Grote et

Input Parameter	Symbol	Unit	Model Parameter Values		Uncertainty Analysis Assumptions			Distribution Type	Comments
			Value	Basis	Lower Bound	Upper Bound	Mode		
									al. (2006)). The EPA TCE RA peer review comments indicate values around 2 to 5 hr^{-1} may be more likely (SCG, 2013). A triangular distribution is used with the mode equal to the midpoint of the range provided by the RA peer reviewer (3.5 is the midpoint of the range 2 to 5 hr^{-1}
Engineering controls effectiveness	EC	%	90	—	—	—	—	—	Wadden et al. (1989) indicates LEV systems for an open-top vapor degreaser can reduce workplace emissions by 90 percent. Because no data on LEV effectivenss were found for dry cleaners, the Wadden et al. (1989) value is cited.
Operating hours per day (multi-zone)	**OH**	hr/day	12	—	—	—	—	—	EPA/OPPT assumed a typical dry cleaner operates 12 hr/day based on engineering judgment.
Operating days per year (multi-zone)	**OD**	day/yr	300	Mode	250	312	300	Triangular	Low-end value based on 5 days per week and 50 weeks per year. Mode is based on 6 days per week and 50 weeks per year. High-end value based on 6 days per week and 52 weeks per year, assuming the dry cleaner is open year-round.

Table_Apx K-5 Input Near-Field/Far-Field Model Parameters and Monte Carlo Simulation Assumptions for 1-BP, Unloading Dry Cleaning Machines (Multi-Zone Model)

Input Parameter	Symbol	Unit	Model Parameter Values		Uncertainty Analysis Assumptions			Distribution Type	Comments
			Value	Basis	Lower Bound	Upper Bound	Mode		
Machine door diameter	D	in	25	EPA/OPPT estimate	—	—	—	—	EPA/OPPT determined an approximate door diameter by reviewing images of several 4th generation PERC machine models manufactured by Bowe and Firbimatic.
Machine door radius	r_D	ft	1.04	EPA/OPPT estimate	—	—	—	—	Calculated as r_D = ½ (D/ 12 in/ft)
Near-field volume	V_D	ft^3	2.37	—	—	—	—	—	Workers are likely to bend over while retrieving garments, such that their breathing zones are at or near the machine opening. EPA/OPPT assumes the near-field consists of a hemispherical volume surrounding the machine door opening, $V_D = \pi * (D / 12 in/ft)^3 / 12$
Free surface area for dry cleaning machine	FSA_D	ft^2	6.82	—	—	—	—	—	Calculated as the surface area of the hemisphere, FSAD = 2 x π x r_D^2
Number of loads per day	LD	loads/day	14	Maximum	1	14		Uniform	EPA/OPPT will assume the number of loads ranges from one to 14 based on the number of loads observed in NIOSH (2010) and Blando et al. (2010).
Cylinder concentration	C_c	ppm	—	—	300	8,600	—	Uniform	Low-end value based on 4th generation machine (300 ppm solvent; (CDC, 1997)). High-end value based on 3rd generation machines, which reduce cylinder concentration to 2,000 to 8,600 ppm (ERG, 2005).

Input Parameter	Symbol	Unit	Model Parameter Values		Uncertainty Analysis Assumptions			Distribution Type	Comments
			Value	Basis	Lower Bound	Upper Bound	Mode		
Cylinder volume	V_c	m^3			0.24	0.64		Uniform	Value based characteristic sizes provided by von Grote et al. (2003). EPA/OPPT does not have U.S. distribution of machine sizes. Therefore, a uniform distribution is assumed.
Initial, spiked concentration	$C_{D,0}$	mg/m^3	—	Calculated	—	—	—	—	Calculated as $C_{D,o} = (C_c \times V_c) / V_D$ with unit conversions.
Starting time	t_1	hr	0	—	—	—	—	—	Constant value.
Exposure Duration	t_2	hr	0.08	—	—	—	—	—	Based on engineering judgment, EPA/OPPT assumed workers take 5 minutes to retrieve garments after each load.
Averaging time	t_{avg}	hr	8	—	—	—	—	—	Work activities are assumed to be split across two 8-hr shifts over each operating day, such that a single worker is exposed for 8 hours a day.

Table_Apx K-6 Input Near-Field/Far-Field Model Parameters and Monte Carlo Simulation Assumptions for Finishing (Multi-Zone Model)

Input Parameter	Symbol	Unit	Model Parameter Values		Uncertainty Analysis Assumptions			Distribution Type	Comments
			Value	Basis	Lower Bound	Upper Bound	Mode		
Near-field volume	V_F	ft^3	300	—	—	—	—	—	For length and width, EPA/OPPT applied the same dimensions used in the final TCE risk assessment (i.e., 10 ft for L_F and W_F) (U.S. EPA, 2014c). EPA/OPPT assumes a height of 3 ft for H_F to cover the upper body of the worker, because workers typically perform finishing while standing.
Free surface area for finishing	FSA_F	ft^2	320		—	—	—	—	Surface area of the near-field, calculated as: $FSA_F = 2(L_F \times W_F) + 2(L_F \times H_F) + 2(W_F \times H_F)$
Residual solvent	R	g/kg	3.75	Maximum	0.26	3.75	—	Discrete	Assume 80% of loads have 0.26 g/kg residual (normal loads) and 20% of loads have 3.75 g/kg residual (off-the-peg loads), per von Grote et al. (2003). EPA/OPPT assumed the same distribution of load types in the United States. These estimates correspond to a non-vented, dry-to-dry machine (3^{rd} generation), which is likely conservative because 4^{th} generation machines may also be used.
Load size	LS	kg/load	32	Maximum	12	32	—	Uniform	Range of capacities for five characteristic machine sizes (von Grote et al., 2003). The data were obtained from a 2002 dry cleaner survey in Germany. EPA/OPPT assumed the cylinder volumes and capacities are similar to those in U.S. machines.
Loading factor	F	Unitless	0.79	Average	—	—	—	—	Because good cleaning results can only be obtained when the machine is not overloaded, EPA/OPPT assumed the

Input Parameter	Symbol	Unit	Model Parameter Values		Uncertainty Analysis Assumptions			Distribution Type	Comments
			Value	Basis	Lower Bound	Upper Bound	Mode		
									each load is not filled to the maximum capacity. The loading factor is an average value derived in a survey carried out by Klein and Kurz (1994).
Number of loads per day	LD	loads/day	14	Maximum	1	14	—	Uniform	EPA/OPPT assumed the number of loads ranges from one to 14 based on the NIOSH (2010) and Blando et al. (2010).
Exposure Duration	t_3	hr	0.33	—	—	—	—	—	EPA/OPPT assumed workers take 20 minutes to press and finish each load. This estimate is approximately consistent with Von Grote et al. (2003), which estimated that residual solvent will evaporate continuously over a period of approximately 11 to 20 minutes.
Vapor generation rate	G_F	mg/hr-load	—	Calculated	—	—	—	—	Calculated as: $G_F = R \times 1{,}000\ mg/g \times LS \times F / t_3$

Table_Apx K-7 Input Near-Field/Far-Field Model Parameters and Monte Carlo Simulation Assumptions for Spot Cleaning (Multi-Zone Model)

Input Parameter	Symbol	Unit	Model Parameter Values		Uncertainty Analysis Assumptions			Distribution Type	Comments
			Value	Basis	Lower Bound	Upper Bound	Mode		
Near-field volume	V_S	ft^3	600	—	—	—	—	—	Same dimensions used in the final risk assessment (i.e., 10 ft for L_{NF} and W_{NF} and 6 ft for H_{NF}) (U.S. EPA, 2014c).
Free surface area for spot-cleaning	FSA_S	ft^2	340	—	—	—	—	—	Surface area of the near-field, calculated as: $FSA_F = (L_F \times W_F) + 2(L_F \times H_F) + 2(W_F \times H_F)$
Starting time	t_1	hr	0	—	—	—	—	—	Constant value.
Exposure Duration	t_2	hr	8	—	—	—	—	Constant	Assumes the activity is performed from hour 2 to hour 10 of each operating day.
Averaging time	t_{avg}	hr	8	—	—	—	—	—	Constant value. Work activities are assumed to be split across two 8-hr shifts over each operating day. The first shift worker spot cleans from hour 2 to hour 8, while the second shift worker spot cleans from hour 8 to hour 10.
Use rate	UR	gal/yr	16	Maximum	13.92	16	—	Uniform	A MassDEP comparative analysis worksheet provides an example case study for a facility, which spends $60 per month on spot cleaner (MassDEP, 2013). The cost of 1-BP is estimated at $45 per gallon (Blando et al., 2009). These numbers translate to 16 gallons per year. We assume the 1-BP concentration could vary uniformly from 87 to 100 percent (Enviro Tech International, 2013).
Vapor generation rate	G_S	mg/hr	—	Calculated	—	—	—	—	Density of DrySolv is 1.33 kg/L (Enviro Tech International, 2013). G_S = UR x (3.785 L/gal) x (1.33 kg/L) x (10^6 mg/kg) / [(8 hr/day) x OD]

Table_Apx K-8 Input Near-Field/Far-Field Model Parameters and Monte Carlo Simulation Assumptions for Spot Cleaning (Stand-Alone Model)

Input Parameter	Symbol	Unit	Model Parameter Values		Uncertainty Analysis Assumptions			Distribution Type	Comments
			Value	Basis	Lower Bound	Upper Bound	Mode		
Near-field volume	V_{NF}	ft^3	600	—	—	—	—	—	EPA/OPPT applied the same dimensions used in the EPA TCE final risk assessment (i.e., 10 ft for L_{NF} and W_{NF} and 6 ft for H_{NF}) (U.S. EPA, 2014c).
Starting time	t_1	hr	0	—	—	—	—	—	Constant value.
Exposure Duration	t_2	hr	8	—	—	—	—	Constant	Equal to operating hours per day.
Averaging time	t_{avg}	hr	8	—	—	—	—	—	Constant value.
Use rate	UR	gal/yr	16	Maximum	13.92	16	—	Uniform	$60 spot cleaner per month (MassDEP, 2013) at a cost of $45 per gallon (Blando et al., 2009) translates to 16 gallons per year. We assume the 1-BP concentration could vary uniformly from 87 to 100 percent (Enviro Tech International, 2013).
Vapor generation rate	G	mg/hr	38,723	Maximum	33,689	38,723	—	Uniform	G is set equal to UR with appropriate unit conversions. Density of DrySolv is 1.33 kg/L (Enviro Tech International, 2013).
Operating hours per day	OH	hr/yr	8	—	—	—	—	—	EPA/OPPT assumed 8 hr/day.
Operating days per year	OD	day/yr	260	—	—	—	—	—	EPA/OPPT assumed 260 day/yr.

Appendix L CONSUMER EXPOSURE ASSESSMENT

L-1 Default Parameters Used in CEM for Emission and Household Characteristics

The Exposure and Fate Assessment Screening Tool Version 2 (E-FAST2) Consumer Exposure Module (CEM) performs assessments of exposures to common products to consumers. This section describes the values that were chosen for the modeling parameters in CEM to provide more support for the 1-BP exposure assessment. This material is also described in the E-FAST2 manual available at http://www.epa.gov/tsca-screening-tools/e-fast-exposure-and-fate-assessment-screening-tool-version-2014.

The default parameters used for household characteristics were all set to mean or median values based on data found in the available literature and these were used in the 1-BP assessment. Consumer behavior patterns were not set to E-FAST2's default settings, alternatively, a hypothetical scenario was created for users of products containing 1-BP. Data from the Westat (1987) survey aligned with the description of the products chosen for modeling in this exposure assessment.

Table_Apx L-1 summarizes the selection and justification of exposure parameters for CEM for the purposes of estimation of indoor air concentrations of 1-BP.

L-2 Air Exchange Rate

The air exchange rate used by OPPT for the 1-BP model runs was the E-FAST/CEM default value of 0.45 air changes per hour (ACH). This choice is consistent with the recommended central tendency value per the current and prior editions of the Exposure Factors Handbook, as shown below in Table_Apx L-1. (U.S. EPA, 2011, 1997b).

Table_Apx L-1 Summary of Parameters Used for Estimation of Indoor Air Concentrations of 1-BP

Modeling Input	Value	Justification/Source
Air exchange rate (air exchanges/hr)	0.45	Recommended 50th percentile value of residential air exchange rate for all regions within the United States (U.S. EPA, 1995)
Overspray fraction (unitless)	0.01	Selection based on professional judgment (U.S. EPA, 2007a).
Whole House Volume (m^3)	492	Recommended whole house volume from the EFH (2011), central estimate.
Emission rate constant (hrs^{-1})	183.09	Estimated using Chinn's algorithm (DTIC DLA, 1981) based on E-FAST model documentation. This algorithm utilizes molecular weight and vapor pressure to estimate emission rates.
Inhalation rate (m^3/hr)	0.74 (During use)	Inhalation rate during product use based on short-term exposure at light activity level (U.S. EPA, 2011) Short term inhalation values during light activity (male and female combined) were taken from the following age groups and averaged to create an estimate for inhalation rate during product use. 21 to <31 years; 31 to <41 years; 41 to <51 years; 51 to <61 years; 61 to <71 years; and 71 to <81 years.
	0.61 (After use)	*After product use:* 0.611 m^3/hr (U.S. EPA, 2011)
Body weight (kg)	80	Mean value of body weights for all adults (≥21 yrs), male and female combined. Value based on EPA analysis of NHANES 1999–2006 data (U.S. EPA, 2011)
Interzonal airflow rate (m^3/hr)	81.73	Air flow rate between the room of use (utility room or zone 1) and the rest of the house (zone 2; (U.S. EPA, 1995)

Figure_Apx L-1 Screen Capture of Summary of Recommended Values for Residential Building Parameters from the Exposure Factors Handbook (2011).

Table 19-1. Summary of Recommended Values for Residential Building Parameters

	Mean	10th Percentile	Source
Volume of Residence[a]	492 m^3 (central estimate)[b]	154 m^3 (lower percentile)[c]	U.S. EPA 2010 analysis of U.S. DOE, 2008a
Air Exchange Rate	0.45 ACH (central estimate)[d]	0.18 ACH (lower percentile)[e]	Koontz and Rector, 1995

[a] Volumes vary with type of housing. For specific housing type volumes, see Table 19-6.
[b] Mean value presented in Table 19-6 recommended for use as a central estimate for all single family homes, including mobile homes and multifamily units.
[c] 10th percentile value from Table 19-8 recommended to be used as a lower percentile estimate.
[d] Median value recommended to be used as a central estimate based across all U.S. census regions (see Table 19-24).
[e] 10th percentile value across all U.S. census regions recommended to be used as a lower percentile value (see Table 19-24).
ACH = Air changes per hour.

L-3 Overspray Fraction

The selection of a default overspray fraction of 0.01 in CEM was based on professional judgement (as cited in E-FAST). We are only using the peak concentration as a model diagnostic in this assessment, not as a tool to understand exposures for any time scale longer than 10 seconds.

L-4 Emission Rate

The emitted mass was addressed in CEM in two ways. When an aerosol product is used, some of the product does not reach the intended application surface but remains in the air. This portion, commonly known as the overspray, was assumed to be 1% of the product emitted during use. This results in the constant emission of 1-BP to the room air over the duration of use. The remaining fraction (99%) was assumed to strike the intended application surface forming a film. This film is treated as an incremental source, as described below (Figure_Apx L-2 Screen Capture of E-FAST Equations for Estimation of Emission Rate).

Figure_Apx L-2 Screen Capture of E-FAST Equations for Estimation of Emission Rate

For a **product that is applied to surface**, such as a general purpose cleaner or a latex paint, an incremental source model is used. This model assumes a constant application rate over the specified duration of use; each instantaneously applied segment has an emission rate that declines exponentially over time, at a rate that depends on the chemical's molecular weight (MW) and vapor pressure (VP).

In the case of a general purpose cleaner, the equation for exponentially declining emissions for each instantaneously applied segment is as follows:

$$E(t) = E(0) \times \exp(-kt) \qquad \text{(Eq. 3-41)}$$

where E (t) is the emission rate (mass/time) at time t (in hours), E (0) is the initial emission rate at time 0, k is a first-order rate constant for the emissions decline (inverse hours), and t is elapsed time (hours). The value of k is determined from an empirical relationship, developed by Chinn (1981), between the time (in hours) required for 90 percent of a pure chemical film to evaporate (EvapTime) and the chemical's molecular weight and vapor pressure:

$$EvapTime = \frac{145}{(MW \times VP)^{0.9546}} \qquad \text{(Eq. 3-42)}$$

The value of k is determined from the 90 percent evaporation time as follows:

$$k = \frac{\ln(10)}{EvapTime} \qquad \text{(Eq. 3-43)}$$

Using Equation 3-42 to calculate *EvapTime*:

$$\text{EvapTime} = \frac{145}{(123 \times 146.3)^{0.9546}}$$

Where,

Molecular weight (MW) = 123 g/mole
Vapor Pressure (VP) = 146.3 torr

Hence, *EvapTime* = 0.0126 hrs or 0.75 min

Using Equation 3-43 to calculate *Emission Rate Constant (k):*

$$k = \frac{\ln(10)}{1.36}$$

Hence, *Emission Rate Constant (k)* = 183.09 hrs^{-1} or 3.05 min^{-1}

Because Chinn's algorithm (DTIC DLA, 1981) assumes a pure chemical film, it tends to produce a lower-bound estimate of the evaporation time; thus, overestimates the peak concentration. In products that are a mixture of chemicals, interaction forces between the different chemicals could alter the evaporation rate of individual constituents.

In the simulation done for this assessment, the outcome was not expected to be strongly dependent on the exact value of *k* due to the long time period the consumer spent in the room of use after the period of product application. All of the 1-BP mass was expected to enter the air before the user leaves the room even if the k value was adjusted to be less conservative. Currently the evaporation time for 90% of the 1-BP in the film on the application surface (0.0126 hrs or 0.75 min) was much less than the time the user spent in the room of use. Even if this value were to increase, due to intermolecular interactions within a more complicated mixture decreasing the emission rate, it would likely still be less than the time spent in the room of use.

L-5 Room and House Volume and Movement Within the Home

The CEM within E-FAST2 currently uses a default house volume (523 m^3) that is based on the calculated volume of a single attached home in the Formaldehyde Indoor Air Model (FIAM). The 2011 edition of the EFH recommends a house volume of 492 m^3 (U.S. EPA, 2011). While the default house volume used in CEM is slightly larger than the average value presented in the EFH, the difference is less than 10% and as noted in the sensitivity analysis, the house volume is an import factor, but is not the largest contributor to potential differences in predicted air concentrations.

The exposure values for the user could be more impacted by the size of the room selected during use. The volume assigned to the room of use was 20 m^3 for a utility room where the volume was represented by a 9 ft x 10 ft room with 8 ft ceilings (720 ft^3 = 20.4 m^3) (U.S. EPA, 2014c), 48 m^3 for the living room (U.S. EPA, 2011), and 118 m^3 for the "garage" (Batterman et al., 2007). The garage volume was used based on an indoor air quality study (Batterman et al., 2007) which included attached garages of 15 homes in Michigan, with a median volume of 118 m^3. The room of use is Zone 1 in the CEM simulations; Zone 2 is the rest of the house (492 m^3). The user and bystander move about the home according to a hypothetical behavior pattern constructed to represent a day spent mostly indoors. Since the behavior patterns do not involve the residents entering the room of use except to use the product, the user spends the rest of the time either in Zone 2 or outside (where there is no expected chemical exposure) and the non-user spends the entire 24 hours either in Zone 2 or outside.

L-6 Inhalation Rate and Body Weight

The inhalation rate and body weight values for the simulation were taken from the 2011 EFH (U.S. EPA, 2011). These values were based on the NHANES data (1999-2006) and correspond to the age groups reported in the (U.S. EPA, 2011). It is important to note that in the exposure assessment only the exposure doses will be affected by these parameters. Indoor air concentrations are determined by the product use patterns, the volume of the room and of the

house, and the physical-chemical properties of 1-BP. Body weight and inhalation rate do not change the calculated indoor air concentrations.

L-7 Consumer Behavior Patterns

E-FAST2/CEM requires the input of consumer behavior pattern information, including mass of product used, duration of use, time spent in the room of use and the volume of the room of use. By default, E-FAST2/CEM uses pre-set, high-end values for a variety of consumer use scenarios when use information is not available for specific products. Under these conditions, the model results tend to over predict the exposure.

EPA/OPPT did not have consumer behavior pattern information for the specific branded products being evaluated in this assessment. Rather than using the E-FAST2/CEM's default inputs, EPA/OPPT relied upon professional judgment and the Household Solvent Products Survey prepared by Westat for EPA in (1987) to inform the selection of input parameters and assumptions representing the consumers' behavior patterns. Table_Apx L-2 provides a summary of the information provided in the Westat (1987) survey, with a comparison to the values used in this assessment.

Table_Apx L-2 Comparison of Westat Survey Data and Simulation Values for 1-BP

Spray Adhesives					
	Mean	**Median (50th %)**	**90th %**	**Simulation values***	
				50th %	**90th %**
Time spent using product	15 min	4 min	30 min	4 min	30 min
Time spent in room after use[a]	69 min	10 min	180 min	60 min	180 min
Amount of product used per event	2.98 oz (84.5 g)	0.25 oz (7.1 g)	2.0 oz (56.7 g)	0.25 oz (7.1 g)	2.0 oz (56.7 g)
Weight fraction 1-BP in product**				0.60	0.85
Room of use	Garage 6% Living Room 12% **Inside Room 61 %**			Utility room	

Table_Apx L-2 Comparison of Westat Survey Data and Simulation Values for 1-BP

Spot Removers					
	Mean	**Median (50th %)**	**90th %**	**Simulation values**	
				50th %	**90th %**
Time spent using product	11 min	5 min	30 min	5 min	30 min
Time spent in room after use[b]	44 min	5 min	120 min	60 min	120 min
Amount of product used per event	3.49 oz (98.9 g)	1.33 oz (37.7 g)	7.5 oz (212.6 g)	1.33 oz (37.7 g)	7.5 oz (212.6 g)
Weight fraction 1-BP in product**				0.55	0.95
Room of use	Basement 9% Living Room 20% **Inside Room 57 %**			Utility room	
Engine Degreasers					
	Mean	**Median (50th %)**	**90th %**	**Simulation values**	
				50th %	**90th %**
Time spent using product	29 min	15 min	60 min	15 min	60 min
Time spent in room after use[c]	5 min	0 min	0 min	60 min	120 min
Amount of product used per event	18.7 oz (530 g)	11.6 oz (329 g)	32 oz (907 g)	11.6 oz (329 g)	32 oz (907 g)
Weight fraction 1-BP in product**				0.75	0.90
Room of use	Garage and Outside 1% Garage 8% **Outside 89 %**			Garage	
Brake Cleaners					
	Mean	**Median (50th %)**	**90th %**	**Simulation values**	
				50th %	**90th %**
Time spent using product	23 min	15 min	50 min	15 min	50 min
Time spent in room after use[d]	10 min	0 min	30 min	60 min	120 min
Amount of product used per event	6 oz (170 g)	4 oz (113 g)	12 oz (340 g)	4 oz (113 g)	12 oz (340 g)
Weight fraction 1-BP in product**				0.75	0.95
Room of use	Garage and Outside 3% Garage 18% **Outside 77%**			Garage	

Table_Apx L-2 Comparison of Westat Survey Data and Simulation Values for 1-BP

Electronics Cleaners					
	Mean	Median (50th %)	90th %	Simulation values	
				50th %	90th %
Time spent using product	9 min	2 min	20 min	2 min	20 min
Time spent in room after use[e]	60 min	60 min	300 min	60 min	300 min
Amount of product used per event	1.8 oz (51 g)	0.5 oz (14 g)	3.5 oz (100 g)	0.5 oz (14 g)	3.5 oz (100 g)
Weight fraction 1-BP in product**				0.35	0.75
Room of use	Basement 6% Other Inside Room36% **Living Room 48 %**			Living Room	

Notes:

*Simulation values for time spent in room of use are for total time in room of use and can only be modeled in increments of 1 hour, with a minimum value of 1 hour. Therefore, for scenarios where survey data indicated that users left the room of use immediately following application, if the application duration was less than one hour, time spent in room of use was modeled as one hour.

** Weight fraction in products based on information from available products as described in Table_Apx A-3.

[a]Percentile rankings included respondents who said they used contact cements, super glues or spray adhesives but did not spend any time in the room of use. In comparison, median time spent in the room of use including only those who spent time in the room of use was 20 minutes and the 90th percentile value was 240 minutes.

[b]Percentile rankings included respondents who said they used spot removers but did not spend any time in the room of use. In comparison, median time spent in the room of use including only those who spent time in the room of use was 10 minutes and the 90th percentile value was 180 minutes.

[c]Percentile rankings included respondents who said they used engine degreasers but did not spend any time in the room of use. In comparison, median time spent in the room of use including only those who spent time in the room of use was 60 minutes and the 90th percentile value was 120 minutes.

[d]Percentile rankings included respondents who said they used brake quieters/cleaners but did not spend any time in the room of use. In comparison, median time spent in the room of use including only those who spent time in the room of use was 30 minutes, and the 90th percentile value was 120 minutes.

[e]Percentile rankings included respondents who said they used specialized electronic cleaners but did not spend any time in the room of use. In comparison, median time spent in the room of use including only those who spent time in the room of use was 60 minutes and the 90th percentile value was 300 minutes.

L-8 Use Data for Contact Cement, Super Glues or Spray Adhesives

The description of this product category in the Westat (1987) survey matches reasonably well with the simulated scenario, however no distinction in the survey statistics was made between the three types of products and therefore it is unknown if these statistics are skewed more towards one product or another. More than 60% of the 4917 respondents in the survey said that they had ever used contact cement, super glues or spray adhesives. Of the 2686 respondents who had recently used any of these products, only 2.9% stated that the product was in the aerosol form. More than 60% of the respondents who used these products stated that they used it in "another inside room", thus EPA/OPPT chose the room of use as the default utility room within the CEM model. The majority of the users (59%) stated they did not have an open window or door for

ventilation and 91% of the users stated that they did use an exhaust fan during use. Furthermore, 75.1% of respondents stated that the door of the room of use was open to the rest of the house. This information supports the assumptions of no ventilation and a second zone with potential bystander exposure used in modeling the indoor air concentration in this assessment. The 90th percentile values for the the mass used and time spent in the room of use were used to present a conservative estimate however this was also balanced by presenting a central tendency estimate by using 50th percentile input values.

L-9 Use Data for Spot Removers

The description of this product category in the survey matches reasonably well with the simulated scenario. Nearly half (43.9%) of the 1388 respondents to the Westat (1987) survey that said that they had recently used spot removers stated that the product was in the aerosol form. More than 57% of the respondents who used these products stated that they used it in "another inside room", thus EPA/OPPT chose the room of use as the default utility room within the CEM model. The majority of the users (55%) stated they did not have an open window or door for ventilation and nearly 91% of the users stated that they did not use an exhaust fan during use. Furthermore, over 80% stated that the door of the room of use was open to the rest of the house. This information supports the assumptions of no ventilation and a second zone with potential bystander exposure used in modeling the indoor air concentration in this assessment. The 90th percentile values for the the mass used and time spent in the room of use were used to present a conservative estimate however this was also balanced by presenting a central tendency estimate by using 50th percentile input values.

L-10 Use Data for Engine Degreasers

The description of this product category in the survey matches reasonably well with the simulated scenario, with some exceptions. More than three quarters (78.9%) of the 577 respondents to the Westat (1987) survey that said that they had recently used engine degreasers stated that the product was in the aerosol form. More than 89% of the respondents who used these products stated that they used it outside, with 7.8% reporting that they used the product in their garage. Although it is clear that the main location of use is outside, E-FAST/CEM does out have the ability to model air concentrations outdoors, thus EPA/OPPT chose the room of use as a garage. The CEM model does not have a default garage volume therefore the utility room was used as a proxy with an adjusted volume. The garage volume was used based on an indoor air quality study (Batterman et al., 2007) which included attached garages of 15 homes in Michigan, with a median volume of 118 m^3. The 90th percentile values for the mass used and time spent in the room of use were used to present a conservative estimate however this was also balanced by presenting a central tendency estimate by using 50th percentile input values.

L-11 Use Data for Brake Quieters/Cleaners

The description of this product category in the survey matches reasonably well with the simulated scenario, with some exceptions. More than half (65.6%) of the 94 respondents to the Westat (1987) survey that said that they had recently used brake quieter/cleaner stated that the product was in the aerosol form. This sampling is not large, therefore there is may be some

uncertainty associated with this use; however, EPA/OPPT was not able to identify other available data to better inform this scenario. More than 77% of the respondents who used these products stated that they used it outdoors, with nearly 18% reporting that they used the product in their garage. As mentioned in Section L-5, E-FAST/CEM does not have the ability to model air concentrations outdoors, thus EPA/OPPT chose the room of use as a garage. Because E-FAST does not have a designated "garage" as a room of use in its default scenarios, EPA/OPPT chose to use the utility room in E-FAST as a proxy by adjusting the room volume.The 90th percentile values for the the mass used and time spent in the room of use were used to present a conservative estimate however this was also balanced by presenting a central tendency estimate by using 50th percentile input values.

L-12 Use Data for Specialized Electronic Cleaners

The description of this product category in the survey matches reasonably well with the simulated scenario, with some exceptions. Less than half (47.5%) of the 541 respondents to the Westat (1987) survey that said that they had recently used specialized electronic cleaners stated that the product was in the aerosol form. Nearly half (47.5%) of the respondents who used these products stated that they used it in the living room with another 36% reporting that they used it in "another inside room", thus EPA/OPPT chose the room of use as the default living room within the CEM model. The majority of the users (66%) stated they did not have an open window or door for ventilation and nearly 94% of the users stated that they did not use an exhaust fan during use. Furthermore, over 70% stated that the door of the room of use was open to the rest of the house. This information supports the assumptions of no ventilation and a second zone with potential bystander exposure used in modeling the indoor air concentration in this assessment. The 90th percentile values for the the mass used and time spent in the room of use were used to present a conservative estimate however this was also balanced by presenting a central tendency estimate by using 50th percentile input values.

L-13 Converting E-FAST ADRs to Air Concentrations

The Exposure and Fate Assessment Screening Tool Version 2 (E-FAST2) Consumer Exposure Module (CEM) performs assessments of exposures to common products to consumers. The ADRs generated using the E-FAST/CEM models are shown in the table below in mg/kg-bw/day (Table_Apx L-3). The only output in the acute exposure scenario expressed as a concentration was the peak concentration, which represented the maximum concentration in air calculated by the model during any 10-second time step during (in this case) 24 hrs. This value did not realistically describe a 24-hr exposure, even as a worst-case scenario.

Table_Apx L-3 Estimated Acute Dose Rates from Consumer Use

Acute Dose Rate (mg/kg-bw/day) – High End										
Age (yrs)	Aerosol Spray Adhesive Use		Aerosol Spot Remover Use		Aerosol Spray Cleaners and Degreasers					
					Engine Degreaser Use		Brake Cleaner Use		Electronics Cleaner Use	
	User	Non-User	User	Non-User	User	Non-User	User	Non-User	User	Non-User
21 to 78	5.1	1.4	21.4	5.9	50.7	18.2	20.6	7.2	6.9	2.3
16 to <21	5.7	1.8	24.0	7.4	59.2	22.3	23.9	8.9	7.8	2.8
11 to <16	--	2.1	--	8.7	--	26.4	--	10.5	--	3.4
6 to <11	--	2.9	--	12.2	--	37.4	--	14.9	--	4.8
3 to <6	--	4.2	--	17.6	--	53.7	--	21.4	--	6.9
1 to <3	--	5.2	--	21.6	--	66.1	--	26.3	--	8.5
<1	--	5.5	--	22.9	--	70.2	--	27.9	--	9.0
Acute Dose Rate (mg/kg-bw/day) – Central Tendency										
21 to 78	0.5	0.1	2.2	0.6	15	5.6	5.1	1.9	0.4	0.2
16 to <21	0.5	0.2	2.4	0.8	17	7.0	5.7	2.4	0.5	0.2
11 to <16	--	0.2	--	0.9	--	8.2	--	2.8	--	0.2
6 to <11	--	0.3	--	1.2	--	12.0	--	4.0	--	0.3
3 to <6	--	0.4	--	1.8	--	17.0	--	5.7	--	0.4
1 to <3	--	0.5	--	2.2	--	20.0	--	7.0	--	0.5
<1	--	0.5	--	2.3	--	22.0	--	7.4	--	0.6

To convert the E-FAST CEM outputs from mg/kg-bw/day to ppm, we used the equation for the potential acute dose rate reported in the E-FAST manual. The general expression for the potential acute dose rate (ADR_{pot}) is as follows:

$$ADR_{pot} = (C_{air} \times InhR \times FQ \times DEv \times ED) / (BW \times AT)$$

Where,

ADR_{pot} = potential acute dose rate (mg/kg-bw/day)
C_{air} = exposure concentration (mg/m^3)
InhR = inhalation rate (m^3/hr)
FQ = frequency of product use (events/year)
DEv = duration of an event (hour/event)
ED = exposure duration (years of product usage)
BW = body weight (kg)
AT = averaging time (days)

Rearranging and simplifying this equation to calculate *an approximation* for C_{air} over the 24-hr averaging time for the ADR_{POT} results in the following equation:

$$Cair \approx \frac{ADRpot \times BW}{InhR \times 24}$$

This simplification is reasonable since the averaging time for acute exposure is one day (24 hrs). In both scenarios, the frequency is just once per day. Although the duration of the event for the two consumer scenarios is 0.5 hrs, for the purposes of this exercise and to convert the model output to a more useable exposure value to compare to the hazard value, there is no correction for this difference. This assumption is still conservative since the values generated were reasonably high exposures that probably overestimated the actual exposures.

An example calculation is presented below, since the final value is in mg/m^3 and the desired units will be in ppm. All calculated values are presented in Table_Apx L-3 and Table_Apx L-4.

For example, the spray adhesive use, 21- to 78-yr-old user:

ADR_{pot} = 5.12 mg/kg-bw/day
InhR (during use; 0.5 hrs) = 0.74 m^3/hr
InhR (other times; 23.5 hrs) = 0.611 m^3/hr
BW = 80 kg [using 2011 EFH (U.S. EPA, 2011)]

And calculating for C_{air}:

$$C_{air} = \frac{(5.12 \text{ mg/kg-bw/day}) \times (80 \text{ kg})}{[(0.74 \text{ m}^3/\text{hr} \times 0.5 \text{ hr}) + (0.611 \text{ m}^3/\text{hr} \times 23.5 \text{ m}^3/\text{hr})]}$$

= 27.81 mg/ m^3;
= 5.5 ppm (rounded to 6 ppm to use a single significant figure given the assumptions in the back-calculation).

However, for the user in all scenarios, the inhalation rates were slightly higher during use of the product, as stipulated in the model outputs. Thus, for example, for the spray adhesive use, an inhalation rate of 0.74 m^3/hr (for 21 to 78 year olds, 0.72 m^3/hr for the 16 to 20 year olds) was used for one 0.5 hrs, and 0.611 m^3/hr (for 21 to 78 yr olds, 0.679 m^3/hr for the 16 to 20 yr olds) for the remaining 23.5 hrs. This correction was not performed for any non-user scenario.

Table_Apx L-4 Estimated Acute Air Concentrations from Consumer Use (rounded to one significant figure)

Acute Air Concentration (ppm) – High End										
Age (yrs)	Aerosol Spray Adhesive Use		Aerosol Spot Remover Use		Aerosol Spray Cleaners and Degreasers					
					Engine Degreaser Use		Brake Cleaner Use		Electronics Cleaner Use	
	User	Non-User	User	Non-User	User	Non-User	User	Non-User	User	Non-User
21 to 78	6	2	23	6	54	20	22	8	7	3
16 to <21	6	2	23	6	54	20	22	8	7	3
11 to <16	--	2	--	6	--	20	--	8	--	3
6 to <11	--	2	--	6	--	20	--	8	--	3
3 to <6	--	2	--	6	--	20	--	8	--	3
1 to <3	--	2	--	6	--	20	--	8	--	3
<1	--	2	--	6	--	20	--	8	--	3
Acute Air Concentration (ppm) – Central Tendency										
21 to 78	0.5	0.1	2	0.7	16	6	5	2	0.5	0.2
16 to <21	0.5	0.1	2	0.7	16	6	5	2	0.5	0.2
11 to <16	--	0.1	--	0.7	--	6	--	2	--	0.2
6 to <11	--	0.1	--	0.7	--	6	--	2	--	0.2
3 to <6	--	0.1	--	0.7	--	6	--	2	--	0.2
1 to <3	--	0.1	--	0.7	--	6	--	2	--	0.2
<1	--	0.1	--	0.7	--	6	--	2	--	0.2

As seen in Table_Apx L-4, each age group is exposed to the same modeled air concentrations and therefore all age groups have the same ADR_{pot} (ppm). The conversion from dose to air concentrations resulted in 24-hr time averaged indoor air concentrations for 1-BP (ppm) that were not sensitive to user specific characteristics such as body weight or respiration rate. This is why the same value was present throughout each column in Table_Apx L-4. Values (ppm) in Table_Apx L-4 were the only values used in the risk assessment. Calculations detailing the conversion from acute dose rates to air concentrations are provided in a supplemental Excel spreadsheet file entitled *"Consumer Exposure Calculations"*.

The age groups are presented in Table_Apx L-3 and Table_Apx L-4 and model output sheets in the supplementary documents. Note that CEM also assumes that the user will be over 16. However, Table_Apx L-4 shows that the age groups are irrelevant for the calculated concentrations of 1-BP in the air. Since there is not sufficiently refined data to create different consumer behavior patterns for different age groups, EPA/OPPT assumed that younger users (<16 yrs) of spray adhesive, spot remover, and aerosol cleaning and degreasing products would be exposed to the same concentrations as other users.

L-14 Sensitivity of Model Parameters

Tier 1 analysis

For the Tier 1 analysis, a plausible range of values was established for each input parameter. This range consisted of a low, medium (baseline scenario), and high value. These plausible values and the justification for the parameter selection for each input parameter are provided in Table_Apx L-5**.**

Table_Apx L-5 Plausible range for input parameters for Tier 1 analysis

Parameters	Low	Medium (Baseline)	High	Source	Selection Justification
Room of Use	18 m^3 (Bathroom)	36 m^3 (Utility Room)	48 m^3 (Living room)	FIAM[1] (Appendix A)	Room volumes obtained from the Formaldehyde Indoor Air Model (FIAM). In the FIAM model, the bathroom is the smallest room and the living room is the largest room.
Whole House Volume	369 m^3	492 m^3	737 m^3	EPA (2011, 1997a)	Low volume selected from EFH (U.S. EPA, 1997a) whole house volume. Medium volume selected from EFH (U.S. EPA, 2011) median house volume. High volume was interpolated based on an approximately 40% increase in volume size from the baseline scenario. The 40% increase is based on the difference in volumes between the low and medium values.
Consumer Product Weight Fraction	75%	85%	95%	EPA	Medium and high values selected from spray adhesive and spot remover scenarios. The low value was interpolated based on the difference (10%) between the medium and high values.
Mass of Product Used per Use	0.25 ounces	1.33 ounces	7.5 ounces	Westat (1987)	Low, medium, and high values selected from the 10 percentile, median, and 90th percentile values of mass (in ounces) of chemical used for spot remover scenario. Data obtained from survey conducted by Westat in 1987 from 1275 recent users ((Westat, 1987) – Table C-18 – page 5-49).
Air Exchange Rate	0.18	0.45	1.26	EPA (2011)	Values were selected from the summary statistics for residential air exchange rates (in air changes per hour) table (Table 19-24) in EPA's EFH (U.S. EPA, 2011). The low value is the 10th percentile, the medium value is the 50th percentile and the high value is the 90th percentile.
Inhalation Rate - during use	0.58	0.74	0.95	EPA (2011)	The medium and high values were selected from Table 6-2 (page 6-4) in EPA's EFH (U.S. EPA, 2011). The medium value represents the average of mean short-term exposure values for inhalation during light activity (males and females combined) for the age classes 21 to <31 years; 31 to <41 years; 41 to <51 years; 51 to <61 years; 61 to <71 years; and 71 to <81 years. The high value represented the average of the 95th percentile short-term exposure values. The low value was interpolated based on an approximately 28.3% increase in volume size between the medium and high values. Thus, the low volume was estimated to be approximately 28.3% lower than the medium value.

Table_Apx L-5 Plausible range for input parameters for Tier 1 analysis

Parameters	Low	Medium (Baseline)	High	Source	Selection Justification
Inhalation Rate - after use	0.463	0.611	0.807	EPA (2011)	The medium and high values were selected from Table 6-1 (page 6-3) in EPA's EFH (U.S. EPA, 2011). The medium value represents the average of mean long-term exposure values for inhalation during light activity (males and females combined) for the age classes 21 to <31 years; 31 to <41 years; 41 to <51 years; 51 to <61 years; 61 to <71 years; and 71 to <81 years. The high value represented the average of the 95th percentile long-term exposure values. The low value was interpolated based on an approximately 32% increase in volume size between the medium and high values. Thus, the low volume was estimated to be approximately 32% lower than the medium value.
Body weight	65.5	80	104	EPA (2011)	Values were selected from Table 8-3 in EPA's EFH (U.S. EPA, 2011) providing mean and percentile body weights derived from NHANES (1999-2006) males and females combined. The low value is the 25th percentile average of ages 21 and over, the medium value is the average of the mean values and the high value is the average of the 90th percentiles.
Event duration (central tendency/high end)	0.25	0.5	1	Professional Judgment	It is assumed that a typical DIY project with spray adhesives would last no more than 30 minutes. The low value was assumed to be half this time and high value was assumed to be double this time.

Note: FIAM – USEPA's Formaldehyde Indoor Air Model

The plausible inputs for each parameter were varied one at a time and the model responses (i.e., changes in the ADR and acute concentration values) were noted. The results were first ranked by their output differences using the maximum response value minus the minimum response value of the plausible range and then by their index of sensitivity. The "index of sensitivity" was calculated by dividing the percent change in ADR by the percent change of the input values for each parameter. The rankings from both were averaged for an overall rank for each parameter tested. This exercise was repeated for the acute air concentration results.

The resulting ADRs (mg/kg-bw) and acute air concentrations (ppm) along with the rankings for each of the tested parameters are provided in Table_Apx L-6 and Table_Apx L-7.

Table_Apx L-6 Tier 1 Sensitivity Rankings for Acute Dose Rate

Parameter	ADR (mg/kg-bw)			Difference Ranking	Index of Sensitivity Ranking	Tier 1 Overall Rank
	Low	Medium (baseline)	High			
Room of Use	3.06	2.63	2.40	6	6	6
Whole House Volume	3.32	2.63	2.03	3	4	**3.5**
Consumer Product weight fraction	2.32	2.63	2.94	7	1.5	4.25
Mass of Product used per use	0.496	2.63	14.9	1	1.5	**1.25**
Air exchange rate	4.83	2.63	1.17	2	5	**3.5**
Inhalation Rate - during use	2.16	2.63	3.26	5	4	4.5
inhalation rate - after use	2.53	2.63	2.77	9	7	8
Body weight	3.22	2.63	2.03	4	3	**3.5**
Event Duration (central/high tendency)	2.72	2.63	2.18	8	8	8
Notes: Bold indicates selected parameters for the Tier 2 pure sensitivity analysis. Ranking from 1 to 9 with 1 being the most sensitive parameter						

Table_Apx L-7 Tier 1 Sensitivity Rankings for Acute Air Concentration

Parameter	Acute Air Concentration (ppm)			Difference Ranking	Index of Sensitivity Ranking	Tier 1 Overall Rank
	Low	Medium (baseline)	High			
Room of Use	3.30	2.84	2.59	4	5	4.5
Whole House Volume	3.58	2.84	2.19	3	3	**3.0**
Consumer Product weight fraction	2.50	2.84	3.17	5	1.5	**3.3**
Mass of Product used per use	0.536	2.84	16.1	1	1.5	**1.3**
Air exchange rate	5.21	2.84	1.26	2	4	**3.0**
Inhalation Rate - during use	N/A			N/A		
inhalation rate - after use	N/A			N/A		
Body weight	N/A			N/A		
Event Duration (central/high tendency)	2.94	2.84	2.34	6	6	6.0

Notes:
Acute air concentration is not affected by inhalation rate or body weight changes.
Bold indicates selected parameters for the Tier 2 pure sensitivity analysis.
Ranking from 1 to 6 with 1 being most sensitive parameter.

The Tier 1 analysis indicated that the four most sensitive parameters affecting the ADR and the acute air concentration were as follows:

Acute Dose Rate

1. mass of product used per use;
2. whole house volume;
3. air exchange rate; and
4. body weight.

Acute air concentration

1. mass of product used per use;
2. whole house volume;
3. air exchange rate; and
4. consumer product weight fraction.

The parameter most influential in determining the acute dose rate and acute air concentration is the mass of product applied per use. The emission rate is directly dependent upon the chemical properties and therefore the mass of product used strongly influences the air concentration and dose rate. Because the modeled scenario follows the user over a 24 hour period limiting the period of use to 0.5 hrs in the utility room, the whole house volumes (the remaining 23.5 hours) plays a larger factor in influencing the final acute dose rate and acute air concentration. As shown in Table_Apx L-6 and Table_Apx L-7, the air exchange rate and product

weight fraction can influence the contaminant concentration but do not play as large a role in the final outcome. The above-mentioned 5 input parameters were chosen for the Tier 2 analysis.

Tier 2 Analysis

For the Tier 2 analysis, all the parameters were adjusted by equal increments from the base value. All of the baseline input values were adjusted by -10% and +10% to calculate sensitivity near the baseline value and by -50% and +50% to calculate sensitivity for values farther removed from the baseline value. The baseline scenario was the same baseline scenario that was used for the Tier 1 analysis with the exception of the consumer product weight fraction. Due to a limitation with this value (since the baseline consumer weight fraction was 85% and we could not increase that by 50% as the model would only consider weight fractions that were less than 100%) the consumer product weight fraction was lowered from 85% to 50% for the baseline scenario. The inputs for the Tier 2 analysis are provided in Table_Apx L-8.

Table_Apx L-8 Range of Input Parameters for Tier 2 Analysis

Parameters	-50%	-10%	Baseline	+10%	+50%
Whole House Volume (m^3)	262	471	523	575	785
Mass of Product used per use (g)	18.9	33.9	37.7	41.5	56.6
Air exchange rate	0.225	0.405	0.450	0.495	0.675
Body weight (kg)	40	72	80	88	120
Consumer Product Weight Fraction	0.25	0.45	0.50	0.55	0.75

Similar to the protocol followed in the Tier 1 analysis, the input parameters were varied one at a time and the model responses (ADR and acute concentration) were recorded. There were a total of four variable runs for each parameter. The sensitivity was calculated near the base value (-10% and +10%) and farther removed from the base value (-50% and +50%) for each of the tested parameters. Table_Apx L-9 provides the calculated sensitivities for the parameters affecting the ADR and Table_Apx L-10 provides the calculated sensitivities for the parameter affecting the acute air concentration.

Table_Apx L-9 Tier 2 Sensitivity Results for ADR

Parameters	ADR (mg/kg-bw)					Average percent change of the -10% and +10% values from the baseline	Average percent change of the -50% and +50% values from the baseline
	-50%	-10%	Baseline	+10%	+50%		
Whole House Volume (m^3)	2.37	1.67	1.55	1.45	1.13	11.0%	62.0%
Mass of Product used per use (g)	0.78	1.39	1.55	1.71	2.33	16.0%	77.7%
Air exchange rate	2.47	1.67	1.55	1.45	1.15	11.0%	66.0%
Body weight (kg)	3.10	1.72	1.55	1.41	1.03	15.5%	104%

Table_Apx L-10 Tier 2 Sensitivity Results for Acute Air Concentration

Parameter	Acute air concentration (ppm)					Average percent change of the -10% and +10% values from baseline	Average percent change of the -50% and +50% values from baseline
	-50%	-10%	Baseline	+10%	+50%		
Consumer Product weight fraction	0.84	1.50	1.7	1.84	2.50	16.7%	83.4%
Whole House Volume (m^3)	2.56	1.80	1.7	1.57	1.22	13.4%	66.9%
Mass of Product used per use (g)	0.84	1.50	1.7	1.85	2.52	17.3%	83.8%
Air exchange rate	2.67	1.80	1.7	1.57	1.24	13.4%	71%

Results of the Tier 2 analysis indicate that the CEM model is most sensitive to changes in body weight when using the ADR as the model output. When the acute concentration is used as the model output, it was the mass of product used that the CEM model is most sensitive to. It should be noted that the sensitivity analysis was conducted using some hypothetical values that were based solely on mathematical interpolation. Although some of these values might not correspond to specific product uses based on aerosol spray adhesive, aerosol spot remover, or aerosol degreaser and cleaner scenarios, they lend themselves in the overall understanding of the model sensitivity.

Appendix M STUDY QUALITY AND SELECTION CONSIDERATIONS

Toxicological studies were evaluated for quality, considering soundness, applicability and utility, clarity and completeness and uncertainty and variability (U.S. EPA, 2014b). Specifically, each laboratory animal-based study was reviewed considering the following factors:

- the adequacy of study design,
- test animals (*e.g.*, species, strain, source, sex, age/lifestage/embryonic stage),
- environment (*e.g.*, husbandry, culture medium),
- test substance (*e.g.*, identification, purity, analytical confirmation of stability and concentration),
- treatment (*e.g.*, dose levels, controls, vehicle, group sizes, duration, route of administration),
- endpoints evaluated (*e.g.*, schedule of evaluation, randomization and blinding procedures, assessment methods) and
- reporting (quality and completeness)

The evaluation also included a number of considerations, as described below in Table_Apx M-1.

Table_Apx M-1 Study Quality Considerations

Feature	Example Questions	
Exposure Quality	• Were the exposures well designed and tightly controlled? • Was the test article/formulation adequately identified and characterized? Are co-exposures expected as a result of test article composition? • Is the administration route relevant to human exposure? • Are the exposure levels relevant? • Inhalation exposure: Were analytical concentrations in the test animals' breathing zone measured and reported (i.e., not just target or nominal concentrations)? • Inhalation exposure: For aerosol studies, were the mass median aerodynamic diameter and geometric standard deviation reported?	• Inhalation exposure: Was the chamber type appropriate? Dynamic chambers should be used; static chambers are not recommended. • Inhalation exposure: Were appropriate methods used to generate the test article and measure the analytical concentration? • Diet/Water Exposure: Was consumption measured to allow for accurate dose determinations? Were stability and homogeneity of the test substance maintained? Was palatability an issue? • Gavage Exposure: Was an appropriate vehicle used? Are there any toxicokinetic differences due to bolus dosing? Consider relevance to human exposures.
Test Animals	• Were the test animals appropriate for evaluation of the specified effect(s)? • Were the species, strain, sex, and/or age of the test animals appropriate for the effect(s) measured? • Were the control and exposed populations matched in all aspects other than exposure?	• Were an appropriate number of animals examined, based on what is known about the particular endpoint(s) in question? • Were there any notable issues regarding animal housing or food and water consumption?
Study Design	• Is the study design appropriate for the effect(s) and chemical analyzed? • Were exposure frequency and duration appropriate for the effect(s) measured? • Were anticipated confounding factors caused by selection bias controlled for in the study design (e.g., correction for potential litter bias; randomization of treatment groups)? • Was the timing of the endpoint evaluation (e.g., latency from exposure) appropriate? • Was it a Good Laboratory Practices (GLP) study?	• Was it designed according to established guidelines (e.g., EPA, OECD)? Was it designed to specifically test the endpoint(s) in question? • Did the study design include other experimental procedures (e.g., surgery) that may influence the results of the toxicity endpoint(s) in question? Were they controlled for? • Was the study design able to detect the most sensitive effects in the most sensitive population(s)? • Were multiple exposure groups tested? Was justification for exposure group spacing given? Was recovery or adaptation tested?
Toxicity Endpoints	• Are the protocols used for evaluating a specific endpoint reliable and the study endpoints chosen relevant to humans? • Are the endpoints measured relevant to humans? Do the endpoints evaluate an adverse effect on the health outcome in question? • Were the outcomes evaluated according to established protocols? If not, were the approaches biologically sound? Were any key protocol details omitted?	• Were all necessary control experiments performed to allow for selective examination of the endpoint in question? • As appropriate, were steps taken to minimize experimenter bias (e.g., blinding)? • Does the methodology employed represent the most appropriate and discriminating option for the chosen endpoint?
Data Presentation and Analysis	• Were statistical methods and presentation of data sufficient to accurately define the direction and magnitude of the observed effect(s)? • Are the statistical methods and comparisons appropriate? • Was sufficient sampling performed to detect a biologically relevant effect (e.g., appropriate number of slides examined)?	• Does the data present pooled groups that should be displayed separately (e.g., pooled exposure groups; pooled sexes) and/or analyzed separately? • Was an unexpectedly high/low level of within-study variability and/or variation from historical measures reported or explained? • As appropriate, were issues such as systemic and maternal toxicity (e.g., body weight) considered?
Reporting	• Are descriptions of study methods and results for all endpoints sufficient to allow for study quality evaluations? • Were the details of the exposure protocols and equipment provided? • Were test animal specifics adequately presented? • Are the protocols for all study endpoints clearly described? Is sufficient detail provided to reproduce the experiment(s)?	• Are the statistical methods applied for data analysis provided and applied in a transparent manner? Was variability reported? • Did the study evaluate a unique cohort of animals (i.e., are multiple studies linked)? • Are group sizes and results reported quantitatively for each exposure group, time-point, and endpoint examined?

Appendix N TOXICOKINETICS

The studies summarized in this section were identified for consideration in the human health hazard assessment, as described in Section 3.1.

Empirical evidence from rodent toxicity studies and from occupational exposure studies 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., 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) (Garner et al., 2006; Jones and Walsh, 1979). Garner and Yu (2014) provided supplemental evidence on the toxicokinetics of 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 humans or as metabolites in the urine and exhaled breath of all species studied (Garner et al., 2006; Kawai et al., 2001). Available toxicokinetic data indicate that glutathione (GSH) conjugation and oxidation via cytochrome P450 (CYP450) significantly contribute to the metabolism of 1-BP (Garner and Yu, 2014; Garner et al., 2006).

N-1 Absorption

The detection of carbon-containing metabolites and elevated bromide ion concentrations in urine samples of workers exposed to 1-BP by inhalation and dermal contact provides qualitative evidence that 1-BP is absorbed by the respiratory tract and the skin in humans (Hanley et al., 2010, 2009; Valentine et al., 2007; Hanley et al., 2006). In addition, reports of neurological and other effects in occupationally exposed subjects provide indirect evidence of absorption of 1-BP (Samukawa et al., 2012; CDC, 2008; Majersik et al., 2007; Raymond and Ford, 2007; NIOSH, 2003; Ichihara et al., 2002; Sclar, 1999).

Dermal absorption characteristics estimated in human epidermal membranes mounted on static diffusion cells included steady-state fluxes averaging 625–960 µg cm^{-2} $hour^{-1}$ with pure 1-BP and 441–722 µg cm^{-2} $hour^{-1}$ with a commercial dry cleaning solvent, an average dermal penetration of about 2% from an applied dose of 13.5 mg/cm^2 under non-occluded conditions, and a dermal permeability coefficient for 1-BP in water of 0.257 cm/hour (Frasch et al., 2011).

Qualitative evidence of absorption by the gastrointestinal and respiratory tracts comes from animal studies (Garner et al., 2006; Jones and Walsh, 1979). ^{13}C-labeled metabolites were detected in urine collected from rats and mice exposed by inhalation to 800 ppm [1,2,3-^{13}C]-1-BP for 6 hours (Garner et al., 2006). A number of mercapturic acid derivative metabolites were detected in pooled urine samples collected from rats given oral doses of 200 mg 1-BP/kg/day in arachis oil for 5 days (Jones and Walsh, 1979).

No other human or animal studies were located that determined the rate or extent of absorption of 1-BP following inhalation, oral, or dermal exposure.

N-2 Distribution

Metabolic disposition studies in rats and mice given single intravenous injections of [1,2,3-^{13}C]-1-BP indicate that 1-BP is not expected to accumulate in tissues (Garner et al., 2006). Following intravenous injection of [1-^{14}C]-1-BP at nominal doses of 5, 20, or 100 mg/kg, radioactivity remaining in the carcass 48 hours after dose administration accounted for about 6, 6, and 2% of the administered dose in rats, and 4, 2, and 4% in mice (Garner et al., 2006). In these studies, most of the administered radioactivity was exhaled as parent material or metabolized CO_2 or excreted as metabolites in the urine.

N-3 Metabolism

The metabolism of 1-BP in mammals involves: (1) conjugation, principally with glutathione, leading to release of the bromide ion and formation of mercapturic acid derivatives and (2) oxidation (catalyzed by cytochrome P-450) of parent material and metabolites leading to metabolites with hydroxyl, carbonyl, and sulfoxide groups, and to CO_2. These concepts are based on studies of urinary metabolites in workers exposed to 1-BP (Hanley et al., 2010, 2009; Valentine et al., 2007; Hanley et al., 2006), *in vivo* metabolic disposition studies in rats and mice (Garner et al., 2007; Garner et al., 2006; Ishidao et al., 2002; Jones and Walsh, 1979; Barnsley et al., 1966), and *in vitro* metabolism studies with rat liver preparations (Kaneko et al., 1997; Tachizawa et al., 1982; Jones and Walsh, 1979).

N-Acetyl-S-propylcysteine has been identified in urine samples from workers in a 1-BP manufacturing plant (Valentine et al., 2007), in foam fabricating plants using spray adhesives containing 1-BP (Hanley et al., 2010, 2009; Hanley et al., 2006), and in degreasing operations in plants using 1-BP as a cleaning solvent in the manufacture of aerospace components, hydraulic equipment, optical glass, and printed electronic circuit assemblies (Hanley et al., 2009). Other urinary metabolites identified in 1-BP workers are the bromide ion (Hanley et al., 2010) and three oxygenated metabolites present at lower urinary concentrations than N-acetyl-S-propylcysteine: N-acetyl-S-propylcysteine-S-oxide (also known as N-acetyl-3-(propylsulfinyl) alanine), N-acetyl-S-(2-carboxyethyl) cysteine, and N-acetyl-S-(3-hydroxy-propyl) cysteine (Cheever et al., 2009; Hanley et al., 2009). The correlations between time weighted average workplace air concentrations of 1-BP and urinary levels of bromide and N-acetyl-S-propylcysteine (Hanley et al., 2010, 2009; Valentine et al., 2007; Hanley et al., 2006) support the hypothesis that conjugation with glutathione is an important pathway in humans (see Figure 3-3). The detection of oxygenated metabolites in urine samples indicates that oxidation pathways also exist in humans (see Figure 3-3 for structures of identified oxygenated metabolites).

Results from metabolic disposition studies in rats and mice illustrate that the metabolism of 1-BP in mammals is complex, involving initial competing conjugation or oxidation steps, followed by subsequent conjugation, oxidation, or rearrangement steps. Figure 3-5 presents proposed metabolic pathways based on results from studies of F-344 rats and B6C3F1 mice

exposed to [1-^{14}C]-1-BP by intravenous injection or [1,2,3-^{13}C]-1-BP by inhalation or intravenous injection (Garner et al., 2006).

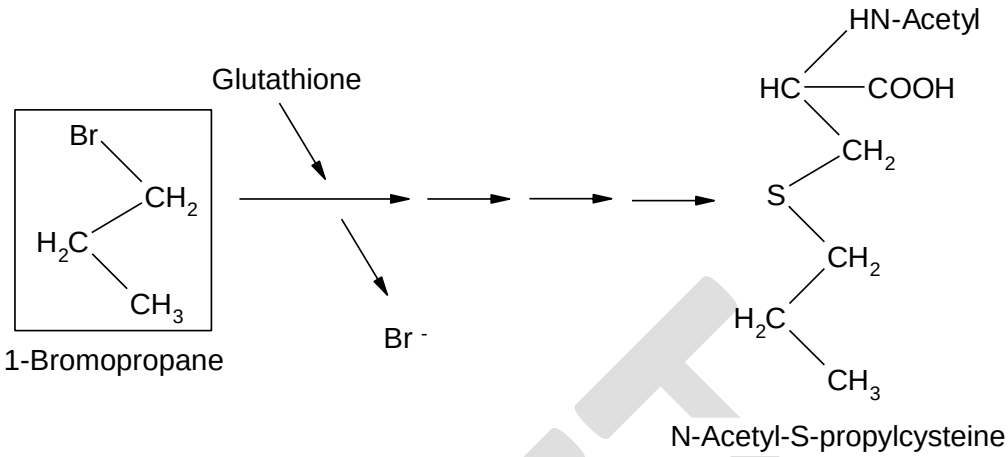
The metabolic scheme shows an oxidation path to CO_2 involving cytochrome P450 (CYP) oxidation steps to 1-bromo-2-propanol and bromoacetone. This path is proposed based on several findings:

1. Following intravenous injection of ^{14}C-1-BP at nominal doses of 5, 20, or 100 mg/kg, radioactivity in CO_2 exhaled in 48 hours accounted for approximately 28, 31, and 10% of the administered dose in rats, and 22, 26, and 19% in mice (Garner et al., 2006). (These data also indicate that oxidative metabolism of 1-BP in rats is more dependent on dose than oxidative metabolism in mice; the decrease in percentage dose exhaled as CO_2 at the highest dose is greater in rats than mice.)

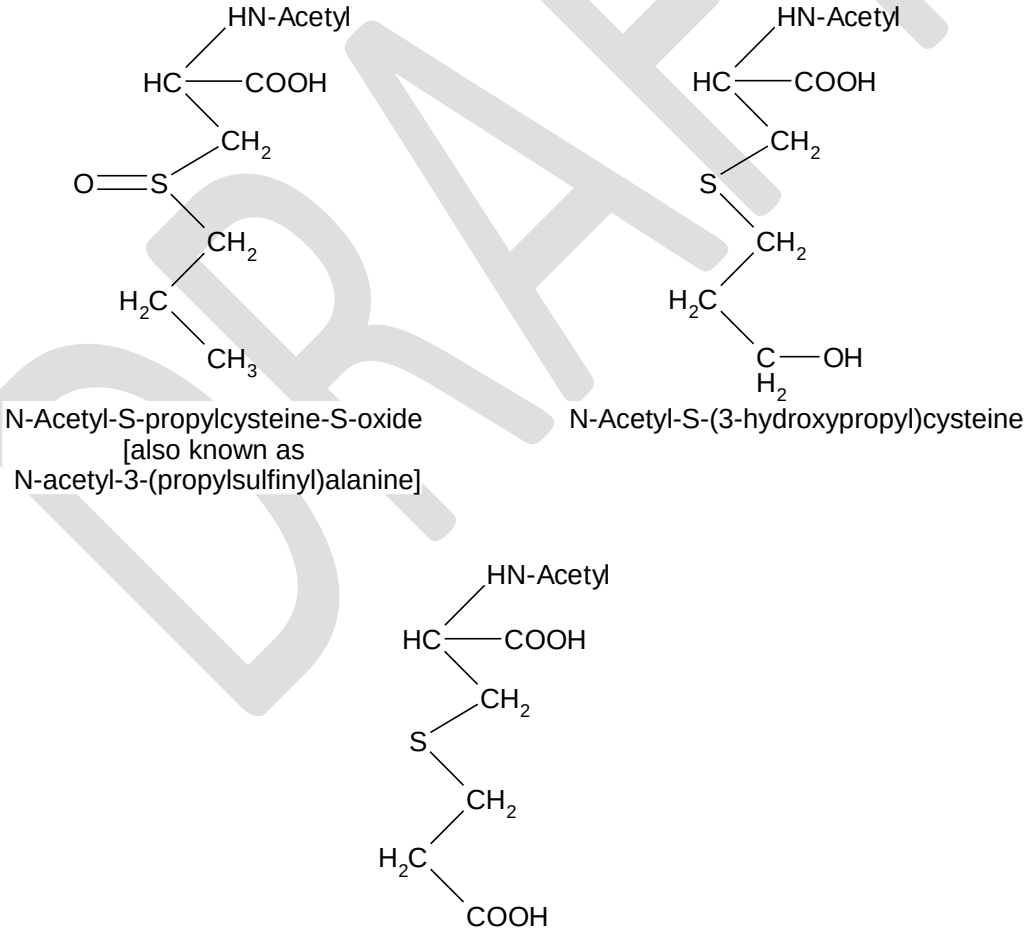
2. Pretreatment of rats with 1-aminobenzotriazole (ABT) before administration of single intravenous doses of ~20 mg/kg ^{14}C-1-BP or inhalation exposure to 800 ppm ^{13}C-1-BP for 6 hours caused decreased exhalation of radioactivity as CO_2 and decreased formation of oxidative urinary metabolites (Garner et al., 2006). ABT is an inhibitor of a number of CYP enzymes (Emoto et al., 2003).

3. Urinary metabolites derived from 1-bromo-2-propanol accounted for over half of all carbon-containing urinary metabolites identified in rats and mice exposed by inhalation or intravenous injection of ^{13}C-1-BP, and no 1-bromo-2-propanol-derived metabolites were found in urine of ABT-pretreated rats exposed to ^{13}C-1-BP (Garner et al., 2006). 1-Bromo-2-propanol and bromoacetone themselves were not detected in urine of 1-BP-exposed.

Figure_Apx N-1 Formation of N-Acetyl-S-Propylcysteine from 1-Bromopropane Via Conjugation with Reduced Glutathione (GSH)



Figure_Apx N-2 Mercapturic Acid Metabolites with a Sulfoxide Group or a Hydroxyl or Carbonyl Group on the Propyl Residue Identified in Urine Samples of 1-Bromopropane-Exposed Workers



Sources: (Cheever et al., 2009; Hanley et al., 2009)

Results from animal metabolic disposition studies indicate that 1-BP is eliminated from the body by exhalation of the parent material and metabolically derived CO_2 and by urinary excretion of metabolites (Garner et al., 2006; Jones and Walsh, 1979). Following single intraperitoneal injections of 200 mg/kg doses of [1-^{14}C]-1-BP in rats, about 60 and 1.4% of the administered dose was in parent material and CO_2 in air expired within 6 hours, respectively, and about 15% of the administered dose was in urine collected for 48 hours (Jones and Walsh, 1979). Following intravenous injection of [1-^{14}C]-1-BP at nominal doses of 5, 20, or 100 mg/kg, radioactivity in CO_2 exhaled in 48 hours accounted for about 28, 31, and 10% of the administered dose in rats, and 22, 26, and 19% in mice (Garner et al., 2006). Radioactivity in exhaled parent material accounted for about 25, 32, and 71% of the administered dose in rats, and 45, 39, and 48% in mice (Garner et al., 2006). Radioactivity in urine collected for 48 hours accounted for about 17, 19, and 13% of the administered dose in rats, and 23, 19, and 14% in mice (Garner et al., 2006). Radioactivity in feces accounted for <4% of administered doses, regardless of dose level, in both species (Garner et al., 2006).

Animal studies also show that the elimination of 1-BP from the body is rapid and accumulation in the body is not expected (Garner and Yu, 2014; Garner et al., 2006; Ishidao et al., 2002). Following intravenous injection of [1-^{14}C]-1-BP at nominal doses of 5, 20, or 100 mg/kg, radioactivity remaining in the carcass 48 hours after dose administration accounted for about 6, 6, and 2% of the administered dose in rats, and 4, 2, and 4% in mice (Garner et al., 2006). (Garner et al., 2006) proposed that radioactivity remaining in the carcass could represent covalently bound residues from reactive metabolites or incorporation of ^{14}C into cellular macromolecules from intermediate metabolic pathways. Following intravenous injection of 5 or 20 mg 1-BP/kg doses into rats, the mean half-times of elimination of 1-BP from the blood were 0.39 and 0.85 hours, respectively (Garner and Yu, 2014) . In gas uptake studies with male and female rats, calculated half-times of elimination for 1-BP were rapid and decreased with increasing air concentrations of 1-BP (Garner and Yu, 2014). Terminal elimination half-times were 0.5, 0.6, 1.1, and 2.4 hours for males, and 1.0, 1.0, 2.0, and 6.1 hours for females, exposed to initial air concentrations of 70, 240, 800, and 2,700 ppm, respectively. Pretreatment of female rats with ABT to inhibit CYP metabolism (intraperitoneal injection of 50 mg 1-BP/kg 4 hours prior to gas uptake measurements) or buthionine sulfoxime, an inhibitor of glutathione synthesis (1,000 mg 1-BP/kg/day orally for 3 days before gas uptake), resulted in longer elimination half-times: 9.6 hours with ABT and 4.1 hours with D,L-butionine(S,R)-sulfoximine (BSO), compared with 2.0 hours in untreated females at 800 ppm 1-BP in the gas uptake chamber (Garner and Yu, 2014). The results with the inhibitors show that both CYP mediated oxidative metabolism and glutathione conjugation play important roles in the elimination of 1-BP. Levels of 1-BP in blood decreased rapidly to detection limits within 0.7 hours after exposure stopped in Wistar rats exposed to 700 or 1,500 ppm 1-BP 6 hours/day for ≥3 weeks (Ishidao et al., 2002). Clearance of the bromide ion from blood and urine, however, showed slower elimination kinetics: elimination half-times for bromide were 4.7–15.0 days in blood and 5.0–7.5 days in urine (Ishidao et al., 2002) .

Based on urinary metabolites identified with nuclear magnetic resonance (NMR) spectroscopy, liquid chromatography-tandem mass spectrometry (LC-MS/MS), and high-performance liquid

chromatography (HPLC) radiochromatography (Garner et al., 2006), the scheme in Figure 3-5 also shows an initial conjugation of 1-BP with glutathione leading to N-acetyl-S-propylcysteine, an oxidation step from 1-bromo-2-propanol to alpha-bromohydrin, a glucuronic acid conjugation step from 1-bromo-2-propanol to 1-bromo-2-hydroxypropane-O-glucuronide, and glutathione conjugation of 1-bromo-2-propanol and bromoacetone followed by oxidation steps leading to metabolites with sulfoxide groups (e.g., N-acetyl-3-[(2-hydroxypropyl)sulfinyl] alanine). The steps involving oxidation of sulfur in the glutathione conjugate derivatives were proposed to be catalyzed by CYP oxygenases or flavin-containing monooxygenases (FMO) as suggested by Krause et al. (2002).

Catalysis of the oxidation steps by a number of CYP enzymes is supported by results from metabolic disposition studies in wild-type and *Cyp2e1-/-* knock-out mice (F1 hybrids of 129/Sv and C57BL/6N strains) exposed by inhalation to 800 ppm ^{13}C-1-BP for 6 hours (Garner et al., 2007). Three major metabolites were identified in urine collected from wild-type mice during exposure: N-acetyl-S-(2-hydroxypropyl) cysteine (34 µmoles in collected urine), 1-bromo-hydroxypropane-*O*-glucuronide (5 µmoles), and N-acetyl-S-propylcysteine (8 µmoles). In *Cyp2e1-/-* mice, the amounts of these metabolites in collected urine were changed to 21, 2, and 24 µmoles, respectively. The ratio of 2-hydroxylated metabolites to N-acetyl-S-propylcysteine was approximately 5:1 in wild-type and 1:1 *Cyp2e1-/-* mice. The results indicate that the elimination of CYP2E1 increased the relative importance of the glutathione conjugation pathway, but did not eliminate the formation of oxygenated metabolites, suggesting the involvement of other CYP enzymes, in addition to CYP2E1, in oxidation steps illustrated in Figure 3-5.

Evidence for the initial conjugation of 1-BP with glutathione leading to the formation of N-acetyl-S-propylcysteine comes from a number of studies in rats and mice (Garner et al., 2007; Garner et al., 2006; Khan and OBrien, 1991; Jones and Walsh, 1979).

1. N-Acetyl-S-propylcysteine was detected in the urine of wild-type and *Cyp2e1-/-* mice exposed to 800 ppm 1-BP for 6 hours, at molar ratios to hydroxylated metabolites of 5:1 and 1:1 (Garner et al., 2007).

2. N-Acetyl-S-propylcysteine and N-acetyl-3-(propylsulfinyl) alanine (i.e., N-acetyl-S-propylcysteine-S-oxide) accounted for approximately 39 and 5% of excreted urinary metabolites, respectively, in urine collected for 24 hours after inhalation exposure of rats to 800 ppm 1-BP for 6 hours (Garner et al., 2006).

3. N-Acetyl-S-propylcysteine was a relatively minor urinary metabolite in rats given single 5-mg 1-BP/kg intravenous doses, but accounted for >80% of urinary metabolites following administration of 100 mg 1-BP/kg (Garner et al., 2006).

4. N-Acetyl-S-propylcysteine and N-acetyl-S-propylcysteine-S-oxide were among the six mercapturic acid derivatives identified in urine from rats given 200 mg 1-BP/kg by gavage (in arachis oil) for 5 days (Jones and Walsh, 1979). The structures of the other

four mercapturic acid derivatives identified were consistent with glutathione conjugation of oxygenated metabolites of 1-BP, rather than 1-BP itself. These included N-acetyl-S-(2-hydroxypropyl) cysteine, N-acetyl-S-(3-hydroxypropyl) cysteine, and N-acetyl-S-(2-carboxyethyl) cysteine (Jones and Walsh, 1979). The techniques used in this study did not determine the relative amounts of the urinary mercapturic acid derivatives.

5. Isolated hepatocytes incubated for 60 minutes with 1-BP showed a decrease in glutathione content (from 58.4 to 40.8 nmol/10^6 cells), consistent with the importance of glutathione conjugation in metabolic disposition of 1-BP in mammals (Khan and OBrien, 1991).

Other studies have identified other metabolites, not included in Figure 3-5, in urine from rats and mice exposed to 1-BP Ishidao (Ishidao et al., 2002; Jones and Walsh, 1979) and in *in vitro* systems (Kaneko et al., 1997; Tachizawa et al., 1982; Jones and Walsh, 1979). (Jones and Walsh, 1979) reported detecting metabolites in urine from rats orally exposed to 1-BP that are consistent with the initial oxidation of the 3-C of 1-BP: N-acetyl-S-(3-hydroxypropyl) cysteine, 3-bromopropionic acid, and N-acetyl-S-(2-carboxyethyl) cysteine. (Garner et al., 2006) were not able to detect these metabolites in urine following administration of single intravenous doses up to 100 mg 1-BP/kg in rats or exposure to 800 ppm for 6 hours in rats or mice. (Garner et al., 2006) proposed that the apparent discrepancy may have been due to an amplification of minor metabolites from the pooling, concentration, and acid hydrolysis processes used in the earlier study. Glycidol (1,2-epoxy-3-propanol) was detected in urine of Wistar rats exposed by inhalation 6 hours/day to 700 ppm for 3 or 4 weeks or 1,500 ppm for 4 or 12 weeks; but no determination of the amount of this compound was made, and the report did not mention the detection of any other carbon-containing metabolites (Ishidao et al., 2002). (Kaneko et al., 1997) monitored the formation of n-propanol during incubation of rat liver microsomes with 1-BP. 3-Bromopropanol and 3-bromopropionic acid were detected when 1-BP was incubated in an *in vitro* oxidizing system, but 1-BP metabolism with rat liver homogenates was not examined due to the low water solubility of 1-BP (Jones and Walsh, 1979). Propene, 1,2-epoxypropane, 1,2-propanediol, and proprionic acid were detected when liver microsomes from phenobarbital-treated rats were incubated with 1-BP, and the addition of glutathione to the reaction mixture led to formation of S-(1' propyl)glutathione and S-(2' hydroxyl-1' propyl) glutathione (Tachizawa et al., 1982). (Garner et al., 2006) reported that propene, propylene oxide, propanediol, and propionic acid were not detected in liver homogenate incubations with 1-BP; they suggested that the use of phenobarbital as a CYP inducer may have resulted (in the (Tachizawa et al., 1982) studies) in the formation of metabolites not generated by constituitive CYP enzymes.

N-4 Elimination

Results from animal metabolic disposition studies indicate that 1-BP is eliminated from the body by exhalation of the parent material and metabolically derived CO_2 and by urinary excretion of metabolites (Garner et al., 2006; Jones and Walsh, 1979). Following single

intraperitoneal injections of 200 mg/kg doses of [1 ^{14}C]-1-BP in rats, about 60 and 1.4% of the administered dose was in parent material and CO_2 in air expired within 6 hours, respectively, and about 15% of the administered dose was in urine collected for 48 hours (Jones and Walsh, 1979). Following intravenous injection of [1 ^{14}C] 1 bromopropane at nominal doses of 5, 20, or 100 mg/kg, radioactivity in CO_2 exhaled in 48 hours accounted for about 28, 31, and 10% of the administered dose in rats, and 22, 26, and 19% in mice (Garner et al., 2006). Radioactivity in exhaled parent material accounted for about 25, 32, and 71% of the administered dose in rats, and 45, 39, and 48% in mice (Garner et al., 2006). Radioactivity in urine collected for 48 hours accounted for about 17, 19, and 13% of the administered dose in rats, and 23, 19, and 14% in mice (Garner et al., 2006). Radioactivity in feces accounted for <4% of administered doses, regardless of dose level, in both species (Garner et al., 2006).

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Appendix O ANIMAL AND HUMAN TOXICITY STUDIES CONSIDERED FOR USE IN RISK ASSESSMENT

O-1 Reproductive Toxicity

A two-generation reproduction study in rats reported adverse effects on male and female reproductive parameters (WIL Research, 2001). The majority of these effects exhibited a dose-response beginning at 250 ppm, with statistical significance at 500 ppm. The F_0 generation experienced significant dose-related decreases in male and female fertility indices at 500 ppm, and in mating indices at 750 ppm (fertility was 52% and 0% at 500 and 750 ppm, respectively). A significant increase in the number of females that displayed evidence of mating without delivery was also observed at 500 (10 of 25, 40%) and 750 ppm (17 of 25, 68%) in the F_0 generation. In the F_1 generation, the number of females that displayed evidence of mating without delivery at 500 ppm was greater than controls, but not statistically significant (8 of 25, 32% versus 3/25, 12% in treated and control dams, respectively). The number of males in the F_0 generation that did not sire a litter numbered 2, 0, 3, 12 and 25 (8, 0, 12, 48 and 100%) in the control, 100, 250 and 750 ppm groups respectively. In addition, two females treated at 500 ppm showed evidence of mating, and were gravid, but did not deliver litters. The number of implantation sites, actual number of litters produced, and live litter size were significantly reduced at 500 ppm in the F_0 and F_1 generations.

Significant changes in female reproductive parameters included a decrease in absolute and relative ovary weights at 750 ppm in the F_0 generation and an increase in estrous cycle length in F_0 and F_1 females (500 ppm). Estrous cycling was not observed in two F_0 females in the 500 ppm group, three F_0 females in the 750 ppm group, three F_1 females in the 250 ppm group, and four F_1 females in the 500 ppm group. This finding is supported by an inhalation study which showed significant treatment-related effects on estrous cycling in female rats and mice following three months of 1-BP inhalation exposure at ≥ 250 ppm (NTP, 2011).

The toxicological significance of these findings is underscored by related findings at comparable doses in F_0 and F_1 generations:

- Decreased fertility (significant in 500 and 750 ppm groups). Because both males and females were treated, the observed decreases in fertility could be due in part, to dose-related impairment of male reproductive function.
- An increase in the number of primordial follicles at the highest dose evaluated (750 ppm in F_0 and 500 ppm in F_1) and a decrease in the number of corpora lutea in F_0 females at ≥ 500 ppm (significant at 750 ppm; endpoint was not measured at 100 or 250 ppm).
- No difference in the numbers of corpora lutea was observed in F_1 females treated at 500 ppm as compared to control (no other doses were evaluated for this endpoint).
- A significantly decreased number of implantation sites in F_0 and F_1 females at ≥ 500 ppm (no implantations observed at 750 ppm).
- Decreased live litter size (significant at 500 ppm in F_0 and F_1 treatment groups).

Statistically significant changes in male reproductive and spermatogenic endpoints included:

- Decreased sperm motility and morphologically normal sperm in the F_0 (≥ 500 ppm) and F_1 generations (500 ppm)
- Reduced absolute weight of the left and right cauda epididymides at ≥ 500 ppm in F_0/F_1
- Decreased absolute prostate weight in F_0 (≥ 250 ppm) and F_1 males (500 ppm)
- Decreased seminal vesicle weight in F_0 (750 ppm) and F_1 males (250 ppm)
- Decreased mean epididymal sperm numbers in F_0 males at 750 ppm

These findings positively correlate with the negative effects on fertility observed at 500 ppm, and the complete lack of fertility observed in F_0 mating pairs treated at 750 ppm.

O-2 Neurotoxicity

A number of laboratory animal studies report that both acute and repeated inhalational exposure to high concentrations of 1-BP produce peripheral neurotoxicity indicated by changes in both function and structure of the peripheral nervous system. The degree or severity of peripheral neurotoxicity produced by 1-BP depends on the concentration as well as duration of exposure. Most studies using concentrations of ≥1000 ppm report ataxia progressing to severely altered gait, hindlimb weakness or loss of hindlimb control, convulsions, and death (e.g., (Banu et al., 2007; Yu et al., 2001; Fueta et al., 2000; Ichihara et al., 2000a; Ohnishi et al., 1999; ClinTrials, 1997a, b). Concentrations of 400-1000 ppm produce neuropathological changes including peripheral nerve degeneration, myelin sheath abnormalities, and spinal cord axonal swelling (Wang et al., 2002; Yu et al., 2001; Ichihara et al., 2000a).

Physiological and behavioral measures have been used to characterize and develop dose-response data for this peripheral neurotoxicity. Motor nerve conduction velocity and latency measured in the rat tail nerve were altered at ≥800 ppm with progressive changes observed from 4 to 12 weeks of exposure (Yu et al., 2001; Ichihara et al., 2000a). These findings in rats agree with neurological symptoms reported in exposed humans, including peripheral weakness, tingling in extremities, and gait disturbances. The nerve conduction velocity endpoint that was altered in rats (Yu et al., 2001; Ichihara et al., 2000a) is directly comparable to the increased latencies and lower conduction velocity measured in a population of female factory workers exposed to 1-BP (Li et al., 2010a; Li et al., 2010b; Ichihara et al., 2004b).

Behavioral tests such as grip strength, landing foot splay, traction (hang) time, and gait score provide dose-response data and appear somewhat more sensitive than neuropathology or physiological changes. Ichihara et al. (2000a) reported progressively worsening effects over 13 weeks of exposure at 400 and 800 ppm including decreased hindlimb and forelimb grip strength, and inability to walk on a slightly-sloped plane; exposure at 200 ppm significantly decreased hindlimb grip only at 4 weeks and otherwise was without effect. Hindlimb grip was preferentially decreased compared to forelimb as is often observed with peripheral neuropathy. Similarly decreased hindlimb strength was reported by Banu et al. (2007) after 6 weeks of 1-BP exposure at 1000 ppm (but not 400 ppm); these changes had not recovered at

14 weeks post exposure. Honma et al. (2003) measured the time for a rat to hang onto a suspended bar, which they called a traction test. The average time to hang appeared to be decreased following 21 days of exposure to 50 ppm, and was significantly so with 200 and 1000 ppm; these changes were still evident when animals were tested 7 days later. The ability to stay on a rotarod was not altered in these rats, suggesting that the weakness is peripherally mediated.

Results reported following oral dosing with 1-BP are similar to those reported following inhalation exposure. Over 16 weeks of dosing (200-800 mg/kg/d), Wang et al. (2012), reported progressively decreased hindlimb grip strength, wider landing foot splay, and increased gait abnormalities. The high-dose group was too debilitated to test after 14 weeks, but at that time their grip strength was decreased by 42%, somewhat comparable to the 56% decrease reported with 13 weeks of 800 ppm inhalational exposure (Ichihara et al., 2000a). Rats exposed to the lowest concentration of 200 mg/kg/d showed less, but still statistically significant changes in gait and decreased (9%) hindlimb grip strength. Subcutaneous administration of 455 or 1353 mg/kg/d (said to be equal to inhalation of 300 or 1000 ppm) over a 4 week period also produced changes in tail motor nerve function (Zhao et al., 1999) similar to the effects reported by others following inhalation exposure.

Some behavioral assays conducted in rats exposed to 1-BP reflect involvement of central as well as peripheral nervous systems. Increased motor activity levels were measured following inhalation of 50 or 200 ppm for three weeks (Honma et al., 2003). Spatial learning and memory measured in a Morris water maze was severely impaired while rats were receiving oral doses of 200 mg/kg/d and greater (Guo et al., 2015; Zhong et al., 2013). Guo et al. (2015) also reported that these cognitive deficits correlated with lowered levels of neuroglobin and glutathione depletion indicative of oxidative stress in the same rats. During inhalational exposure, water maze performance was impaired at concentrations of 200 ppm and above (Honma et al., 2003). However, these concentrations also produced neuromotor difficulties, which would interfere with performance of the task. There were no changes in water maze performance when training was initiated after exposure ended. Furthermore, there were no differences in memory of a passive avoidance task when the initial learning took place before exposures began (Honma et al., 2003).

A number of features reflecting CNS neurotoxicity have been reported for 1-BP. Brain pathology has been reported in several, but not all, studies, which may be due to experimental differences such as tissue sampling, staining, and measurement. Histological examination of the brain showed widespread pathology at 1000 and 1600 ppm, and mild myelin vacuolization at 400 ppm, following 28 days of exposure (ClinTrials, 1997b); however, the same testing laboratory reported no neuropathology with exposures up to 600 ppm for 13 weeks (ClinTrials, 1997a). In the cerebellum, exposure at 400 ppm and higher produced degeneration of Purkinje cells (Mohideen et al., 2013; Ohnishi et al., 1999) without morphological changes in the hippocampus (Mohideen et al., 2013). Similar exposure levels decreased noradrenergic but not serotonergic axonal density in frontal cortex and amygdala (Guo et al., 2015; Mohideen et al., 2011). In contrast to these reports, no degeneration was observed across several brain sections

up to 800 ppm despite marked peripheral and spinal cord changes in the same rats (Wang et al., 2002; Ichihara et al., 2000a). In two other studies conducted in the same laboratory, one reported no histological or morphological changes in brain following exposures up to 1250 ppm for 13 weeks (Sohn et al., 2002) and another reported no neuropathology after daily exposures of 1800 ppm for up to eight weeks (Kim et al., 1999a), even though in the latter study other indicators of neurotoxicity were observed.

Decreased absolute brain weight has been reported in several studies, both in the context of adult exposures and long-term exposures during a 2-generation reproductive study. Studies involving exposures from 4 to 12 weeks reported decreased brain weight at 800 and 1000 ppm (Subramanian et al., 2012; Wang et al., 2003; Ichihara et al., 2000a). Kim et al. (1999a) also reported decreased brain weight at 300 ppm for 8 weeks, but only provided relative brain:body weight data. In the parental generation of a 2-generation study, exposure for at least 16 weeks also produced brain weight changes, with males being more sensitive (NOAEL=100 ppm, LOAEL=250 ppm) than females (NOAEL=250 ppm) (WIL Research, 2001). The F_1 generation, which was exposed during gestation and at least 16 weeks after weaning, had lower brain weight at 100 ppm in males, and again females were less sensitive (NOAEL=250 ppm). Histopathological evaluations in the WIL study revealed no correlative macroscopic or microscopic alterations in unperfused brain tissue. Two studies have measured brain weight and reported no effects: 1) (Wang et al., 2002), in which exposure was only 7 days and may not have been a sufficient exposure duration, and 2) the 13-wk study of (ClinTrials, 1997a), even though the same laboratory reported decreased brain weight at the same concentration with only 4 weeks of exposure.

Fueta and colleagues (Fueta et al., 2007; Ueno et al., 2007; Fueta et al., 2004; Fueta et al., 2002a; Fueta et al., 2002b; Fueta et al., 2000), reported a series of studies using electrophysiological measures of hippocampal slices (dentate gyrus and CA1 regions) from rats exposed to 1-BP for four to 12 weeks. Concentrations of 400 ppm and higher showed disinhibition in paired-pulse population spikes, and the effect was dependent on exposure concentration and duration. This hyperexcitability appeared to be due to a reduction in feedback inhibition rather than a change in excitatory synaptic drive. There was a moderate correlation with the level of bromide ion in the brain. Pharmacological probes, proteins and receptor mRNA levels suggest that these effects are related to actions on the GABA and NMDA neural systems, and/or intracellular signaling cascades (Ueno et al., 2007; Fueta et al., 2004; Fueta et al., 2002a; Fueta et al., 2002b). A recent Society of Toxicology presentation (abstract only available) reported similar effects in hippocampal slices from 14-day old rat pups whose mothers were exposed to 400 or 700 ppm during gestation (Fueta et al., 2013).

A number of investigators have probed potential molecular mechanisms for some of these CNS effects. Exposures of 200 ppm and greater produce changes in biomarkers and proteome expressions suggesting alterations in the function and maintenance of neural and astrocytic cell populations. Some of these include indicators of oxidative stress (reactive oxygen species, glutathione depletion), ATP loss, protein damage, altered apoptotic signaling, neurotransmitter dysregulation, decreased hippocampal neurogenesis, and others (Huang et al., 2015; Mohideen

et al., 2013; Zhang et al., 2013; Zhong et al., 2013; Huang et al., 2012; Subramanian et al., 2012; Huang et al., 2011; Yoshida et al., 2007; Wang et al., 2003; Wang et al., 2002). Concentrations as low as 50 ppm for three weeks were reported to decrease levels of the serotonin metabolite 5-HIAA in frontal cortex and taurine in midbrain, while concentrations of 200 ppm and greater impacted additional markers (protein levels, mRNA) of monoaminergic and amino acid neurotransmitter systems (Zhang et al., 2013; Mohideen et al., 2009; Suda et al., 2008; Ueno et al., 2007). Overall these data suggest several and perhaps overlapping cellular and molecular mechanisms that could contribute to the functional and structural alterations reported for 1-BP.

O-3 Human Case Reports

Several case studies have reported various neurological effects in workers exposed to 1-BP (Samukawa et al., 2012; CDC, 2008; Majersik et al., 2007; Raymond and Ford, 2007; Ichihara et al., 2002; Sclar, 1999). Some of the neurological effects experienced by workers included peripheral neuropathy, muscle weakness, pain, headaches, numbness, gait disturbance, confusion, ocular symptoms, slowed mental activity, and dizziness. In some instances, the effects were still observed many months after exposure had ceased or had been reduced.

Workers described in the case reports were exposed to 1-BP in the following activities: metal cleaning, circuit board cleaning, and gluing foam cushions or furniture. In almost all of the cases reported in the table below, personal protective equipment was not used and air concentrations of 1-BP, when available, were greater than 100 ppm. Bromide levels, both serum and in a few cases, urinary, were provided in some of the studies and are included in the table below. Bromide concentrations have been used as a biomarker of exposure to 1-BP. A description of the use of bromide levels and the investigation into using other biomarkers of exposure are included in Section 2.3 of the 1-BP Report.

(Raymond and Ford, 2007) reported high levels of urinary arsenic, as well as serum bromide, in the workers described in their case report of four employees who required hospitalization, suggesting arsenic and bromide synergism. All four of the workers had total (organic and inorganic) urinary arsenic levels greater than 200 µg/L, but the source of the arsenic could not be identified. NIOSH reported on these 4 employees in a HHE on a plant where workers applied spray adhesive to cushions, and concluded that the exposure was likely not occupational and could not have been the sole cause of ataxia and paresthesias that the four hospitalized workers experienced

Table_Apx O-1 Case Reports on 1-BP

Reference	# Cases	Primary Symptoms	Activity	Air levels	Serum Bromide levels (mg/dL)[1]
(Majersik et al., 2007)	6	Headache, nausea, dizziness, lower extremity numbness, pain, paresthesias, difficulty walking/balance	Foam cushion gluing at furniture plant (glue contained 70% 1-BP)	130 ppm (range, 91-176); TWA 108 ppm (range, 92-127)	Peak range: 44-170
(Sclar, 1999)	1	Peripheral neuropathy, weakness of lower extremities and hand, numbness, dysphagia	Metal stripping (degreasing and cleaning)	Not available	Not available
(CDC, 2008)	2	Confusion, dysarthria, dizziness, paresthesias, ataxia; Headache, nausea, dizziness, malaise	Cleaning circuit boards (spray) Solvent in dry cleaning	178 ppm 75-250x background levels	48 mg/dL and not available for case #2
(Samukawa et al., 2012)	1	Muscle weakness, pain, numbness in lower extremities, gait disturbance	Metal cleaning	553 ppm, mean TWA (range, 353-663)	58 µg/mL (peak)
(Raymond and Ford, 2007) (4 cases from NIOSH (2003) HHE report on Marx Industries)	4	Dizziness, anorexia, dysesthesias, nausea, numbness, ocular symptoms, unsteady gait, weakness, weight loss	Gluing in furniture making	Mean 107 ppm (range, 58-254 ppm) collected 9 months after workers became ill	3.0 - 12.5 mEq/L (100 mg/dL) Arsenic levels > 200 µg/L for all 4 employees[2]
(NIOSH, 2003)	16 (incl. 4 from Raymond (2007)	Headache, anxiety, feeling “drunk”, numbness and “pins and needles”	Spray application of glue to polyurethane foam to	1999 (16 personal breathing zone samples):	Serum GM: 4.8 mg/dL (2.7-43.5; n=39); Urinary:

Table_Apx O-1 Case Reports on 1-BP

Reference	# Cases	Primary Symptoms	Activity	Air levels	Serum Bromide levels (mg/dL)[1]
		sensation in legs and feet	make cushions	GM 81.2 ppm (range, 18-254 ppm); 2001 (13 PBZ samples): GM 45.7 ppm (range, 7-281 ppm)	46.5 mg/dL (15.4-595.4, n=40) Includes both exposed and "unexposed workers
(Ichihara et al., 2002)	3	Staggering gait, paresthesia in lower extremities, numbness in legs, headache, urinary incontinence, decr in vibration sense in legs	Spray application of glue to polyurethane foam to make cushions	Mean 133 ppm, (range, 60-261 ppm daily TWA); avg over 11 days 133 ± 67 ppm--after ventilation improved	Not available
Biomarker Studies also Containing Case Report Data					
(Hanley et al., 2006)	13	(focused on exposure and urinary Br)	Spray application of glue to polyurethane foam to make cushions	Mean 92 ppm (range, 45-200 ppm)	Urinary: 190 (43-672; composite of 2 days)
(Ichihara et al., 2004b; Ichihara et al., 2004a)	24 female 13 male China	Nose, throat, eye irritation; malaise, headache, dizziness	1-BP production	3.3-90.2 ppm No severe neurological effects < 170 ppm	Urinary bromide measured but not reported

[1]Serum bromide unless otherwise indicated; Reference ranges vary by report
[2]Arsenic Reference range: <0.06

O-4 Human Epidemiology Studies

Three studies of workers occupationally exposed to 1-BP were located in the literature (Li et al., 2010a; Toraason et al., 2006; Ichihara et al., 2004b), two of the studies report neurologic effects and the third describes DNA damage in workers' leukocytes.

Twenty-three female workers involved in 1-BP production in China were surveyed in 2001 and compared with age-matched controls from a beer factory located in the same city (Ichihara et al., 2004b). The study authors did not report the method of recruitment. Neurological tests (vibration sensation, electrophysiologic studies), blood tests, neurobehavioral tests and postural sway tests were administered. Passive sampling indicated individual exposure levels ranging from 0.34 – 49.2 ppm in an 8-hour shift (median 1.61 ppm; geometric mean 2.92 ppm). Some of the employees in this plant were also exposed to 2-BP and were analyzed separately. Although some of the neurologic measures indicated reduced function in exposed workers compared to controls, because of the past exposures to 2-BP and the small number of cases who entered the study after 2-BP was no longer used (n= 12 pairs), it was difficult to interpret the results of this study. In workers who were employed at the plant after 2-BP was no longer used, Benton visual memory test scores, POMS depression, and POMS fatigue were significantly different. It is not clear whether this indicates a lack of power to detect differences in the larger group or whether the exposure to 2-BP affected the results.

As a follow-up to the Ichihara et al. 2004 study described above, (Li et al., 2010a) combined data from three 1-BP production facilities in China to analyze a larger sample of workers. Sixty female and 26 male workers and controls from other types of factories matched by age, sex and geographic region were analyzed from four time periods (2001, 2003, 2004, 2005). Data were collected over 3 days between 2001 and 2005. The authors did not describe the recruitment process, and it is not clear whether the same workers included in the Ichihara 2004 study were recruited for this study. The authors reported that none of the workers had a history of diabetes.

Exposures were measured for each plant using passive samplers. Exposure was measured either once or twice over 8 or 12 hour work shifts. TWA exposure concentrations to 1-BP ranged from 0.07-106.4 ppm for female workers and 0.06-114.8 ppm for male workers. It was reported that none of the workers wore gloves or masks in the plant. However, the authors later clarified that some workers wore gloves (Ichihara et al., 2011). Employees were placed into low-, medium-, and high-exposure groups (for females) to include equal numbers. Median exposures for the three groups (n=20 per group) were 1.28, 6.60 and 22.58 ppm for females and 1.05 (low) and 12.5 (high) ppm for males (n=13 per group). Ambient exposure levels varied by job and by plant and were collected in different years for each plant. For example, the ambient concentrations of “raw product collection” were more than 3 times higher at the Yancheng plant (analyzed in 2003) than at the Yixing plant (Li et al., 2010a).

Clinical chemistries were obtained, and electrophysiological studies and neurological and neurobehavioral tests were conducted for each employee. A single neurologist performed most of the neurological assessments except for those collected in 2004 from one plant, which included 5 female workers. Electrophysiological tests conducted included: motor nerve conduction velocity, distal latency (DL), F-wave conduction velocity in the tibial nerve, sensory nerve conduction velocity in the sural nerve (SNCV), and amplitude of the electromyogram induced by motor nerve stimulation, F-wave, and potential of sensory nerve. Vibration sense,

reflex, and muscle strength were measured using a tuning fork on the big toe. Neurobehavioral tests and blood tests were also performed.

In regression analyses, the authors reported a statistically significant increase (p<0.05) in mean tibial motor distal latency and a decrease in mean sural nerve conduction velocity in women in the middle exposure group only (compared to controls). Statistically significant decreased vibration sense in toes (vibration loss) was reported in all exposure groups compared to controls. In addition, thyroid stimulating hormone (TSH) was significantly different in the middle and high exposure groups compared to controls and FSH in low and medium exposure groups in females. Red blood cell count was significantly decreased in all exposure groups compared to controls in females. In males, the only statistically significant difference between the high exposure group and controls was for blood urea nitrogen.

Analyses of cumulative exposure measures (exposure level x duration) indicated statistically significant (p<0.05) increases in vibration sense in toes in females across all exposure levels when compared to controls (5.6 ± 4.3, 6.4 ± 3.8, and 6.5 ± 3.4 secs, mean ± SD for low, medium and high cumulative exposure groups, respectively). In females, only the high cumulative exposure group for tibial motor DL was statistically higher than in controls and only the low cumulative exposure group for sural NCV. Analyses to adjust for other factors that could influence vibration loss (examining neurologist, age, height, body weight, alcohol consumption) were conducted using analysis of covariance in female workers. The effect of 1-BP exposure on vibration loss was significant (p = 0.0001 or p = 0.0002) based on cumulative exposures as well as exposures not considering duration of exposure, respectively, but the effect of examining neurologist was also significant (p < 0.0001).

Both of the neurological studies described above (Li et al., 2010a; Ichihara et al., 2004b) showed neurological effects related to 1-BP exposure. The co-exposures to 2-BP and the small sample size of workers exposed only to 1-BP was a limitation in the Ichihara et al. 2004 study. Li et al. (2010a) selected workers exposed to 1-BP from 3 plants to include more study participants; however, the exposure data reported by plant were limited, the job activities were somewhat different between plants (but for those jobs with similar activities between plants, some exposures were more than 3 times higher at one plant than another), and ambient exposure levels of 1-BP and 2-BP reported by job and by plant were collected in different years for each plant. Several of these issues could lead to exposure misclassification of the workers. TWAs (8- and 12- hour) were used to assign exposure groups, based on either 1 or 2 samples. Using the TWA does not account for the fluctuations or potential peaks that may have occurred during the shift. In addition, the median exposure level of the high exposure group for females was 22.58 ppm but the range was 15.28-106.4 ppm, indicating that some of the workers were exposed to levels much higher than the lowest exposed workers in that group. In addition, the cumulative exposure measures were based on only 1-3- day measurements of individual exposure levels.

Skin temperature is important when conducting electrophysiological studies; however, the only control for temperature in this study was to acclimate study participants to 24^{o} C in a room for

30 minutes. Individual skin temperatures should have been taken at the site of the test (on the foot) because the results are affected by temperature. Vibration sense can be influenced by BMI, but it was not reported or controlled in the study. As acknowledged in the report by the study authors, vibration sense is inherently imprecise (based on the sensitivity of the subject relative to the examiner). Evidence of a high degree of variability was shown in the large standard deviations reported for vibration sense in females (2.9 ± 3.9, mean ± SD for controls; 5.6 ± 4.4, low exposure group). Other than RBC, only vibration sense in females using the cumulative exposure measure was concentration-dependent. RBC in females could have been influenced by other factors (e.g., menstruation, dehydration) that were not examined in the study.

Toraason et al. (2006) analyzed DNA damage in peripheral leukocytes of workers exposed to 1-BP during spray application of adhesives in the manufacture of foam cushions for upholstered furniture. Sixty-four workers (18 males, 46 females) at two plants were included in the analysis. There were no unexposed groups. Fifty of 64 workers wore personal air monitors for 1-3 days. Workers employed as sprayers had the highest exposures; 1-BP 8-hr TWA concentrations were substantially higher (4 times) for sprayers at one of the plants than the other. TWA exposures ranged from 0.2 to 271 ppm across both plants. DNA damage was assessed using comet assay. DNA damage was measured by tail moment in leukocytes of workers. At both the start and end of the work week, DNA leukocyte damage was higher for sprayers than non-sprayers but the increases were not statistically significant. In addition, the facility with lower exposures had higher measures of DNA damage than the higher exposure facility at the beginning of the week but not the end. Tail moment dispersion coefficients did not indicate an exposure-response relationship. Three different biomarkers of exposure, 1-BP TWA concentrations and serum and urinary bromide levels, were evaluated in multivariate analyses. After controlling for various potential confounders, starting and ending work week comet tail moments in leukocytes were significantly associated with serum bromide quartiles and ending work week values of 1-BP TWA concentrations. None of the models that examined associations between DNA damage and dispersion coefficients was statistically significant. There was a slight risk for DNA damage in workers' leukocytes in vitro in workers exposed to 1-BP but the results of the in vivo data were not consistent.

Table_Apx O-2 Summary of the Epidemiological and Toxicological Database for 1-BP

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Death	Rat (n=10/group)	Inhalation	6040, 7000, 7400 or 8500 ppm	4 hours	LC_{50} = 7000	Death (acute inflammatory response and alveolar edema)	(Elf Atochem S.A., 1997)	GLP study - provides evidence of a steep concentration-response curve for lethality
Death	Rat (n=10/group)	Inhalation	11,000, 13,000, 15,000 or 17,000 ppm	4 hours	LC_{50} = 14,374	Death	(Kim et al., 1999b)	GLP study - evidence of steep concentration response curve for lethality
Death	Rat (male) (n=50/group)	Inhalation	125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 105 weeks	NOAEL= 250	Decreased survival	(NTP, 2011)	GLP study - cause of death attributed to neoplasms not related to 1-BP exposure
Death	Mouse (male) (n=5/group)	Inhalation	125, 250, 500, 1000 or 2000 ppm	6.2 hours/day, 5 days/week for 17 days	NOAEL= 250	Decreased survival	(NTP, 2011)	GLP study - cause of death was not specified
Death	Mouse (male) (n=24/group)	Inhalation	50, 110 or 250 ppm	8 hours/day, 7 days/week for 4 weeks	NOAEL= 110	Death (two of three strains affected)	(Liu et al., 2009)	GLP study - hepatocellular necrosis observed at 250 ppm in all strains
Death	Mouse (female) (n=8/group)	Inhalation	125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 4 or 10 weeks	NOAEL= 250	Death (first week on study)	(Anderson et al., 2010)	GLP study - cause of death not specified
Death	Mouse (n=20/group)	Inhalation	62.5, 125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 14 weeks	NOAEL= 250	Decreased survival rate	(NTP, 2011)	GLP study - cause of death was not specified
Death	Rat (n=10/group)	Oral	2000 mg/kg	Single exposure	LD_{50} > 2000	Death	(Elf Atochem S.A., 1993a)	GLP study - no route-to-route extrapolation
Body weight	Rat (male) (n=10/group)	Inhalation	6040, 7000, 7400 or 8500 ppm	4 hours	NOAEL= 8500	No effects on body weight	(Elf Atochem S.A., 1997)	GLP study

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Body weight	Rat (male) (n=9/group)	Inhalation	200, 400 or 800 ppm	8 hours/day for 7 days	NOAEL= 400	Decreased body weight	(Wang et al., 2002)	GLP study - data on food consumption not provided
Body weight	Rat (male) (n=12/group)	Inhalation	400, 800 or 1000 ppm	8 hours/day for 7 days	NOAEL= 400	Decreased body weight	(Zhang et al., 2013)	GLP study - data on food consumption not provided
Body weight	Rat (n=10/group)	Inhalation	125, 250, 500, 1000 or 2000 ppm	6.2 hours/day, 5 days/week for 16 days	NOAEL= 1000	Decreased body weight	(NTP, 2011)	GLP study - data on food consumption not provided
Body weight	Rat (male) (n=5/group)	Inhalation	10, 50, 200 or 1000 ppm	8 hours/day, 7 days/week for 3 weeks	NOAEL= 50	Increased body weight	(Honma et al., 2003)	GLP study - corresponding changes in food consumption noted
Body weight	Rat (female) (n=7-8/group)	Inhalation	50, 200 or 1000 ppm	8 hours/day, 7 days/week for 3 weeks	NOAEL= 1000	No effects on body weight	(Sekiguchi et al., 2002)	GLP study - data on food consumption not provided
Body weight	Rat (n=20/group)	Inhalation	398, 994 or 1590 ppm	6 hours/day, 5 days/week for 4 weeks	NOAEL= 398	Decreased weight gain	(ClinTrials, 1997b)	GLP study - decreased food consumption noted
Body weight	Rat (male) (n=12/group)	Inhalation	400, 800 or 1000 ppm	8 hours/day, 7 days/week for 4 weeks	NOAEL= 800	Decreased body weight	(Subramanian et al., 2012)	GLP study - data on food consumption not provided
Body weight	Rat (male) (n=9/group)	Inhalation	1000 ppm	8 hours/day, 7 days/week for 5 or 7 weeks	LOAEL= 1000	Decreased body weight	(Yu et al., 2001)	Not suitable for dose-response analysis because only one exposure group was used
Body weight	Rat (male) (n=24/group)	Inhalation	400, 800 or 1000 ppm	8 hours/day, 7 days/week for 6 weeks	NOAEL= 400	Decreased body weight	(Banu et al., 2007)	GLP study - data on food consumption were not provided
Body weight	Rat (n=20/group)	Inhalation	50, 300 or 1800 ppm	6 hours/day, 5 days/week for 8 weeks	NOAEL= 300	Decreased body weight	(Kim et al., 1999a)	GLP study - no change in food consumption
Body weight	Rat (male) (n=9/group)	Inhalation	200, 400 or 800 ppm	8 hours/day, 7 days/week for 12 weeks	NOAEL= 200	Decreased body weight	(Ichihara et al., 2000a)	GLP study - data on food consumption not provided

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Body weight	Rat (male) (n=9/group)	Inhalation	200, 400 or 800 ppm	8 hours/day, 7 days/week for 12 weeks	NOAEL= 200	Decreased body weight	(Wang et al., 2003)	GLP study - data on food consumption were not provided
Body weight	Rat (female) (n=10/group)	Inhalation	200, 400 or 800 ppm	8 hours/day, 7 days/week for up to 12 weeks	NOAEL= 400	Decreased body weight	(Yamada et al., 2003)	GLP study - data on food consumption were not provided
Body weight	Rat (n=30/group)	Inhalation	100, 200, 400 or 600 ppm	6 hours/day, 5 days/week for 13 weeks	NOAEL= 600	No effects on body weight	(ClinTrials, 1997a)	GLP study - no change in food consumption
Body weight	Rat (n=10/group)	Inhalation	200, 500, or 1250 ppm	6 hours/day, 5 days/week for 13 weeks	NOAEL= 1250	No effects on body weight	(Sohn et al., 2002)	GLP study
Body weight	Rat (male) (n=10/group)	Inhalation	62.5, 125, 250 or 1000 ppm	6.2 hours/day, 5 days/week for 14 weeks	NOAEL= 500	Decreased body weight	(NTP, 2011)	GLP study data on food consumption not provided
Body weight	Rat (n=100/group)	Inhalation	125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 105 weeks	NOAEL= 500	No effects on body weight	(NTP, 2011)	GLP study data on food consumption not provided
Body weight	Rat (female) (n=10/group)	Inhalation	100, 199, 598 or 996 ppm	6 hours/day on GDs 6-19 and lactation days 4-20	NOAEL= 100	Decreased body weight gain during gestation	(Huntingdon Life Sciences, 1999)	GLP study – observed body weight changes were not statistically significant
Body weight	Rat (female) (n=25/group)	Inhalation	103, 503 or 1005 ppm	6 hours/day on GDs 6-19	NOAEL= 103	Decreased body weight gain during gestation	(Huntingdon Life Sciences, 2001)	GLP study
Body weight	Rat (female) (n=10/group)	Inhalation	100, 400 or 800 ppm	8 hours/day during gestation (GDs 0-20) and lactation (PNDs 1-20)	NOAEL= 400	Decreased body weight at PND 21	(Furuhashi et al., 2006)	Quantitative body weight data provided for the high-exposure group only

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Body weight	Rat (female) (n = 8-25/group)	Inhalation	100, 250, 500 or 750 ppm	6 hrs/day during pre-mating (≥ 70 days), through mating, and until sacrifice in males; or until GD 20 and from PND 5 until weaning of offspring (~PND 21) in females	NOAEL= 250	Decreased body weight (F_0 and F_1)	(WIL Research, 2001)	GLP study peer-reviewed by NTP
Body weight	Mouse (male) (n=5/group)	Inhalation	125, 250, 500, 1000 or 2000 ppm	6.2 hours/day, 5 days/week for 17 days	NOAEL= 500	Decreased body weight gain	(NTP, 2011)	GLP study – effect not observed in females
Body weight	Mouse (male) (n=24/group)	Inhalation	50, 110 or 250 ppm	8 hours/day, 7 days/week for 4 weeks	NOAEL= 250	No effects on body weight	(Liu et al., 2009)	GLP study
Body weight	Mouse (female) (n=8/group)	Inhalation	125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 4 or 10 weeks	LOAEL= 125	Decreased body weight	(Anderson et al., 2010)	GLP study - effects on body weight only observed in mice exposed for 4 weeks
Body weight	Mouse (n=20/group)	Inhalation	62.5, 125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 14 weeks	NOAEL= 500	No effects on body weight	(NTP, 2011)	GLP study - body weights appeared to stay within 10% of controls based on data presented graphically in the study report
Body weight	Mouse (n=100/group)	Inhalation	62.5, 125 or 250 ppm	6.2 hours/day, 5 days/week for 105 weeks	NOAEL= 250	No effects on body weight	(NTP, 2011)	GLP study
Body weight	Rat (n=10/group)	Oral	2000 mg/kg	Single exposure	NOAEL=2000	No effects on body weight	(Elf Atochem S.A., 1993a)	GLP study - not able to do route-to-route extrapolation

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Body weight	Rat (male) (n=10/group)	Oral	200, 400 or 800 mg/kg-day	12 days	NOAEL= 400	Decreased final body weight. Used for weight of evidence; no route-to-route extrapolation.	(Zhong et al., 2013)	GLP study - not able to do route-to-route extrapolation
Body weight	Rat (male) (n=7/group)	Oral	1000 mg/kg-day	14 days	LOAEL= 1000	Decreased body weight	(Xin et al., 2010)	GLP study – not able to do route-to-route extrapolation
Body weight	Rat (male) (n=10/group)	Oral	200, 400 or 800 mg/kg-day	16 weeks	NOAEL= 400	Decreased body weight	(Wang et al., 2012)	Abstract in English, with partial translation of study methods and results provided by primary author. GLP study - not able to do route-to-route extrapolation
Body weight	Rat (male) (n=14/group)	Oral	100, 200, 400 or 800 mg/kg-day	12 days	NOAEL=400	Decreased body weight	(Guo et al., 2015)	GLP study - not able to do route-to-route extrapolation
Body weight	Mouse (female) (n=5/group)	Oral	200, 500 or 1000 mg/kg	Single exposure for 6, 12, 24 or 48 hrs	NOAEL= 1000	No effects on body weight	(Lee et al., 2007)	GLP study - not able to do route-to-route extrapolation
Body weight	Mouse (male) (n=20/group)	Oral	300 or 600 mg/kg-day	Exposed for 10 days prior to mating	NOAEL= 600	No effects on body weight	(Yu et al., 2008)	GLP study - not able to do route-to-route extrapolation
Cardiovascular	Rat (male) (n=9/group)	Inhalation	200, 400 or 800 ppm	8 hours/day, 7 days/week for 12 weeks	NOAEL= 800	No effects on heart weight or histopathology	(Ichihara et al., 2000b)	GLP study - conducted in males only, peer reviewed literature

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Cardiovascular	Rat (n=20/group)	Inhalation	50, 300 or 1800 ppm	6 hours/day, 5 days/week for 8 weeks	NOAEL= 1800	No effects on heart weight or histopathology	(Kim et al., 1999a)	GLP study, peer reviewed literature
Cardiovascular	Rat (n=30/group)	Inhalation	100, 200, 400 or 600 ppm	6 hours/day, 5 days/week for 13 weeks	NOAEL= 600	No effects on heart weight or histopathology	(ClinTrials, 1997a)	GLP study
Cardiovascular	Rat (n=20/group)	Inhalation	62.5, 125, 250, 500 or 1000 ppm	6.2 hours/day, 5 days/week for 14 weeks	NOAEL= 1000	No effects on heart weight	(NTP, 2011)	GLP study
Cardiovascular	Rat (n=100/group)	Inhalation	125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 105 weeks	NOAEL= 500	No effects on histopathology	(NTP, 2011)	GLP study
Cardiovascular	Mouse (male) (n=5/group)	Inhalation	125, 250, 500, 1000 or 2000 ppm	6.2 hours/day, 5 days/week for 17 days	NOAEL= 2000	Decreased absolute and relative heart weight	(NTP, 2011)	GLP study
Cardiovascular	Mouse (n=20/group)	Inhalation	62.5, 125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 14 weeks	NOAEL= 500	No effects on heart weight or histopathology	(NTP, 2011)	GLP study
Cardiovascular	Mouse (n=50/group)	Inhalation	62.5, 125 or 250 ppm	6.2 hours/day, 5 days/week for 105 weeks	NOAEL= 250	No effects on histopathology	(NTP, 2011)	GLP study
Dermal	Rat (n=30/group)	Inhalation	100, 200, 400 or 600 ppm	6 hours/day, 5 days/week for 13 weeks	NOAEL= 600	No effects on histopathology	(ClinTrials, 1997a)	GLP study - no route-to-route extrapolation
Dermal	Rat (n=20/group)	Inhalation	62.5, 125, 250, 500 or 1000 ppm	6.2 hours/day, 5 days/week for 14 weeks	NOAEL= 1000	No effects on histopathology	(NTP, 2011)	GLP study - no route-to-route extrapolation
Dermal	Rat (n=100/group)	Inhalation	125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 105 weeks	NOAEL= 500	No effects on histopathology	(NTP, 2011)	GLP study - no route-to-route extrapolation
Dermal	Mouse (n=20/group)	Inhalation	62.5, 125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 14 weeks	NOAEL= 500	No effects on histopathology	(NTP, 2011)	GLP study - no route-to-route extrapolation
Dermal	Mouse (n=100/group)	Inhalation	62.5, 125 or 250 ppm	6.2 hours/day, 5 days/week for 105 weeks	NOAEL= 250	No effects on histopathology	(NTP, 2011)	GLP study - no route-to-route extrapolation

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Endocrine	Human (60 female; 26 male)	Inhalation	0.06-114.8 ppm (8-hr TWA concentration)	About 40 months		Statistically significant Increase in serum TSH in middle and high exposure group compared to controls; FSH higher in low and middle exposure group in females	(Li et al., 2010a)	Limited evaluation of worker exposure, peer reviewed literature
Endocrine	Rat (male) (n=12/group)	Inhalation	400, 800 or 1000 ppm	8 hours/day for 7 days	NOAEL= 1000	No effects on adrenal gland weight or plasma corticosterone	(Zhang et al., 2013)	GLP study, peer reviewed literature
Endocrine	Rat (n=20/group)	Inhalation	50, 300 or 1800 ppm	6 hours/day, 5 days/week for 8 weeks	NOAEL= 1800	No effects on organ weights or histopathology	(Kim et al., 1999a)	GLP study, peer reviewed literature
Endocrine	Rat (male) (n=9/group)	Inhalation	200, 400 or 800 ppm	8 hours/day, 7 days/week for 12 weeks	NOAEL= 800	No effects on organ weights or histopathology	(Ichihara et al., 2000a; Ichihara et al., 2000b)	GLP study - conducted in males only, peer reviewed literature
Endocrine	Rat (female) (n=10/group)	Inhalation	200, 400 or 800 ppm	8 hours/day, 7 days/week for up to 12 weeks	NOAEL= 800	No effects on organ weights or histopathology	(Yamada et al., 2003)	GLP study - conducted in females only, peer reviewed literature
Endocrine	Rat (n=30/group)	Inhalation	100, 200, 400 or 600 ppm	6 hours/day, 5 days/week for 13 weeks	NOAEL= 600	No effects on organ weights or histopathology	(ClinTrials, 1997a)	GLP study
Endocrine	Rat (n=20/group)	Inhalation	62.5, 125, 250, 500 or 1000 ppm	6.2 hours/day, 5 days/week for 14 weeks	NOAEL= 1000	No effects on organ weights	(NTP, 2011)	GLP study

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Endocrine	Rat (n=100/group)	Inhalation	125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 105 weeks	NOAEL= 500	No effects on histopathology	(NTP, 2011)	GLP study
Endocrine	Rat (male) (n=24/group)	Inhalation	100, 250, 500 or 750 ppm	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until sacrifice in males; or until GD 20 and from PND 5 until weaning of offspring (~PND 21) in females	NOAEL= 500	Decreased absolute weights of adrenals and pituitary (F_1)	(WIL Research, 2001)	GLP study peer-reviewed by NTP – these effects were not observed in females
Endocrine	Mouse (female) (n=10/group)	Inhalation	62.5, 125 or 500 ppm	6.2 hours/day, 5 days/week for 14 weeks	NOAEL= 250	Necrosis of adrenal cortex (moderate to marked)	(NTP, 2011)	GLP study - no exposure-related, non-neoplastic changes were observed in other endocrine glands
Endocrine	Mouse (n=100/group)	Inhalation	62.5, 125 or 250 ppm	6.2 hours/day, 5 days/week for 105 weeks	NOAEL= 250	No effects on histopathology	(NTP, 2011)	GLP study
Gastrointestinal	Rat (n=30/group)	Inhalation	100, 200, 400 or 600 ppm	6 hours/day, 5 days/week for 13 weeks	NOAEL= 600	No effects on histopathology	(ClinTrials, 1997a)	GLP study
Gastrointestinal	Rat (n=20/group)	Inhalation	62.5, 125, 250, 500 or 1000 ppm	6.2 hours/day, 5 days/week for 14 weeks	NOAEL= 1000	No effects on histopathology	(NTP, 2011)	GLP study
Gastrointestinal	Rat (n=100/group)	Inhalation	125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 105 weeks	NOAEL= 500	No effects on histopathology	(NTP, 2011)	GLP study
Gastrointestinal	Mouse (n=20/group)	Inhalation	62.5, 125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 14 weeks	NOAEL= 500	No effects on histopathology	(NTP, 2011)	GLP study

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Gastrointestinal	Mouse (n=100/group)	Inhalation	62.5, 125 or 250 ppm	6.2 hours/day, 5 days/week for 105 weeks	NOAEL= 250	No effects on histopathology	(NTP, 2011)	GLP study
Hematological	Human (n = 43)	Inhalation	81.2 ppm GM; range 18-254 pm)	2 weeks to 2 months		No effects on hematology parameters	(NIOSH, 2003)	No effects noted; not used in quantitative analysis
Hematological	Human (60 female; 26 male)	Inhalation	0.06-114.8 ppm (8-hr TWA concentration)	About 40 months		RBC in females only significantly decreased across exposure groups	(Li et al., 2010a; Li et al., 2010b)	No other related clinical chemistries affected; limited evaluation of worker exposure. Not used in quantitative analysis.
Hematological	Human (n = 43)	Inhalation	168.9 ppm; (mean)	4-9 years		No statistically significant effects on hematology parameters	(NIOSH, 2002a)	No statistically significant effects reported
Hematological	Rat (male) (n=10/group)	Inhalation	6040, 7000, 7400 or 8500 ppm	4 hours	NOAEL=8500	No effects on hematology parameters	(Elf Atochem S.A., 1997)	GLP study
Hematological	Rat (n=20/group)	Inhalation	398, 994 or 1590 ppm	6 hours/day, 5 days/week for 4 weeks	NOAEL= 398	Decreased erythrocyte parameters	(ClinTrials, 1997b)	GLP study
Hematological	Rat (male) (n=9/group)	Inhalation	1000 ppm	8 hours/day, 7 days/week for 5 or 7 weeks	LOAEL= 1000	Decreased mean corpuscular volume	(Yu et al., 2001)	Not suitable for dose-response analysis because only one exposure group was used
Hematological	Rat (n=20/group)	Inhalation	50, 300 or 1800 ppm	6 hours/day, 5 days/week for 8 weeks	NOAEL= 300	Decreased WBCs, RBCs, hematocrit and MCV; increased Hgb and MCH	(Kim et al., 1999a)	GLP study - peer reviewed literature biological relevance uncertain

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Hematological	Rat (male) (n=9/group)	Inhalation	200, 400 or 800 ppm	8 hours/day, 7 days/week for 12 weeks	NOAEL= 400	Decreased MCHC; increased MCV	(Ichihara et al., 2000b)	GLP study - conducted in males only, peer reviewed literature
Hematological	Rat (female) (n=15/group)	Inhalation	100, 200, 400 or 600 ppm	6 hours/day, 5 days/week for 13 weeks	NOAEL= 400	Decreased WBC and absolute lymphocytes (at 6 weeks)	(ClinTrials, 1997a)	GLP study - effects not observed after 13 weeks of exposure
Hematological	Rat (n=20/group)	Inhalation	62.5, 125, 250, 500 or 1000 ppm	6.2 hours/day, 5 days/week for 14 weeks	NOAEL= 1000	No effects on hematology parameters	(NTP, 2011)	GLP study
Hematological	Mouse (n=20/group)	Inhalation	62.5, 125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 14 weeks	NOAEL= 500	No effects on hematology parameters	(NTP, 2011)	GLP study
Immune	Rat (female) (n=8/group)	Inhalation	250, 500 or 1000 ppm	6.2 hours/day, 5 days/week for 4 or 10 weeks	NOAEL= 500	Decreased spleen IgM response to SRBC; decreased T cells	(Anderson et al., 2010)	GLP study - IgM response occurred in the absence of effects on spleen cellularity or serum IgM (at 10 weeks)
Immune	Rat (n=20/group)	Inhalation	50, 300 or 1800 ppm	6 hours/day, 5 days/week for 8 weeks	NOAEL= 1800	No effects on histopathology (thymus and spleen)	(Kim et al., 1999a)	GLP study, peer reviewed literature
Immune	Rat (male) (n=9/group)	Inhalation	200, 400 or 800 ppm	8 hours/day, 7 days/week for 12 weeks	NOAEL= 800	No effects on organ weights or histopathology (spleen and thymus)	(Ichihara et al., 2000b)	GLP study - conducted in males only, peer reviewed literature
Immune	Rat (female) (n=10/group)	Inhalation	200, 400 or 800 ppm	8 hours/day, 7 days/week for up to 12 weeks	NOAEL= 800	No effects or organ weights or histopathology (spleen and thymus)	(Yamada et al., 2003)	GLP study - conducted in females only, peer reviewed literature

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Immune	Rat (n=30/group)	Inhalation	100, 200, 400 or 600 ppm	6 hours/day, 5 days/week for 13 weeks	NOAEL= 600	No immune effects	(ClinTrials, 1997a)	GLP study
Immune	Rat (n=20/group)	Inhalation	62.5, 125, 250, 500 or 1000 ppm	6.2 hours/day, 5 days/week for 14 weeks	NOAEL= 1000	No effects on histopathology (lymphoreticular tissues)	(NTP, 2011)	GLP study
Immune	Rat (n=100/group)	Inhalation	125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 105 weeks	NOAEL= 500	No effects on histopathology (lymphoreticular tissues)	(NTP, 2011)	GLP study
Immune	Rat (n=25/group)	Inhalation	100, 250, 500 or 750 ppm	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until sacrifice in males; or until GD 20 and from PND 5 until weaning of offspring (~PND 21) in females	NOAEL= 750	Increased brown pigment in the spleen	(WIL Research, 2001)	GLP study peer-reviewed by NTP
Immune	Mouse (female) (n=8/group)	Inhalation	125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 4 or 10 weeks	LOAEL= 125	Decreased spleen IgM response to SRBC	(Anderson et al., 2010)	GLP study - effect occurred in the absence of an effect on serum IgM. Quantitative data not available.
Immune	Mouse (n=20/group)	Inhalation	62.5, 125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 14 weeks	NOAEL= 500	No effects on histopathology (lymphoreticular tissues)	(NTP, 2011)	GLP study

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Immune	Mouse (n=100/group)	Inhalation	62.5, 125, 250, 500 or 250 ppm	6.2 hours/day, 5 days/week for 105 weeks	NOAEL= 250	No effects on histopathology (lymphoreticular tissues)	(NTP, 2011)	GLP study
Immune	Mouse (female) (n=5/group)	Oral	200, 500 or 1000 mg/kg	Single exposure for 6, 12, 24 or 48 hrs	LOAEL= 200	Reduced antibody response to T-antigen. Used for weight of evidence; no route-to-route extrapolation.	(Lee et al., 2007)	GLP study - not able to do route-to-route extrapolation
Liver	Human (60 female, 26 male)	Inhalation	0.06-114.8 ppm (8-hr TWA concentration)	About 40 months		No effects on liver clinical chemistry parameters	(Li et al., 2010a)	No effects noted; not used in quantitative analysis
Liver	Rat (male) (n=5/group)	Inhalation	125, 250, 500, 1000 or 2000 ppm	6.2 hours/day, 5 days/week for 16 days	NOAEL= 125	Increased absolute and relative liver weights	(NTP, 2011)	GLP study - evidence of histopathological changes observed in the liver
Liver	Rat (male) (n=9/group)	Inhalation	1000 ppm	8 hours/day, 7 days/week for 5 or 7 weeks	LOAEL= 1000	No effects on histopathology	(Yu et al., 2001)	Not suitable for dose-response analysis because only one exposure group was used
Liver	Rat (male) (n=10/group)	Inhalation	50, 300 or 1800 ppm	6 hrs/day, 5 days/wk for 8 wks	NOAEL= 50	Increased relative liver weight	(Kim et al., 1999b)	GLP study - no histopathology or clinical chemistry changes indicative of liver damage were identified
Liver	Rat (male) (n=10/group)	Inhalation	700 or 1500 ppm	6 hours/day, 5 days/week for 4 and 12 weeks	LOAEL= 700	Decreased plasma ALT activity	(Fueta et al.)	GLP study - no microscopic examination of liver conducted, peer reviewed literature

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Liver	Rat (male) (n=9/group)	Inhalation	200, 400 or 800 ppm	8 hours/day, 7 days/week for 12 weeks	NOAEL= 400	Increased absolute and relative liver weight	(Ichihara et al., 2000a)	GLP study - conducted in males only, peer reviewed literature
Liver	Rat (female) (n=10/group)	Inhalation	200, 400 or 800 ppm	8 hours/day, 7 days/week for up to 12 weeks	LOAEL= 200	Increased absolute and relative liver weight	(Yamada et al., 2003)	GLP study - conducted in females only; liver histopathology observed at the highest exposure concentration
Liver	Rat (male) (n=15/group)	Inhalation	100, 200, 400 or 600 ppm	6 hours/day, 5 days/week for 13 weeks	LOAEL= 100	Increased incidence of cytoplasmic vacuolization	(ClinTrials, 1997a)	GLP study
Liver	Rat (female) (n=10/group)	Inhalation	62.5, 125, 250, 500 or 1000 ppm	6.2 hours/day, 5 days/week for 14 weeks	NOAEL= 125	Increased liver weight; increased incidence of cytoplasmic vacuolization	(NTP, 2011)	GLP study
Liver	Rat (n=100/group)	Inhalation	125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 105 weeks	NOAEL= 500	No effects on histopathology	(NTP, 2011)	GLP study
Liver	Rat (male) (n=25/group)	Inhalation	100, 250, 500 or 750 ppm	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until sacrifice	NOAEL=100	Increased incidence of vacuolization of centrilobular hepatocytes (F_0)	(WIL Research, 2001)	GLP study peer-reviewed by NTP

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Liver	Rat (female) (n=25/group)	Inhalation	100, 250, 500 or 750 ppm	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until GD 20; from PND 5 until weaning of offspring (~PND 21)	NOAEL=250	Increased incidence of vacuolization of centrilobular hepatocytes (F_0)	(WIL Research, 2001)	GLP study peer-reviewed by NTP
Liver	Mouse (male) (n=5/group)	Inhalation	125, 250, 500, 1000 or 2000 ppm	6.2 hours/day, 5 days/week for 17 days	NOAEL= 250	Centrilobular necrosis (mild to moderate)	(NTP, 2011)	GLP study - increased liver weight reported in males and females at this dose
Liver	Mouse (male) (n=24/group)	Inhalation	50, 110 or 250 ppm	8 hours/day, 7 days/week for 4 weeks	LOAEL= 50	Hepatocellular degeneration and focal necrosis	(Liu et al., 2009)	GLP study - one of three strains affected at this concentration, peer reviewed literature
Liver	Mouse (male) (n=8/group)	Inhalation	100 or 300 ppm	8 hours/day, 7 days/week for 4 weeks	LOAEL= 100	Necrosis and hepatocyte degeneration	(Liu et al., 2010)	GLP study - magnitude of change was small (< 1%), but statistically significant
Liver	Mouse (n=20/group)	Inhalation	62.5, 125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 14 weeks	NOAEL= 250	Necrosis and hepatocyte degeneration	(NTP, 2011)	GLP study
Liver	Mouse (n=100/group)	Inhalation	62.5, 125 or 250 ppm	6.2 hours/day, 5 days/week for 105 weeks	NOAEL= 250	No effects on histopathology	(NTP, 2011)	GLP study

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Liver	Rat (male) (n=10/group)	Oral	200, 400 or 800 mg/kg-day	16 weeks	LOAEL= 200	Increased relative liver weight. Used for weight of evidence; no route:to:route extrapolation	(Wang et al., 2012)	GLP study - not able to do route-to-route extrapolation
Liver	Mouse (female) (n=5/group)	Oral	200, 500 or 1000 mg/kg	Single exposure for 6, 12, 24 or 48 hrs	NOAEL= 200	Centrilobular hepatocyte swelling	(Lee et al., 2007)	GLP study – not able to do route-to-route extrapolation
Metabolic	Rat (n=30/group)	Inhalation	100, 200, 400 or 600 ppm	6 hours/day, 5 days/week for 13 weeks	NOAEL= 600	No effects on electrolyte or glucose levels	(ClinTrials, 1997a)	GLP study
Musculoskeletal	Rat (male) (n=11/group)	Inhalation	200, 400 or 800 ppm	8 hours/day, 7 days/week for 12 weeks	NOAEL= 400	Alteration in soleus muscle myofilaments	(Ichihara et al., 2000a)	GLP study
Musculoskeletal	Rat (n=30/group)	Inhalation	100, 200, 400 or 600 ppm	6 hours/day, 5 days/week for 13 weeks	NOAEL= 600	No effects on histopathology	(ClinTrials, 1997a)	GLP study
Musculoskeletal	Rat (n=20/group)	Inhalation	62.5, 125, 250, 500 or 1000 ppm	6.2 hours/day, 5 days/week for 14 weeks	NOAEL= 1000	No effects on histopathology	(NTP, 2011)	GLP study
Musculoskeletal	Rat (n=100/group)	Inhalation	125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 105 weeks	NOAEL= 500	No effects on histopathology	(NTP, 2011)	GLP study
Musculoskeletal	Mouse (n=20/group)	Inhalation	62.5, 125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 14 weeks	NOAEL= 500	No effects on histopathology	(NTP, 2011)	GLP study
Musculoskeletal	Mouse (n=100/group)	Inhalation	62.5, 125, or 250 ppm	6.2 hours/day, 5 days/week for 105 weeks	NOAEL= 250	No effects on histopathology	(NTP, 2011)	GLP study

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Nervous System	Human (3 female, 1 male)	Inhalation	107 ppm (geometric mean; range: 58-254 ppm)	< 2 weeks	N/A	Clinical signs of neurotoxicity (including headache, dizziness, numbness, weakness)	(Raymond and Ford, 2007)	Case reports. Arsenic levels (from unidentified source) also high in all 4 cases
Nervous System	Human (female, n = 3)	Inhalation	133 ppm (daily TWA concentration); range: 60-261 ppm	2 to 12 months	N/A	Staggering, lower extremity paresthesias and dysesthesia, ataxia, numbness in back, legs, hips, weakness, autonomic dysfunction, mood changes)	(Ichihara et al., 2002)	Case reports. Air samples collected (for 1 case) only after ventilation was improved
Nervous System	Human (1 male)	Inhalation	533 ppm (TWA concentration) range, 353-663 ppm)	18 months	N/A	Severe ataxia, motor and sensory impairments, axonal damage (based on sural nerve biopsy)	(Samukawa et al., 2012)	Case report on 1 male. Symptoms subsided after several months without exposure
Nervous System	Human (23 female cases; 23 controls)	Inhalation	2.92 ppm (geometric mean; range 0.34 – 49.2 pm)	27 months (mean)		Increased distal latency, decreased vibration sense in toes, decreased Benton visual memory test scores	(Ichihara et al., 2004b)	Some exposure to both 1-BP and 2-BP. Only 12 pairs exposed to 1-BP only; may lack statistical power to detect differences in this subgroup.

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Nervous System	Human (n = 32)	Inhalation	81.2 ppm GM; (range 18-254 ppm)	2 weeks to 2 months		Dizziness, lower extremity weakness, difficulty standing or walking, paresthesias.	(NIOSH, 2003)	Health Hazard Evaluation reporting health effects from 1-BP and 2-BP exposures. Urinary arsenic levels were also high in workers.
Nervous System	Human (4 female, 2 male)	Inhalation	108 ppm (7-hr TWA concentration)	> 3 years		Inability to walk, spastic paraparesis distal sensory loss, hyperreflexia	(Majersik et al., 2007)	Case reports
Nervous System	Human (60 female, 26 male)	Inhalation	0.06-114.8 ppm (8-hr TWA concentrations)	About 40 months		Stat signif decreased vibration sense in toes in all exposure groups compared to controls; increased tibial motor distal latency and decreased sural nerve conduction velocity compared to controls but stat signif in middle exposure group only	(Li et al., 2010a)	No clear dose-response relationship for DL or SNCV-not statistically significant; possible exposure misclassification by combination of plants collected over years based on 1 or 2 samples; skin temperature not taken individually and BMI not adjusted for electrophysiological tests.

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Nervous System	Human (n=43)	Inhalation	168.9 ppm (mean)	4-9 years		Headache, tingling in hands or feet, tremor	(NIOSH, 2002a)	The study is limited by small sample size of employees reporting symptoms
Nervous System	Rat (male) (n=10/group)	Inhalation	50, 300, or 1800 ppm	6 hours/day, 5 days/week for 8 weeks	NOAEL= 50	Decreased relative brain weight	(Kim et al., 1999b)	Data only provided as brain:body weight ratio; peer-reviewed literature
Nervous System	Rat (n=10/group)	Inhalation	11,000, 13,000, 15,000 or 17,000 ppm	4 hours	LOAEL=11,000	Ataxia, lacrimation, decreased activity	(Kim et al., 1999b)	Effects were observed at both exposure concentrations (incidence not reported). Lethality at ≥ 13,000 ppm; peer-reviewed literature
Nervous System	Rat (male) (n=9/group)	Inhalation	200, 400 or 800 ppm	8 hours/day for 7 days	LOAEL= 200	Altered neuron-specific proteins and ROS	(Wang et al., 2002)	Mechanistic data; peer-reviewed literature
Nervous System	Rat (male) (n=6-12/group)	Inhalation	200, 400, 800 or 1000 ppm	8 hours/day for 7 or 28 days	LOAEL= 200	Decreased hippocampal glucocorticoid receptor expression	(Zhang et al., 2013)	Mechanistic data; peer-reviewed literature
Nervous System	Rat (male) (n=6-13/group)	Inhalation	1500 ppm	6 hours/day, 5 days/week for 1, 3, or 4 weeks	LOAEL= 1500	Paired pulse disinhibition (DG and CA1 pyramidal neuron); behavioral abnormalities	(Fueta et al., 2002a; Fueta et al., 2002b)	Not suitable for dose-response analysis because only one exposure group was used; peer-reviewed literature
Nervous System	Rat (male) (n=9/group)	Inhalation	400 or 1000 ppm	8 hours/day, 7 days/week for 1 or 4 weeks	LOAEL= 400	Altered regulation and expression of hippocampal proteins	(Huang et al., 2011)	Mechanistic data; peer-reviewed literature

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Nervous System	Rat (male) (n=9/group)	Inhalation	400 or 1000 ppm	8 hours/day, 7 days/week for 1 or 4 weeks	LOAEL= 400	Increased hippocampal ROS levels	(Huang et al., 2012)	Mechanistic data; peer-reviewed literature
Nervous System	Rat (male) (n=9/group)	Inhalation	400 or 1000 ppm	8 hours/day, 7 days/week for 1 or 4 weeks	LOAEL= 400	Altered regulation and expression of hippocampal proteins	(Huang et al., 2015)	Mechanistic data; peer-reviewed literature
Nervous System	Rat (male) (n=4/group)	Inhalation	10, 50 or 200 ppm	8 hours/day, 7 days/week for 3 weeks	NOAEL= 10	Increased spontaneous locomotor activity	(Honma et al., 2003)	Activity changes persisted 3-4 days after exposure ended; peer-reviewed literature
Nervous System	Rat (male) (n=5/group)	Inhalation	10, 50, 200 or 1000 ppm	8 hours/day, 7 days/week for 3 weeks	NOAEL= 50	Decreased time hanging from a suspended bar	(Honma et al., 2003)	Data selected by EPA for dose-response analysis; peer-reviewed literature
Nervous System	Rat (male) (n=4-5/group)	Inhalation	50, 200 or 1000 ppm	8 hours/day, 7 days/week for 3 weeks	LOAEL= 50	Altered neurotransmitter and metabolites	(Suda et al., 2008)	Mechanistic data; peer-reviewed literature
Nervous System	Rat (n=20/group)	Inhalation	398, 994 or 1590 ppm	6 hours/day, 5 days/week for 4 weeks	LOAEL= 398	Histopathological abnormalities in the CNS	(ClinTrials, 1997b)	GLP study
Nervous System	Rat (male) (n=9/group)	Inhalation	400 to 1000 ppm	8 hours/day, 7 days/week for 4 weeks	NOAEL= 400	Changes in the mRNA expression of serotonin, dopamine, and GABA receptors	(Mohideen et al., 2009)	Mechanistic data; peer-reviewed literature
Nervous System	Rat (male) (n=6/group)	Inhalation	400 to 1000 ppm	8 hours/day, 7 days/week for 4 weeks	NOAEL= 400	Decreased density of noradrenergic axons in frontal cortex and amygdala	(Mohideen et al., 2011)	Mechanistic data; peer-reviewed literature

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Nervous System	Rat (male) (n=12/group)	Inhalation	400 to 1000 ppm	8 hours/day, 7 days/week for 4 weeks	LOAEL= 400	Increased astrogliosis	(Mohideen et al., 2013)	Mechanistic data. Only 3 rats/exposure group were subjected to microscopic evaluations; peer-reviewed literature
Nervous System	Rat (male) (n=12/group)	Inhalation	400, 800 or 1000 ppm	8 hours/day, 7 days/week for 4 weeks	LOAEL= 400	Morphological changes in cerebellar microglia and increased ROS	(Subramanian et al., 2012)	Mechanistic data; peer-reviewed literature
Nervous System	Rat (male) (n=8/group)	Inhalation	1500 ppm	6 hours/day, 5 days/week for 4 weeks	LOAEL= 1500	Decreased activity, behavioral abnormalities, movement disorders, histopathological changes in Purkinje cells	(Ohnishi et al., 1999)	Not suitable for dose-response analysis because only one exposure group was used; peer-reviewed literature
Nervous System	Rat (male) (n=13/group)	Inhalation	1500 ppm	6 hours/day, 5 days/week for 4 weeks	LOAEL= 1500	Paired pulse disinhibition, neuronal dysfunction in dentate gyrus; convulsive behaviors	(Fueta et al., 2002b)	Not suitable for dose-response analysis because only one exposure group was used; peer-reviewed literature
Nervous System	Rat (male) (n=7-14/group)	Inhalation	700 ppm	6 hours/day, 5 days/week for 4, 8, or 12 weeks	LOAEL=700	Paired pulse disinhibition in ex vivo hippocampal slices (DG and CA1 pyramidal neuron)	(Fueta et al., 2004)	Not suitable for dose-response analysis because only one exposure group was used; peer-reviewed literature

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Nervous System	Rat (n=9/group)	Inhalation	1000 ppm	8 hours/day, 7 days/week for 5 or 7 weeks	LOAEL= 1000	Movement disorder, altered motor nerve conduction velocity and distal nerve latency in tail nerve); histopathological changes to CNS and PNS	(Yu et al., 2001)	Not suitable for dose-response analysis because only one exposure group was used. Same data reported in two publications. Peer-reviewed literature
Nervous System	Rat (male) (n=24/group)	Inhalation	400, 800 or 1000 ppm	8 hours/day, 7 days/week for 6 weeks	NOAEL= 400	Movement disorder, decreased hind limb grip strength	(Banu et al., 2007)	Peer-reviewed literature
Nervous System	Rat (male) (n=12/group)	Inhalation	700 ppm	6 hours/day, 5 days/week for 8 weeks	LOAEL= 700	Paired pulse disinhibition in ex vivo hippocampal slices (DG and CA1 pyramidal neuron); increased protein kinase activities	(Fueta et al., 2002a)	Not suitable for dose-response analysis because only one exposure group was used; peer-reviewed literature
Nervous System	Rat (male) (n=6/group)	Inhalation	200 or 400 ppm	6 hours/day, 5 days/week for 8 or 12 weeks	NOAEL= 200	Paired pulse disinhibition in ex vivo hippocampal slices (DG and CA1 pyramidal neuron)	(Fueta et al., 2007)	This study was conducted in males only; peer-reviewed literature
Nervous System	Rat (n=20/group)	Inhalation	50, 300 or 1800 ppm	6 hours/day, 5 days/week for 8 weeks	NOAEL= 1800	No effects on brain histopathology	(Kim et al., 1999a)	Peer-reviewed literature

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Nervous System	Rat (male) (n=11/group)	Inhalation	200, 400 or 800 ppm	8 hours/day, 7 days/week for 12 weeks	LOAEL=200	Decreased hind limb grip strength	(Ichihara et al., 2000a)	Lowest concentration significant during but not at end of exposure; peer-reviewed literature
Nervous System	Rat (male) (n=9/group)	Inhalation	200, 400 or 800 ppm	8 hours/day, 7 days/week for 12 weeks	LOAEL= 200	Altered neuron-specific proteins and increased ROS	(Wang et al., 2003)	Mechanistic data; peer-reviewed literature
Nervous System	Rat (male) (n=6/group)	Inhalation	400 ppm	6 hours/day, 5 days/week for 12 weeks	LOAEL= 400	Changes in gene expression of anti-apoptotic proteins in astrocytes	(Yoshida et al., 2007)	Mechanistic data; peer-reviewed literature
Nervous System	Rat (male) (n=8/group)	Inhalation	400 ppm	6 hours/day, 5 days/week for 12 weeks	LOAEL= 400	Decreased paired pulse inhibition in ex vivo hippocampal slices (dentate gyrus)	(Ueno et al., 2007)	Not suitable for dose-response analysis because only one exposure group was used. Peer-reviewed literature
Nervous System	Rat (n=30/group)	Inhalation	100, 200, 400 or 600 ppm	6 hours/day, 5 days/week for 13 weeks	NOAEL= 600	No changes based on functional observational battery, motor activity, organ weight, or histopathology	(ClinTrials, 1997a)	GLP study
Nervous System	Rat (n=10/group)	Inhalation	200, 500 or 1250 ppm	6 hours/day, 5 days/week for 13 weeks	NOAEL= 1250	No effects histopathology of central or peripheral nervous tissues	(Sohn et al., 2002)	Peer-reviewed literature

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Nervous System	Rat (n=10/group)	Inhalation	125, 250, 500, 1000 or 2000 ppm	6.1 hours/day, 5 days/week for 16 days	NOAEL=1000 ppm	Hindlimb splay	(NTP, 2011)	No mention of brain histopathology results; GLP study
Nervous System	Rat (n=20/group)	Inhalation	62.5, 125, 250, 500 or 1000 ppm	6.2 hours/day, 5 days/week for 14 weeks	NOAEL= 1000	No effects	(NTP, 2011)	No mention of brain histopathology results; GLP study
Nervous System	Rat (n=100/group)	Inhalation	125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 105 weeks	NOAEL= 500	No effects	(NTP, 2011)	No mention of brain histopathology results; GLP study
Nervous System	Rat (n=25/group)	Inhalation	100, 250, 500 or 750 ppm	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until sacrifice in males; or until GD 20 and from PND 5 until weaning of offspring (~PND 21) in females	NOAEL= 100	Decreased brain weight (F_0)	(WIL Research, 2001)	GLP study peer-reviewed by NTP
Nervous System	Rat (male) (n=24-25/group)	Inhalation	100, 250, 500 or 750 ppm	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until sacrifice in males; or until GD 20 and from PND 5 until weaning of offspring (~PND 21) in females	LOAEL= 100	Decreased brain weight (weanling and adult F_1)	(WIL Research, 2001)	GLP study peer-reviewed by NTP. Females less sensitive.

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Nervous System	Rat (n=15-22/group)	Inhalation	100, 250, 500 or 750 ppm	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until sacrifice in males; or until GD 20 and from PND 5 until weaning of offspring (~PND 21) in females	NOAEL= 250	Decreased brain weight (weanling F_2)	(WIL Research, 2001)	GLP study peer-reviewed by NTP
Nervous System	Mouse (n=10/group)	Inhalation	125, 250, 500, 1000 or 2000 ppm	6.1 hours/day, 5 days/week for 17 days	NOAEL=2000 ppm	No effects	(NTP, 2011)	No mention of brain histopathology results; GLP study
Nervous System	Mouse (n=20/group)	Inhalation	62.5, 125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 14 weeks	NOAEL= 500	No effects	(NTP, 2011)	No mention of brain histopathology results; GLP study
Nervous System	Mouse (n=100/group)	Inhalation	62.5, 125, 250 or 250 ppm	6.2 hours/day, 5 days/week for 105 weeks	NOAEL= 250	No effects	(NTP, 2011)	No mention of brain histopathology results; GLP study
Nervous System	Rat (male) (n=14/group)	Oral	100, 200, 400 or 800 mg/kg-day	12 days	LOAEL=100	Impaired spatial learning and memory; neuron loss in prelimbic cortex; increased ROS in cerebral cortex	(Guo et al., 2015)	Not able to do route-to-route extrapolation; peer-reviewed literature

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Nervous System	Rat (male) (n=10/group)	Oral	200, 400 or 800 mg/kg-day	12 days	LOAEL= 200	Impaired spatial learning and memory. Used for weight of evidence	(Zhong et al., 2013)	Not able to do route-to-route extrapolation; peer-reviewed literature
Nervous System	Rat (male) (n=10/group)	Oral	200, 400 or 800 mg/kg-day	16 weeks	LOAEL= 200	Decreased hindlimb grip strength; increased gait score. Used for weight of evidence; no route-to-route extrapolation.	(Wang et al., 2012)	English abstract and partial translation of methods and results. Used for weight of evidence. Peer-reviewed literature able to do route-to-route
Nervous System	Rat (male) (n=7-9/group)	Subcutaneous	3.7 or 11 mmol/kg-day	4 weeks	LOAEL= 3.7	Increased tail motor nerve latency	(Zhao et al., 1999)	Not able to do route-to-route extrapolation; peer-reviewed literature
Ocular	Rat (n=30/group)	Inhalation	100, 200, 400 or 600 ppm	6 hours/day, 5 days/week for 13 weeks	NOAEL= 600	No effects on histopathology	(ClinTrials, 1997a)	GLP study
Ocular	Rat (n=20/group)	Inhalation	62.5, 125, 250, 500 or 1000 ppm	6.2 hours/day, 5 days/week for 14 weeks	NOAEL= 1000	No effects on histopathology	(NTP, 2011)	GLP study
Ocular	Rat (n=100/group)	Inhalation	125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 105 weeks	NOAEL= 500	No effects on histopathology	(NTP, 2011)	GLP study
Ocular	Mouse (n=20/group)	Inhalation	62.5, 125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 14 weeks	NOAEL= 500	No effects on histopathology	(NTP, 2011)	GLP study
Ocular	Mouse (n=100/group)	Inhalation	62.5, 125 or 250 ppm	6.2 hours/day, 5 days/week for 105 weeks	NOAEL= 250	No effects on histopathology	(NTP, 2011)	GLP study

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Kidney	Human (n = 43)	Inhalation	81.2 ppm GM; (range 18-254 ppm)	2 weeks to 2 months		No effects on clinical chemistry parameters for kidney effects	(NIOSH, 2003)	No effects noted; not used in quantitative analysis
Kidney	Human (n= 60 female, 26 male)	Inhalation	0.06-114.8 ppm (8-hr TWA concentration)	About 40 months		No effects on clinical chemistry parameters related to kidney	(Li et al., 2010a)	Limited evaluation of worker exposure
Kidney	Rat (female) (n=5/group)	Inhalation	125, 250, 500, 1000 or 2000 ppm	6.2 hours/day, 5 days/week for 16 days	LOAEL= 125	Increased relative kidney weight	(NTP, 2011)	GLP study - Effects occurred at all concentrations no NOAEL was identified
Kidney	Rat (n=20/group)	Inhalation	398, 994 or 1590 ppm	6 hours/day, 5 days/week for 4 weeks	NOAEL= 398	Changes in BUN, total bilirubin, and total protein levels	(ClinTrials, 1997b)	GLP study - Histopathological changes reported at the highest exposure concentration (in the absence of effects on urinalysis parameters)
Kidney	Rat (male) (n=9/group)	Inhalation	1000 ppm	8 hours/day, 7 days/week for 5 or 7 weeks	NOAEL= 1000	No effects on histopathology	(Yu et al., 2001)	Not suitable for dose-response analysis because only one exposure group was used.

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Kidney	Rat (n=10/group)	Inhalation	50 to 1800 ppm	6 hours/day, 5 days/week for 8 weeks	NOAEL= 300	Decreased urobilinogen (males); increased bilirubin (females)	(Kim et al., 1999b)	Accompanying effects included tubular casts in females (incidence not reported), increased relative kidney weight (no data on absolute kidney weight)
Kidney	Rat (male) (n=9/group)	Inhalation	200, 400 or 800 ppm	8 hours/day, 7 days/week for 12 weeks	NOAEL= 800	No effects on kidney weight or histopathology	(Ichihara et al., 2000b)	GLP study – peer reviewed literature
Kidney	Rat (female) (n=10/group)	Inhalation	200, 400 or 800 ppm	8 hours/day, 7 days/week for up to 12 weeks	LOAEL= 200	Increased absolute and relative kidney weight	(Yamada et al., 2003)	Effects occurred at all exposure concentrations; no NOAEL was identified. Renal histopathology observed only at the highest exposure concentration.
Kidney	Rat (male) (n=15/group)	Inhalation	100, 200, 400 or 600 ppm	6 hours/day, 5 days/week for 13 weeks	NOAEL= 600	No effects on urinalysis parameters, or organ weights	(ClinTrials, 1997a)	GLP study
Kidney	Rat (female) (n=10/group)	Inhalation	62.5, 125, 250, 500 or 1000 ppm	6.2 hours/day, 5 days/week for 14 weeks	NOAEL= 500	Increased absolute and relative kidney weights	(NTP, 2011)	GLP study - There were no supporting effects on clinical chemistry parameters or kidney histopathology
Kidney	Rat (n=100/group)	Inhalation	125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 105 weeks	NOAEL= 500	No effects on histopathology	(NTP, 2011)	GLP study

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Kidney	Rat (male) (n=25/group)	Inhalation	100 to 750 ppm	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until sacrifice	NOAEL = 100	Increased incidence of pelvic mineralization (F_0)	(WIL Research, 2001)	GLP study peer-reviewed by NTP
Kidney	Rat (female) (n=25/group)	Inhalation	100, 250, 500 or 750 ppm	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until GD 20; from PND 5 until weaning of offspring (~PND 21)	NOAEL = 100	Increased incidence of pelvic mineralization (F_0)	(WIL Research, 2001)	GLP study peer-reviewed by NTP
Kidney	Mouse (female) (n=5/group)	Inhalation	125, 250, 500, 1000 or 2000 ppm	6.2 hours/day, 5 days/week for 17 days	NOAEL= 500	Increased absolute and relative kidney weights	(NTP, 2011)	GLP study - These effects were not observed in males; no evidence of renal histopathology
Kidney	Mouse (female) (n=10/group)	Inhalation	62.5, 125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 14 weeks	NOAEL= 250	Increased absolute and relative kidney weights	(NTP, 2011)	GLP study - These effects were not observed in males; no evidence of renal histopathology
Kidney	Mouse (n=100/group)	Inhalation	62.5, 125 or 250 ppm	6.2 hours/day, 5 days/week for 105 weeks	NOAEL= 250	No effects on histopathology	(NTP, 2011)	GLP study
Reproductive System	Human (n = 9 males)	Inhalation	81.2 ppm GM; (range 18-254 ppm)	2 weeks – 2 months		No decrease in sperm number, shape, or motility	(NIOSH, 2003)	No effects noted; not used in quantitative analysis

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Reproductive System	Rat (male) (n=5/group)	Inhalation	6040, 7000, 7400 or 8500 ppm	4 hours	NOAEL= 8500	No effects on histopathology of the testes	(Elf Atochem S.A., 1997)	No effects noted
Reproductive System	Rat (female) (n=7-8/group)	Inhalation	50, 200 or 1000 ppm	8 hours/day, 7 days/week for 3 weeks	NOAEL= 1000	No effects on number of days per estrous cycle or ovary and uterus weights	(Sekiguchi et al., 2002)	No effects noted
Reproductive System	Rat (male) (n=10/group)	Inhalation	398, 994 or 1590 ppm	6 hours/day, 5 days/week for 4 weeks	NOAEL= 994	Microscopic lesions in male reproductive system	(ClinTrials, 1997b)	GLP study - Specific tissues and lesions not described
Reproductive System	Rat (male) (n=24/group)	Inhalation	400, 800 or 1000 ppm	8 hours/day, 7 days/week for 6 weeks	LOAEL= 400	Decreased epididymal sperm count	(Banu et al., 2007)	GLP study - conducted in males only. Effects occurred at both exposure concentrations; no NOAEL was identified.
Reproductive System	Rat (male) (n=9/group)	Inhalation	1000 ppm	8 hours/day, 7 days/week for 5 or 7 weeks	NOAEL= 1000	No effects on testis histopathology	(Yu et al., 2001)	Not suitable for dose-response analysis because only one exposure group was used
Reproductive System	Rat (female) (n=10/group)	Inhalation	200, 400 or 800 ppm	8 hours/day, 7 days/week for up to 12 weeks	LOAEL= 200	Decreased number of antral follicles	(Yamada et al., 2003)	Peer reviewed literature
Reproductive System	Rat (n=10/group)	Inhalation	50 to 1800 ppm	6 hours/day, 5 days/week for 8 weeks	NOAEL= 300	Increased relative ovary weight	(Kim et al., 1999b)	Peer reviewed literature. Effect confounded by decreased body weight at the same exposure concentration

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Reproductive System	Rat (male) (n=9/group)	Inhalation	200, 400 or 800 ppm	8 hours/day, 7 days/week for 12 weeks	LOAEL = 200	Decreased relative seminal vesicle weight	(Ichihara et al., 2000b)	GLP study – peer reviewed literature
Reproductive System	Rat (n=30/group)	Inhalation	100, 200, 400 or 600 ppm	6 hours/day, 5 days/week for 13 weeks	NOAEL= 600	No effects on organ weights	(ClinTrials, 1997a)	GLP study
Reproductive System	Rat (male) (n=10/group)	Inhalation	62.5, 125, 250, 500 or 1000 ppm	6.2 hours/day, 5 days/week for 14 weeks	LOAEL= 250	Decreased sperm motility	(NTP, 2011)	Not all exposure groups were evaluated for reproductive effects; a NOAEL could be not identified
Reproductive System	Rat (female) (n=10/group)	Inhalation	62.5, 125, 250, 500 or 1000 ppm	6.2 hours/day, 5 days/week for 14 weeks	LOAEL= 250	Alterations in estrous cycles	(NTP, 2011)	Not all exposure groups were evaluated for reproductive effects; a NOAEL could be not identified
Reproductive System	Rat (n=100/group)	Inhalation	125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 105 weeks	NOAEL= 500	No effects on histopathology of reproductive organs	(NTP, 2011)	GLP study
Reproductive System	Rat (male) (n=25/group)	Inhalation	100, 250, 500 or 750 ppm	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until sacrifice	NOAEL= 250	Decreased percent motile sperm (F_0)	(WIL Research, 2001)	GLP study peer-reviewed by NTP
Reproductive System	Rat (male) (n=25/group)	Inhalation	100, 250, 500 or 750 ppm	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until sacrifice	NOAEL= 250	Decreased percent normal sperm morphology (F_0)	(WIL Research, 2001)	GLP study peer-reviewed by NTP

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Reproductive System	Rat (male) (n=25/group)	Inhalation	100, 250, 500 or 750 ppm	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until sacrifice	NOAEL= 100	Decreased absolute prostate weight (F_0)	(WIL Research, 2001)	GLP study peer-reviewed by NTP. Absolute prostate weights were decreased by about the same amount at all exposure concentrations (i.e. there was no dose-response); there were also no significant effects on relative prostate weight. There were no significant changes in absolute or relative prostate weights in F1 adults.
Reproductive System	Rat (female) (n=25/group)	Inhalation	100, 250, 500 or 750 ppm	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until GD 20; from PND 5 until weaning of offspring (~PND 21)	NOAEL= 250	Increase in estrous cycle length (F_0)	(WIL Research, 2001)	GLP study peer-reviewed by NTP
Reproductive System	Mouse (male) (n=24/group)	Inhalation	50, 110 or 250 ppm	8 hours/day, 7 days/week for 4 weeks	LOAEL= 50	Decreased sperm count and motility and/or increased abnormal sperm	(Liu et al., 2009)	Effects occurred at all exposure concentrations; peer reviewed literature. No NOAEL was identified

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Reproductive System	Mouse (male) (n=10/group)	Inhalation	62.5, 125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 14 weeks	NOAEL= 125	Decreased epididymis weight and sperm motility	(NTP, 2011)	Not all exposure groups were evaluated for reproductive effects. There were no effects on reproductive organ weights or histopathology.
Reproductive System	Mouse (female) (n=10/group)	Inhalation	62.5, 125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 14 weeks	LOAEL= 125	Alterations in estrous cycles	(NTP, 2011)	Not all exposure groups were evaluated for reproductive effects; a NOAEL could be not identified
Reproductive System	Mouse (n=100/group)	Inhalation	62.5, 125 or 250 ppm	6.2 hours/day, 5 days/week for 105 weeks	NOAEL= 250	No effects on histopathology of reproductive organs	(NTP, 2011)	GLP study
Reproductive System	Rat (male) (n=7/group)	Oral	1000 mg/kg-day	14 days	LOAEL= 1000	Decreased epididymal sperm count; decreased epididymis and prostate + seminal vesicle weights	(Xin et al., 2010)	Not able to do route-to-route extrapolation. Peer reviewed literature
Reproductive System	Mouse (male) (n=20/group)	Oral	300 or 600 mg/kg-day	Exposed for 10 days prior to mating	LOAEL= 600	Degeneration of pachytene spermatocytes. Used for weight of evidence; no route-to-route extrapolation.	(Yu et al., 2008)	No able to do route-to-route extrapolation. Peer reviewed literature
Respiratory	Rat (n=10/group)	Inhalation	6040, 7000, 7400 or 8500 ppm	4 hours	NOAEL=6040	Pulmonary edema and emphysema	(Elf Atochem S.A., 1997)	GLP study

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Respiratory	Rat (male) (n=5/group)	Inhalation	125, 250, 500, 100 or 2000 ppm	6.2 hours/day, 5 days/week for 16 days	NOAEL= 250	Nasal lesions (including suppurative inflammation and respiratory epithelial necrosis)	(NTP, 2011)	These effects were not observed in females. There were no significant changes in lung weight.
Respiratory	Rat (n=20/group)	Inhalation	398, 994 or 1590 ppm	6 hours/day, 5 days/week for 4 weeks	NOAEL= 994	Histopathological changes in nasal cavities	(ClinTrials, 1997b)	GLP study
Respiratory	Rat (male) (n=9/group)	Inhalation	200, 400 or 800 ppm	8 hours/day, 7 days/week for 12 weeks	NOAEL= 800	No effects on lung weight or histopathology	(Ichihara et al., 2000a)	Study conducted in males only; peer reviewed literature
Respiratory	Rat (n=20/group)	Inhalation	50, 300 or 1800 ppm	6 hours/day, 5 days/week for 8 weeks	NOAEL= 1800	No effects on lung weight or histopathology	(Kim et al., 1999a)	GLP study
Respiratory	Rat (n=30/group)	Inhalation	100, 200, 400 or 600 ppm	6 hours/day, 5 days/week for 13 weeks	NOAEL= 600	No effects on lung weight or histopathology	(ClinTrials, 1997a)	GLP study
Respiratory	Rat (n=20/group)	Inhalation	62.5, 125, 250, 500 or 1000 ppm	6.2 hours/day, 5 days/week for 14 weeks	NOAEL= 1000	No effects on lung weight or histopathology	(NTP, 2011)	GLP study
Respiratory	Rat (n=100/group)	Inhalation	125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 105 weeks	LOAEL= 125	Chronic active nasal inflammation and squamous metaplasia in the larynx	(NTP, 2011)	GLP study

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Respiratory	Rat (n=25/group)	Inhalation	100, 250, 500 or 750 ppm	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until sacrifice in F_0 males; or until GD 20 and from PND 5 until weaning of offspring (~PND 21) in F_0 females	NOAEL= 750	No effects on lung weight or histopathology	(WIL Research, 2001)	GLP study peer-reviewed by NTP
Respiratory	Mouse (n=10/group)	Inhalation	125, 250, 500, 1000 or 2000 ppm	6.2 hours/day, 5 days/week for 17 days	NOAEL= 250	Lesions in the lung and nose	(NTP, 2011)	GLP study
Respiratory	Mouse (n=20/group)	Inhalation	62.5, 125, 250 or 500 ppm	6.2 hours/day, 5 days/week for 14 weeks	NOAEL= 250	Cytoplasmic vacuolization in the nose, larynx, trachea, and lung	(NTP, 2011)	Lesions were detected almost exclusively in animals that died early
Respiratory	Mouse (n=100/group)	Inhalation	62.5, 125 or 250 ppm	6.2 hours/day, 5 days/week for 105 weeks	LOAEL= 62.5	Histopathological lesions in the nasal respiratory epithelium, larynx, trachea, and bronchioles	(NTP, 2011)	Effects occurred at all exposure concentrations; no NOAEL was identified
Developmental Effects	Rat (n=10/group)	Inhalation	100 , 400 or 800 ppm	8 hours/day during gestation (GDs 0-21) and lactation (PNDs 1-21)	NOAEL= 100	Decreased survival during lactation	(Furuhashi et al., 2006)	Quantitative data not available for pup survival, peer reviewed literature

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Developmental Effects	Rat (n=10/group)	Inhalation	100, 199, 598 or 996 ppm	6 hours/day on GDs 6-19; PNDs 4-20	NOAEL= 199	Decreased body weight gain in pups	(Huntingdon Life Sciences, 1999)	GLP study - effect coincided with decreased body weight gains during gestation (at ≥ 199 ppm)
Developmental Effects	Rat (n=25/group)	Inhalation	103, 503 or 1005 ppm	6 hours/day on GDs 6-19; PNDs 4-20	LOAEL = 103	Decreased fetal weight	(Huntingdon Life Sciences, 2001)	GLP study - effect coincided with decreased body weight gains during gestation (503 ppm and above)
Developmental Effects	Rat (n=25/group)	Inhalation	100, 250 or 500 ppm	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until sacrifice in males; or until GD 20 and from PND 5 until weaning of offspring (~PND 21) in females	NOAEL= 250	Decreased live litter size (F_1 females)	(WIL Research, 2001)	GLP study peer-reviewed by NTP
Developmental Effects	Rat (n=10-24/group)	Inhalation	100, 250 or 500 ppm	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until sacrifice in males; or until GD 20 and from PND 5 until weaning of offspring (~PND 21) in females	NOAEL = 100	Decreased pup body weights (F_1 PND 28 males)	(WIL Research, 2001)	GLP study peer-reviewed by NTP

Target Organ/ System[1]	Species[2]	Exposure Route	Concentration[3]	Duration[4]	POD[5] (ppm or mg/kg-day)	Effect[6]	Reference[7]	Comments[8]
Developmental Effects	Rat (n=10-24/group)	Inhalation	100, 250 or 500 ppm	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until sacrifice in males; or until GD 20 and from PND 5 until weaning of offspring (~PND 21) in females	NOAEL = 250	Decreased pup body weights (F_2 PNDs 14 and 21 males)	(WIL Research, 2001)	GLP study peer-reviewed by NTP
Developmental Effects	Rat (n=10-24/group)	Inhalation	100, 250 or 500 ppm	6 hours/day during pre-mating (≥ 70 days), throughout mating, and until sacrifice in males; or until GD 20 and from PND 5 until weaning of offspring (~PND 21) in females	NOAEL = 250	Decreased pup body weights (F_2 PNDs 14 and 21 females)	(WIL Research, 2001)	GLP study peer-reviewed by NTP

Notes:
[1]Inclusion of an entry in this table was based on availability of data deemed reliable from selected secondary sources. Therefore, this table is not comprehensive; additional information may be available from primary sources.
[2]Species (and sex in which the effect(s) at the POD were observed, if reported in only one sex). Studies were conducted in both sexes unless indicated otherwise in the Comments column.
[3]Control concentrations or doses are not included in the table.
[4]Acute exposures defined as those occurring within a single day. Chronic exposures defined as 10% or more of a lifetime (U.S. EPA, 2011).
[5]POD type can be LD_{50}, LC_{50}, NOAEL, LOAEL, or BMDL. Units are ppm for inhalation exposure and mg/kg-day for oral exposure. For repeated-dose studies, the preference was BMDL > NOAEL > LOAEL.
[6]The effect(s) listed were the most sensitive effects observed for that target organ/system in that study (i.e., the effect(s) upon which the POD was based).
[7]This column lists the primary reference for the reported data. The secondary source(s) from which the data were extracted are listed in the Comments column. Full citations for the primary references can be found in the associated secondary source(s).
[8]Information included in this column is variable, depending on the nature and extent of information provided in the secondary source(s) from which the entry was extracted.

GD = gestational day; PND = postnatal day

O-5 Carcinogenicity and Mutagenicity

There are no epidemiological studies on the effects of 1-BP exposure on human cancer.

The carcinogenicity of 1-BP has been studied in rats and mice in a two-year bioassay by the National Toxicology Program (NTP, 2011). Groups of 50 male and 50 female rats and mice were exposed to 1-BP vapor at concentrations of 62.5, 125, or 250 ppm (mice) and 125, 250, or 500 ppm (rats), 6 hours per day, 5 days per week for up to 105 weeks. Similar groups of 50 animals were exposed to clean air in the same inhalation chambers as the control groups. All animals were observed twice daily. Clinical findings were recorded for all animals every 4 weeks through week 93, every 2 weeks thereafter, and at the end of the studies. Rats and mice were weighed initially, weekly for the first 13 weeks, then every 4 weeks through week 93, every 2 weeks thereafter, and at the end of the studies. Complete necropsies and microscopic examinations were performed on all rats and mice.

At the end of the two-year bioassay, there were treatment-related skin tumors in male rats and large intestine tumors in female rats. Significantly increased incidence of lung tumors was found in female mice. Based on increased incidences of tumors in rats and mice, at multiple sites and the occurrence of rare tumors, it has been concluded that there is sufficient evidence of carcinogenicity in experimental animals for 1-BP. Each of these tumor types is described below.

O-5-1 Skin Tumors

In male rats, there were exposure concentration treatment-related increased incidences of keratoacanthoma, keratoacanthoma or squamous cell carcinoma (combined); and keratoacanthoma, basal cell adenoma, basal cell carcinoma, or squamous cell carcinoma (combined). The incidences of keratoacanthoma and of keratoacanthoma or squamous cell carcinoma (combined) in 250 ppm (12%) and 500 ppm (12%) males were significantly increased as compared to the controls (0% and 2%), and exceeded the historical control ranges (0-8%) for inhalation studies. The incidences of keratoacanthoma, basal cell adenoma, basal cell carcinoma, or squamous cell carcinoma (combined) were significantly increased in all exposed groups of males (125 ppm: 14%; 250 ppm: 18%; and 500 ppm: 20%) as compared to the controls (2%) and exceeded the historical control range (0-10%) for inhalation studies. In female rats, there were increased incidences of squamous cell papilloma, keratoacanthoma, basal cell adenoma, or basal cell carcinoma (combined) in the 500 ppm group (8%) as compared to the control (2%). Although the increased incidences were not significant, they exceeded the respective historical control ranges for inhalation studies.

O-5-2 Large Intestine Tumors

Large intestine tumors are rare tumors in the rat. The incidence of adenoma of the large intestine (colon or rectum) in 500 ppm females (5/50, 10%) was significantly greater than that in the controls (0%). The incidences in the 250 ppm (2%) and 500 ppm (4%) groups of females exceeded the historical controls in inhalation studies (0.1%). In 250 (4%) and 500 (2%) ppm

males, the incidences of adenoma of the large intestine were slightly increased compared to that in the controls (0%); although the increases were not statistically significant, the incidence in the 250 ppm group (4%) exceeded the historical control ranges (0-2%) for inhalation studies.

O-5-3 Lung Tumors

In the female mice, there were treatment-related increased incidences of alveolar/bronchiolar adenoma, alveolar/bronchiolar carcinoma, and alveolar/bronchiolar adenoma or carcinoma (combined). The incidence of alveolar/bronchiolar adenoma in 250 ppm females (20%) and the incidences of alveolar/bronchiolar carcinoma in 62.5 ppm (14%) and 125 ppm (10%) females were significantly increased as compared to the controls (0-2%). The incidences of alveolar/bronchiolar adenoma or carcinoma (combined) were significantly increased in all exposed groups (18%, 16% and 28% in low-, mid- and high-dosed groups) as compared to the controls (2%).

O-5-4 Pancreatic Tumors

The evidence that 1-BP exposure was associated with an increased incidence of pancreatic islet adenoma in male rats was equivocal. Although the incidences of pancreatic islet adenoma were significantly increased in all exposed groups compared to the chamber controls (0%, 10%, 8%, 10%), the incidences were within the historical control ranges for inhalation studies (0% to 12%). The incidences of pancreatic islet carcinoma in exposed male rats were not significantly different from that in the chamber controls and were not considered treatment related. The incidences of pancreatic islet adenoma or carcinoma (combined) were significantly increased only in the low-dose (20%) and mid-dose groups (18%) as compared with the chamber controls (6%); only the incidence in the low-dose group (20%) exceeded the historical control ranges for inhalation studies (6% to 18%).

O-5-5 Malignant Mesothelioma

There were increased incidences of malignant mesothelioma in male rats exposed to 1-BP as compared to the chamber controls: control, 0%; low-dose, 4%; mid-dose, 4%; and high-dose, 8%. The incidence of malignant mesothelioma in high-dose group (8%) was significantly greater than that of the chamber controls (0%) and exceeded that of the historical controls (0-6%) in inhalation studies. The overall strength of this evidence was considered equivocal because the increased incidence in the high-dose (500 ppm) group was s barely outside the historical control range (0% to 6%).

Under the conditions of these 2-year inhalation studies, there was clear evidence of carcinogenic activity of 1-BP in female F344/N rats based on increased incidences of adenoma of the large intestine. Increased incidences of skin neoplasms may also have been related to 1-BP exposure. There was some evidence of carcinogenic activity of 1-BP in male F344/N rats based on the increased incidences of epithelial neoplasms of the skin (keratoacanthoma, squamous cell carcinoma, and basal cell neoplasms). Increased incidences of malignant mesothelioma and pancreatic islet adenoma and carcinoma (combined) may also have been related to 1-BP exposure. There was clear evidence of carcinogenic activity of 1-BP in female B6C3F1 mice based on increased incidences of alveolar/bronchiolar neoplasms. There was no

evidence of carcinogenic activity of 1-BP in male B6C3F1 mice exposed to concentrations of 62.5, 125, or 250 ppm 1-BP. Based on increased incidences of tumors in rats and mice, at multiple sites and the occurrence of rare tumors, it has been concluded that there is sufficient evidence of carcinogenicity in experimental animals for 1-BP. The compound has been considered to be "reasonably to be anticipated as a human carcinogen" and will be listed in the next issue of Report on Carcinogens of the National Toxicology Program (NTP, 2013).

The tumor data on the skin, large intestine and lung in male and female rats and female mice (Table_Apx O-3) may be used for quantitative assessment of the potential risk of humans exposed to 1-BP.

Table_Apx O-3 Tumors induced by 1-BP in Rats and Mice

Animal	Tumor	Concentration (ppm)	Incidence
F344/N rats, male	Skin (keratoacanthoma, squamous-cell carcinoma, basal-cell adenoma or carcinoma combined)	0	1/50 (2%)
		125	7/50* (14%)
		250	9/50** (18%)
		500	10/50** (20%)
		Trend	p=0.003
F344/N rats, female	Large intestine (colon or rectum adenoma)	0	0/50 (0%)
		125	1/50 (2%)
		250	2/50 (4%)
		500	5/50* (10%)
		Trend	p=0.004
B6C3F1 mice, female	Lung (alveolar /bronchiolar adenoma or carcinoma combined)	0	1/50 (2%)
		62.5	9/50** (18%)
		125	8/50* (16%)
		250	14/50*** (28%)
		Trend	p<0.001

*$p\leq0.05$; **$p\leq0.01$; ***$p\leq0.001$

O-5-6 Genotoxicity

1-BP has been shown to bind covalently to DNA to form N7-guanine adducts in an *in vitro* system using calf thymus DNA (Lee et al., 2007). This is supportive of possible genotoxic potential; however, further studies are needed to identify the DNA adducts in animals exposed to 1-BP, particularly in *in vivo* studies, to provide information for mode of action consideration.

Mixed results have been reported in genotoxicity tests using bacteria. 1-BP was mutagenic in a dose-dependent manner in Salmonella typhimurium (*S. typhimurium*) strains TA100 and TA1535 when the assay was conducted using closed chambers/desiccators specifically designed for testing volatile substances (Barber et al., 1981). The data suggest that 1-BP may be a direct-acting mutagen since similar responses were observed both with and without metabolic

activation. A number of other studies reported negative responses in *S. typhimurium* and *Escherichia coli* (*E. coli*) but some of these studies were not conducted using the ppropriate methodology (*i.e*., treatment and incubation in a closed chamber) for testing a volatile substance (NTP, 2011; Kim et al., 1998; Elf Atochem S.A., 1993b). An NTP peer review committee considered the Barber (1981) study to be a well conducted, strong study (NTP, 2013).

1-BP was shown to induce base-pair mutations in the L5178Y mouse lymphoma cell assay, with and without S9 metabolic activation (Elf Atochem S.A., 1996b). Using the comet assay, (Toraason et al., 2006) demonstrated DNA damage in human leukocytes exposed to 1 mM 1-BP *in vitro*; there was also limited evidence that leukocytes from workers exposed to 1-BP may present a small risk for increased DNA damage. In contrast to these *in vitro* studies, negative results were reported with *in vivo* micronucleus assays in mice exposed to 1-BP via intraperitoneal (ip) injection, and in rats exposed via inhalation (Kim et al., 1998) and (NTP, 2011; Elf Atochem S.A., 1995). It should be noted, however, that a recent compilation of *in vivo* micronucleus data by (Benigni et al., 2012) showed that overall, a low correlation exists between *in vivo* micronucleus data and carcinogenicity, suggesting a potential for false negative carcinogenicity predictions. 1-BP was also negative in dominant lethal mutation assays conducted in ICR mice (Yu et al., 2008) and Sprague-Dawley rats (Saito-Suzuki et al., 1982).

Several known or proposed metabolites of 1-BP have been shown to be mutagenic (NTP, 2014; IARC, 2000, 1994). For example, both glycidol and propylene oxide are mutagenic in bacteria, yeast, Drosophila, and mammalian cells. These compounds have also been shown to induce DNA and chromosomal damage in rodent and human cells, and can form DNA adducts *in vitro*. α-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*. The available *in vivo* test results for glycidol indicate that it induces micronucleus formation, but not chromosomal aberrations in mice. Studies of propylene oxide indicated chromosomal damage evidenced by positive responses for micronucleus induction in mouse bone marrow and chromosomal aberration tests; DNA damage was evident in the sister chromatid exchange (SCE) assay.

Table_Apx O-4 Genotoxicity of 1-BP In Vitro

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	Reverse mutation	– (open test system)	– (open test system)	(Barber et al., 1981)
S. typhimurium TA100, TA1535	Reverse mutation	+ (closed test system)	+ (closed test system)	(Barber et al., 1981)
S. typhimurium TA97, TA98, TA100, TA 1535	Reverse mutation	–	–	(NTP, 2011)
Escherichia coli Wp2 uvrA/pKM101	Reverse mutation	–	–	(NTP, 2011)
Mammalian cells:				
Human hepatoma cell-line (HepG2)	DNA damage and repair, single strand breaks	–		(Hasspieler et al., 2006)
Human hepatoma cell-line (HepG2)	DNA damage and repair, repair activity	–		(Hasspieler et al., 2006)
Human leukocyte cells	DNA damage and repair	+		(Toraason et al., 2006)

+ = positive results; – = negative results

O-5-7 Metabolism, Structure-Activity Relationships and Mechanism/Mode of Action

Studies in experimental animals and humans indicate that 1-BP can be absorbed following inhalation, oral, or dermal exposure (Cheever et al., 2009; NIOSH, 2007). Metabolism studies show that oxidation by P450 enzymes (e.g., CYP2E1) and glutathione conjugation are the primary metabolic pathways (Garner et al., 2006; Ishidao et al., 2002). Over 20 metabolites have been identified in rodent studies, including the four metabolites that can be detected in urine samples of workers exposed to 1-BP (Hanley et al., 2009). Besides being a direct-acting alkylating agent, 1-BP can also be metabolically activated to the epoxide intermediate via hydroxylation at the 2-position followed by dehydrobromination. Mice appear to have a greater capacity to oxidize 1-BP than rats (Garner et al., 2006). This species difference in metabolic capacity may explain why mice were found to be more sensitive to 1-BP toxicity than rats. The identified or putative reactive intermediates for 1-BP include glycidol, propylene oxide,

α-bromohydrin and 2-oxo-1-BP (NTP, 2014; Ishidao et al., 2002; Mitchell et al., 1998). Detoxification of 1-BP metabolites occurs primarily via glutathione-S-transferase (GST) - mediated conjugation with glutathione (NTP, 2014; Liu et al., 2009; Garner et al., 2006).

1-BP is expected to be a good alkylating agent because bromine is a good leaving group. Two of its closest homologs, bromoethane and 1-bromobutane, were both shown to be mutagenic in the Ames Salmonella test; in both cases, use of desiccators was needed to show positive results (NTP, 1989; Simmon et al., 1977). Bromoethane is a known carcinogen via the inhalation route of exposure (NTP, 1989), whereas 1-bromobutane has not been tested for carcinogenic activity. 1-BP is a relatively soft electrophile which is expected to preferentially react with sulfhydryl (-SH) residues on glutathione and proteins before binding to DNA. Besides being a direct-acting alkylating agent, 1-BP may be metabolically activated to genotoxic intermediates (see above). A number of other structurally-related halogenated alkanes such as 1,2-dibromoethane (ethylene dibromide) (IARC, 1999e), dichloromethane (IARC, 1999d), 1,2-dichloroethane (IARC, 1999b), 1,2-dibromo-3-chloropropane (IARC, 1999a) and 1,2,3-trichloropropane (IARC, 1999c) have been classified as "probably carcinogenic to humans (group 2A)" or "possibly carcinogenic to human carcinogens" (group 2B) by the International Agency for Research on Cancer; however, some of these chemicals may have different mechanisms.

The exact mechanism/mode of action for 1-BP carcinogenesis is not clearly understood. More research (e.g., organ-specific *in vivo* DNA adduct studies, oxidative stress) is needed to identify key molecular events. Since 1-BP can induce tumors in multiple organs and can act directly as an alkylating agent, as well as indirectly via metabolically activated reactive intermediates such as glycidol and propylene oxide, it may have different mechanisms in different target organs. At least four possible mechanisms---genotoxicity, oxidative stress, immunosuppression, and cell proliferation—have been suggested (NTP, 2013). These mechanisms can act synergistically to complete the multi-stage process of carcinogenesis.

As discussed in the previous section on genotoxicity, 1-BP and its genotoxic reactive intermediates can induce DNA mutations and/or chromosome aberrations. Although the results are not as clear cut for 1-BP itself, some of the discrepancies may be explained by testing limitations. Available *in vitro* DNA binding studies and structure-activity relationship analyses support the genotoxic potential of 1-BP. The induction of tumors in multiple targets by 1-BP is also a common characteristic of genotoxic carcinogens. Overall, there is a justifiable basis to support a probable mutagenic mode of action for 1-BP carcinogenesis.

Oxidative stress due to cellular glutathione depletion could contribute to the carcinogenicity of 1-BP (Morgan et al., 2011). Oxidative stress is an important epigenetic mechanism that can contribute to all three stages of carcinogenesis - oxidation can induce initiation (as a result of DNA damage), promotion (as a result of compensatory cell proliferation in response to cell necrosis), and progression (via oxidative changes in signal transduction and gene expression; *rev*. (Woo and Lai, 2003). Exposure to 1-BP has also been shown to deplete glutathione in various tissues (e.g., (Liu et al., 2009; Lee et al., 2007; Wang et al., 2003), which can lead to a loss of protection against electrophiles.

Besides genotoxicity and oxidative stress, 1-BP has been shown to cause immunosuppression in rodents (Anderson et al., 2010; Lee et al., 2007). Immunosuppression can facilitate tumor progression by lowering the immunosurveillance process against tumor growth. There is also some evidence that 1-BP can cause γ-aminobutyric acid (GABA) dysfunction and thereby impact cell proliferation, differentiation and migration of neuronal cells (NTP, 2013).

Appendix P BENCHMARK DOSE ANALYSIS

BMD modeling was performed using USEPA's BMD Software package (BMDS Version 2.6), in a manner consistent with EPA Benchmark Dose Technical Guidance. Continuous models were used to fit dose-response data and BMRs were selected for each endpoint individually. In particular a BMR of 5% was used for developmental endpoints (Kavlock et al., 1995). The dose metric for all endpoints was the exposure concentration in ppm.

P-1 Benchmark Dose Modeling of Non-Cancer Effects for Acute Exposures

EPA/OPPT selected the decreased live litter size observed in the 2-generation reproductive and developmental study by WIL Research (2001) as the most relevant endpoint for calculating risks associated with acute worker and consumer scenarios. A BMR of 5% was used to address the relative severity of this endpoint (U.S. EPA, 2012a) see section 3.4.1. For comparison the modeling results with a BMR of 1 standard deviation and 1% relative deviation are also shown. The doses and response data used for the modeling are presented in Table_Apx P-1.

Table_Apx P-1 Litter Size Data Selected for Dose-Response Modeling for 1-BP

Dose (ppm)	Number of litters	Mean litter size	Standard Deviation
0	23	14.4	2.21
100	25	13.3	3.72
250	22	12.3	4.47
500	11	8.3	4.1

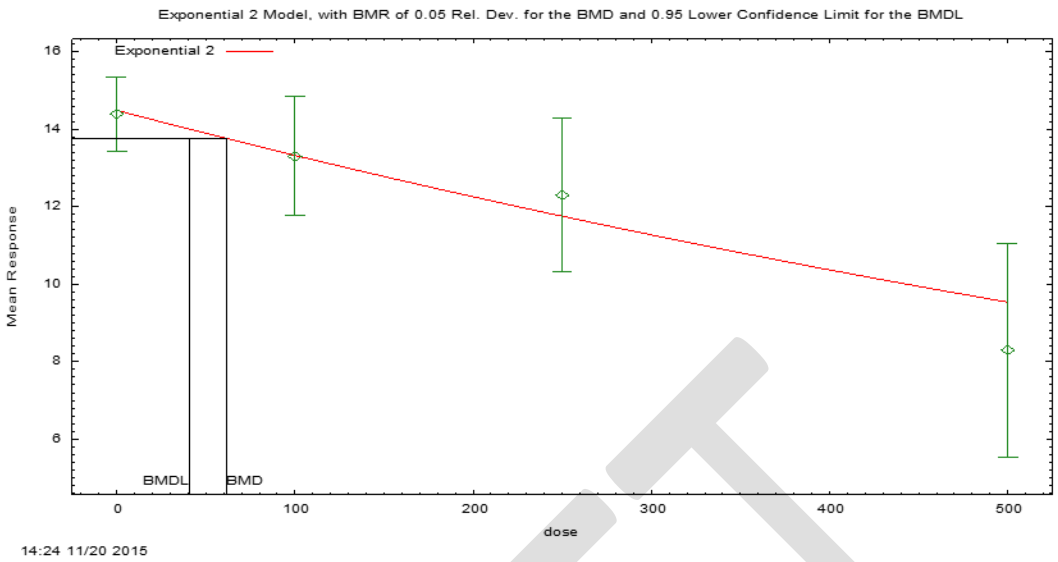
The best fitting model was selected based on Akaike information criterion (AIC; lower value indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit), ratio of the BMC:BMCL (lower value indicates less model uncertainty) and visual inspection. Comparisons of model fits obtained are provided in Table_Apx P-2. The best-fitting model (Exponential M2), based on the criteria described above, is indicated in bold. For the best fitting model a plot of the model is shown in Figure_Apx P-1, the model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown. Although the means were well-modeled the variances are not well modeled by the non-homogeneous variance model (the non-homogeneous variance model was used because the BMDS test 2 *p*-value = 0.0130). To investigate the effect of the poor modeling of the variances on the BMDL, the models were run using the smallest dose standard deviation (2.21), highest (4.47) and

pooled (3.54) for all dose levels and the results are summarized in Table_Apx P-3. As shown in the last column of Table_Apx P-3 the ratios BMDLs for the lowest to the highest variance for the two best fitting models the Linear and Exponential (M2) models are 1.15 and 1.20, respectively. Overall the adjustment of the variances from most-variable to least-variable for all of the models makes little difference on the BMDL. This is strong evidence that the poor variance modeling for the original data is not substantially impacting the BMDL estimates. It is reasonable to use the non-homogeneous Exponential M2 model for the original data because it has the lowest AIC of all the model choices for the original data and therefore a BMDL of 41 ppm (40.7 ppm rounded to two significant figures) was selected for this endpoint.

Table_Apx P-2 Summary of BMD Modeling Results for Reduced Litter Size in F_0 Generation Exposed to 1-BP by Inhalation; BMRs of 1 Standard Deviation, and 5% and 1% Relative Deviation From Control Mean.

Model[a]	Goodness of fit		BMD_{1SD} (ppm)	$BMDL_{1SD}$ (ppm)	BMD_{5RD} (ppm)	$BMDL_{5RD}$ (ppm)	BMD_{1RD} (ppm)	$BMDL_{1RD}$ (ppm)	Basis for model selection
	p-value	AIC							
Exponential (M2) **Exponential (M3)[b]**	**0.533**	**291.10**	256	158	**61.3**	**40.7**	12.0	7.97	**The Exponential (M2) model was selected based on the lowest AIC and adequate fit by visual inspection.**
Power[c] Polynomial 3°[d] Polynomial 2°[e] Linear	0.433	291.51	281	189	69.9	49.8	14.0	9.95	
Hill	0.722	291.96	178	error[g]	35.8	10.4	6.36	1.69	
Exponential (M4) Exponential (M5)[f]	0.622	292.08	181	69.4	40.4	17.8	7.48	3.23	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.0130), selected model in bold; scaled residuals for selected model for doses 0, 100, 250, and 500 ppm were -0.16, -0.05, 0.66, -0.76, respectively.
[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.
[c] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.
[d] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[e] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[f] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.
[g] BMDL computation failed for this model.



Figure_Apx P-1 Plot of Mean Response by Dose in ppm with Fitted Curve for Exponential (M2) Model with Modeled Variance for Reduced Litter Size in F_0 Generation Exposed to 1-BP by Inhalation; BMR = 5% Relative Deviation from Control Mean.

Exponential Model. (Version: 1.10; Date: 01/12/2015)
The form of the response function is: Y[dose] = a * exp(sign * b * dose)
A modeled variance is fit

Benchmark Dose Computation.
BMR = 5% Relative deviation
BMD = 61.3264
BMDL at the 95% confidence level = 40.6605

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	10.4606	6.08025
rho	-3.14328	-1.44632
a	14.4915	10.5312
b	0.000836398	0.00102437
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	23	14.4	14.49	2.21	2.8	-0.1569
100	25	13.3	13.33	3.72	3.19	-0.04505
250	22	12.3	11.76	4.47	3.88	0.6554
500	11	8.3	9.54	4.1	5.4	-0.7614

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-143.3786	5	296.7571
A2	-137.9879	8	291.9758
A3	-140.9173	6	293.8347
R	-153.5054	2	311.0108
2	-141.5475	4	291.095

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	31.03	6	<0.0001
Test 2	10.78	3	0.01297
Test 3	5.859	2	0.05343
Test 4	1.26	2	0.5325

Table_Apx P-3 BMD Modeling Results for Reduced Litter Size in F_0 Generation Following Inhalation Exposure of Parental Rats to 1-BP in a Two-Generation Study with Variances Fixed at Smallest, Pooled and Highest Values.

Model[a]	Smallest Standard Deviation				Pooled Standard Deviation				Largest Standard Deviation				Ratio BMDLs Smallest to Largest Std Dev
	Goodness of fit		BMD_{5RD} (ppm)	$BMDL_{5RD}$ (ppm)	Goodness of fit		BMD_{5RD} (ppm)	$BMDL_{5RD}$ (ppm)	Goodness of fit		BMD_{5RD} (ppm)	$BMDL_{5RD}$ (ppm)	
	p-value	AIC			*p*-value	AIC			*p*-value	AIC			
Linear	0.279	213.92	**63.5**	**53.5**	0.605	288.69	**63.5**	**49.2**	0.729	326.11	**63.5**	**46.6**	**1.15**
Exponential (M2)	0.112	215.74	**54.9**	**44.1**	0.420	289.42	**54.9**	**39.4**	0.579	326.57	**54.9**	**36.7**	**1.20**
Exponential (M4)	0.112	215.74	54.9	42.6	0.420	289.42	54.9	34.4	0.579	326.57	54.9	29.1	1.46
Polynomial 3°	0.506	213.81	96.4	58.4	0.678	289.86	96.4	51.1	0.742	327.58	96.4	47.8	1.22
Polynomial 2°	0.393	214.09	105	57.4	0.593	289.97	105	50.8	0.672	327.65	105	47.6	1.21
Power	0.303	214.43	115	56.4	0.519	290.10	115	50.5	0.609	327.74	115	47.4	1.19
Exponential (M3)	0.239	214.75	127	56.1	0.461	290.23	127	42.6	0.559	327.82	127	38.7	1.45
Exponential (M5)	0.239	214.75	127	56.1	N/A[b]	292.23	127	42.6	0.559	327.82	127	33.0	1.70
Hill	N/A[b]	216.43	115	56.4	N/A[b]	292.10	116	50.3	N/A[b]	329.74	116	47.2	1.19

[a] Constant variance case presented (BMDS Test 2 *p*-value = 1.000, BMDS Test 3 *p*-value = 1.000), no model was selected as a best-fitting model.
[b] No available degrees of freedom to calculate a goodness of fit value.

P-2 Benchmark Dose Modeling of Non-Cancer Effects for Chronic Exposures

EPA/OPPT selected multiple endpoints for quantitative dose-response analysis with BMDS and calculating risks associated with chronic worker scenarios including: include liver toxicity, kidney toxicity, neurotoxicity, reproductive toxicity, and developmental toxicity. The doses, response data and BMD modeling results are presented below by effect.

P-2-1 Increased Incidence of Vacuolization of Centrilobular Hepatocytes in Males

Increased incidence of vacuolization of centrilobular hepatocytes was observed in males of the F_0 generation of the reproductive and developmental study by WIL Laboratories (2001). Dichotomous models were used to fit dose response data. A BMR of 10% added risk was choosen per EPA Benchmark Dose Technical Guidance (U.S. EPA, 2012a). The doses and response data used for the modeling are presented in Table_Apx P-4.

Table_Apx P-4 Incidence of Vacuolization of Centrilobular Hepatocytes Selected for Dose-Response Modeling for 1-BP

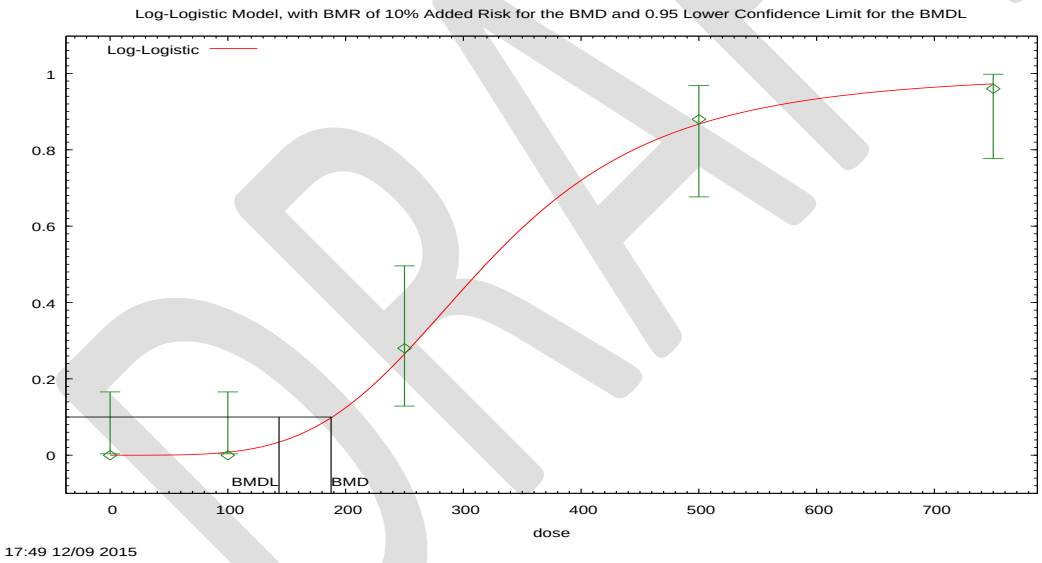
Dose (ppm)	Number of animals	Incidence
0	25	0
100	25	0
250	25	7
500	25	22
750	25	24

The BMD modeling results for vacuolization of centrilobular hepatocytes are summarized in Table_Apx P-5. The best fitting model was the LogLogistic based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. For the best fitting model a plot of the model is shown in Figure_Apx P-2. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below.

Table_Apx P-5 BMD Modeling Results for Vacuolization of Centrilobular Hepatocytes in Male F_0 Rats Following Inhalation Exposure to 1-BP in a Two-Generation Study

Model[a]	Goodness of fit		$BMD_{10PctAdd}$ (ppm)	$BMDL_{10PctAdd}$ (ppm)	Basis for model selection
	p-value	AIC			
LogLogistic	**0.939**	**60.974**	**188**	**143**	**LogLogistic model was selected based on the lowest AIC, highest goodness of fit *p*-value and adequate fit by visual inspection.**
LogProbit	0.907	60.980	185	142	
Gamma	0.691	61.912	178	130	
Multistage 2°	0.538	63.187	129	98.5	
Weibull	0.360	64.026	158	110	
Logistic	0.146	65.548	186	142	
Probit	0.0542	66.345	177	133	
Quantal-Linear	0.0025	81.794	41.1	32.2	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 100, 250, 500, and 750 ppm were 0, -0.45, 0.12, 0.15, -0.41, respectively.



Figure_Apx P-2 Plot of Mean Response by Dose with Fitted Curve for the Selected Model (LogLogistic) for Vacuolization of Centrilobular Hepatocytes in Male Rats Exposed to 1-BP Via Inhalation in ppm; BMR 10% Added Risk.

Logistic Model. (Version: 2.14; Date: 2/28/2013)
The form of the probability function is: P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]
Slope parameter is restricted as slope >= 1

Benchmark Dose Computation.
BMR = 10% Added risk
BMD = 187.639
BMDL at the 95% confidence level = 143.489

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0	0
intercept	-2.4067E+01	-2.0600E+01
slope	4.17795	3.60147

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	*p*-value
Full model	-28.2	5			
Fitted model	-28.49	2	0.58301	3	0.9
Reduced model	-85.19	1	113.996	4	<.0001

AIC: = 60.9741

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	25	0
100	0.0079	0.199	0	25	-0.45
250	0.2693	6.731	7	25	0.12
500	0.8696	21.74	22	25	0.15
750	0.9732	24.33	24	25	-0.41

Chi^2 = 0.41 d.f = 3 *p*-value = 0.9391

P-2-2 Increased Incidence of Vacuolization of Centrilobular Hepatocytes in Males

Increased incidence of vacuolization of centrilobular hepatocytes was observed in males of the ClinTrials study (1997a). Dichotomous models were used to fit dose response data. A BMR of 10% added risk was choosen per EPA Benchmark Dose Technical Guidance (U.S. EPA, 2012a). The doses and response data used for the modeling are presented in Table_Apx P-6.

Table_Apx P-6 Incidence of Vacuolization of Centrilobular Hepatocytes Selected for Dose-Response Modeling for 1-BP

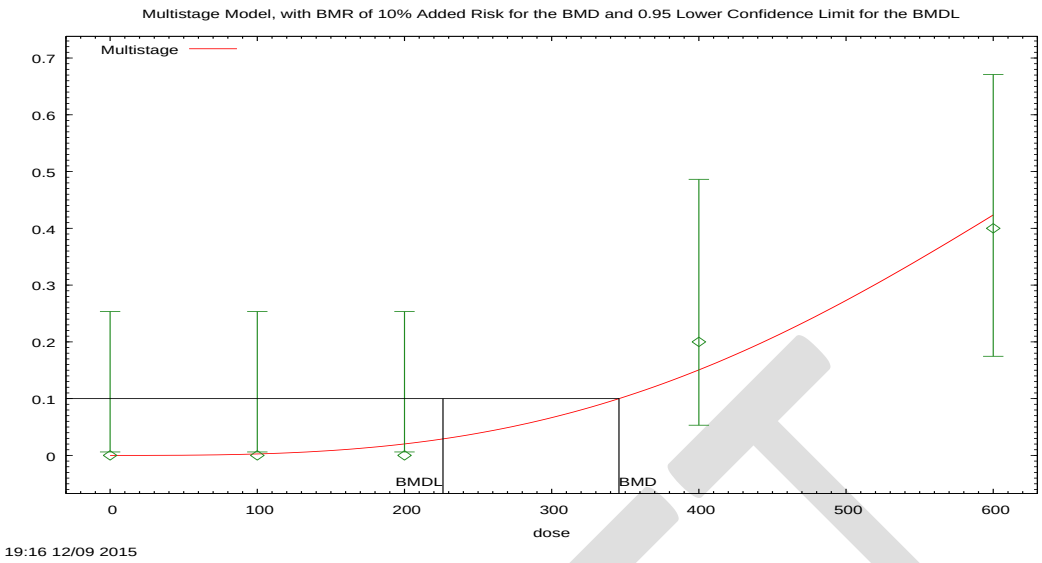
Dose (ppm)	Number of animals	Incidence
0	15	0
100	15	0
200	15	0
400	15	3
800	15	6

The BMD modeling results for vacuolization of centrilobular hepatocytes are summarized inTable_Apx P-7. The best fitting model was the LogLogistic based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. For the best fitting model a plot of the model is shown in Figure_Apx P-3. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below.

Table_Apx P-7 BMD Modeling Results for Vacuolization of Centrilobular Hepatocytes in Male Rats Following Inhalation Exposure to 1-BP

Model[a]	Goodness of fit		$BMD_{10PctAdd}$ (ppm)	$BMDL_{10PctAdd}$ (ppm)	Basis for model selection
	p-value	AIC			
Multistage 3°	**0.955**	**38.189**	**346**	**226**	**Multistage 3° model was selected based on the lowest AIC, highest goodness of fit *p*-value and adequate fit by visual inspection.**
Multistage 2°	0.898	39.202	289	198	
LogProbit	0.951	39.678	345	225	
Gamma	0.919	39.874	349	227	
LogLogistic	0.903	40.003	349	224	
Weibull	0.872	40.180	351	222	
Probit	0.773	40.585	370	275	
Logistic	0.662	41.195	382	290	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 100, 200, 400, and 600 ppm were 0, -0.2, -0.56, 0.54, -0.18, respectively.



Figure_Apx P-3 Plot of Mean Response by Dose with Fitted Curve for the Selected Model (Multistage 3°) for Vacuolization of Centrilobular Hepatocytes in Male Rats Exposed to 1-BP Via Inhalation in ppm; BMR 10% Added Risk.

Multistage Model. (Version: 3.4; Date: 05/02/2014)
The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

Benchmark Dose Computation.
BMR = 10% Added risk
BMD = 345.704
BMDL at the 95% confidence level = 226.133

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0	0
Beta(1)	0	0
Beta(2)	0	1.4788E-06
Beta(3)	2.5502E-09	0

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	*p*-value
Full model	-17.6	5			
Fitted model	-18.09	1	0.986987	4	0.91
Reduced model	-27.52	1	19.8363	4	0

AIC: = 38.1894

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	15	0
100	0.0025	0.038	0	15	-0.2
200	0.0202	0.303	0	15	-0.56
400	0.1506	2.259	3	15	0.54
600	0.4235	6.353	6	15	-0.18

Chi^2 = 0.67 d.f = 4 *p*-value = 0.9552

P-2-3 Increased Incidence of Vacuolization of Centrilobular Hepatocytes in Females

Increased incidence of vacuolization of centrilobular hepatocytes was observed in females of the F_0 generation of the reproductive and developmental study by WIL Laboratories (2001). Dichotomous models were used to fit dose response data. A BMR of 10% added risk was choosen per EPA Benchmark Dose Technical Guidance (U.S. EPA, 2012a). The doses and response data used for the modeling are presented in Table_Apx P-8.

Table_Apx P-8 Incidence of Vacuolization of Centrilobular Hepatocytes Selected for Dose-Response Modeling for 1-BP

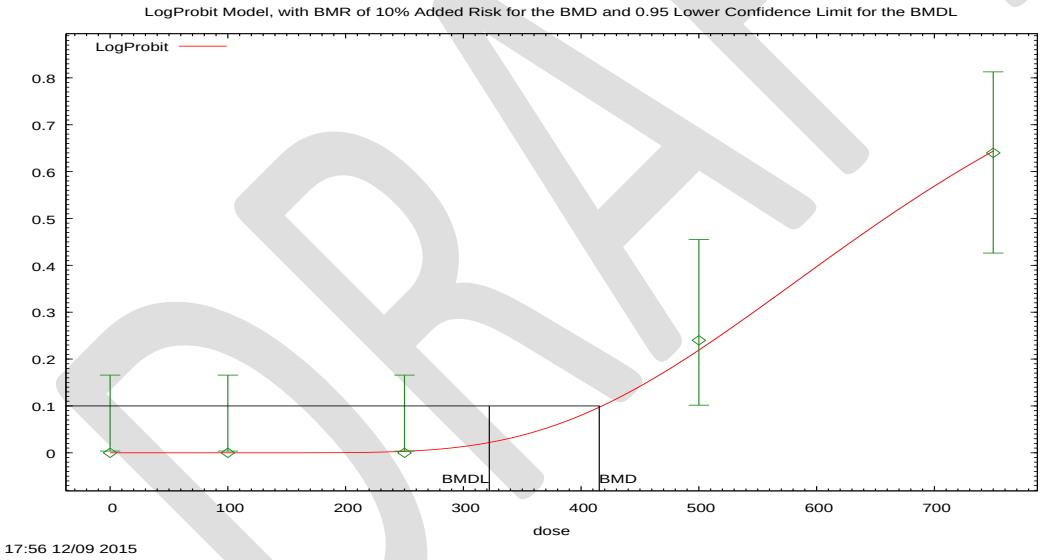
Dose (ppm)	Number of animals	Incidence
0	25	0
100	25	0
250	25	0
500	25	6
750	25	16

The BMD modeling results for vacuolization of centrilobular hepatocytes are summarized in Table_Apx P-9. The best fitting model was the LogProbit based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. For the best fitting model a plot of the model is shown in Figure_Apx P-4. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below.

Table_Apx P-9 BMD Modeling Results for Vacuolization of Centrilobular Hepatocytes in Female F_0 Rats Following Inhalation Exposure to 1-BP in a Two-Generation Study

Model[a]	Goodness of fit		$BMD_{10PctAdd}$ (ppm)	$BMDL_{10PctAdd}$ (ppm)	Basis for model selection
	p-value	AIC			
LogProbit	**0.988**	**64.438**	**415**	**322**	**LogProbit model was selected based on the lowest AIC, highest goodness of fit *p*-value and adequate fit by visual inspection.**
Gamma	0.965	64.648	416	320	
LogLogistic	0.945	64.843	415	320	
Weibull	0.879	65.283	411	310	
Probit	0.826	65.496	423	335	
Logistic	0.661	66.491	431	347	
Multistage 2°	0.410	68.583	279	228	
Quantal-Linear	0.0134	80.285	153	109	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 100, 250, 500, and 750 ppm were 0, 0, -0.29, 0.19, -0.11, respectively.



Figure_Apx P-4 Plot of Mean Response by Dose with Fitted Curve for the Selected Model (LogLogistic) for Vacuolization of Centrilobular Hepatocytes in Female Rats Exposed to 1-BP Via Inhalation in ppm; BMR 10% Added Risk.

Probit Model. (Version: 3.3; Date: 2/28/2013)
The form of the probability function is: P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),where CumNorm(.) is the cumulative normal distribution function
Slope parameter is not restricted

Benchmark Dose Computation.
BMR = 10% Added risk

BMD = 415.388
BMDL at the 95% confidence level = 322.058

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0	0
intercept	-1.8305E+01	-7.9627E+00
slope	2.82354	1.1917

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	*p*-value
Full model	-30.11	5			
Fitted model	-30.22	2	0.213311	3	0.98
Reduced model	-58.16	1	56.0935	4	<.0001

AIC: = 64.4382

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0	0	0	25	0
100	0	0	0	25	0
250	0.0033	0.083	0	25	-0.29
500	0.2242	5.605	6	25	0.19
750	0.6505	16.263	16	25	-0.11

Chi^2 = 0.13 d.f = 3 *p*-value = 0.9879

P-2-4 Increased Incidence of Renal Pelvic Mineralization in Males

Increased incidence of renal pelvic mineralization was observed in males of the F_0 generation of the reproductive and developmental study by WIL Laboratories (2001). Dichotomous models were used to fit dose response data. A BMR of 10% added risk was choosen per EPA Benchmark Dose Technical Guidance (U.S. EPA, 2012a). The doses and response data used for the modeling are presented in Table_Apx P-10.

Table_Apx P-10 Incidence of Renal Pelvic Mineralization Selected for Dose-Response Modeling for 1-BP

Dose (ppm)	Number of animals	Incidence
0	25	1
100	25	0
250	25	1
500	25	2
750	25	6

The BMD modeling results for vacuolization of renal pelvic mineralization are summarized inTable_Apx P-11. The best fitting model was the Multistage 3° based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. For the best fitting model a plot of the model is shown in Figure_Apx P-5. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below.

Table_Apx P-11 BMD Modeling Results for Renal Pelvic Mineralization in Male F_0 Rats Following Inhalation Exposure to 1-BP in a Two-Generation Study

Model[a]	Goodness of fit		$BMD_{10PctAdd}$ (ppm)	$BMDL_{10PctAdd}$ (ppm)	Basis for model selection
	p-value	AIC			
Multistage 3°	**0.789**	**63.835**	**571**	**386**	**Multistage 3° model was selected based on the lowest AIC, highest goodness of fit *p*-value and adequate fit by visual inspection**
Multistage 2°	0.668	64.258	527	368	
Logistic	0.629	64.260	545	434	
Probit	0.567	64.488	526	408	
Weibull	0.603	65.825	581	375	
LogLogistic	0.602	65.835	579	371	
Gamma	0.597	65.856	575	371	
LogProbit	0.597	65.894	577	355	
Quantal-Linear	0.326	66.496	507	284	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 100, 250, 500, and 750 ppm were 0.6, -0.76, 0.26, -0.18, 0.07, respectively.

Figure_Apx P-5 Plot of Mean Response by Dose with Fitted Curve for the Selected Model (Multistage 3°) for Renal Pelvic Mineralization in Male Rats Exposed to 1-BP Via Inhalation in ppm; BMR 10% Added Risk.

Multistage Model. (Version: 3.4; Date: 05/02/2014)
The form of the probability function is: P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2...)]

Benchmark Dose Computation.
BMR = 10% Added risk
BMD = 571.342
BMDL at the 95% confidence level = 385.532

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.0222219	0.00963337
Beta(1)	0	0
Beta(2)	0	0
Beta(3)	5.7848E-10	5.8917E-10

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	*p*-value
Full model	-29.14	5			
Fitted model	-29.92	2	1.5483	3	0.67
Reduced model	-34.85	1	11.4055	4	0.02

AIC: = 63.8352

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0222	0.556	1	25	0.6
100	0.0228	0.57	0	25	-0.76
250	0.031	0.776	1	25	0.26
500	0.0904	2.261	2	25	-0.18
750	0.234	5.849	6	25	0.07

Chi^2 = 1.05 d.f = 3 *p*-value = 0.7887

P-2-5 Increased Incidence of Renal Pelvic Mineralization in Females

Increased incidence of renal pelvic mineralization was observed in females of the F_0 generation of the reproductive and developmental study by WIL Laboratories (2001). Dichotomous models were used to fit dose response data. A BMR of 10% added risk was choosen per EPA Benchmark Dose Technical Guidance (U.S. EPA, 2012a). The doses and response data used for the modeling are presented in Table_Apx P-12.

Table_Apx P-12 Incidence of Renal Pelvic Mineralization Selected for Dose-Response Modeling for 1-BP

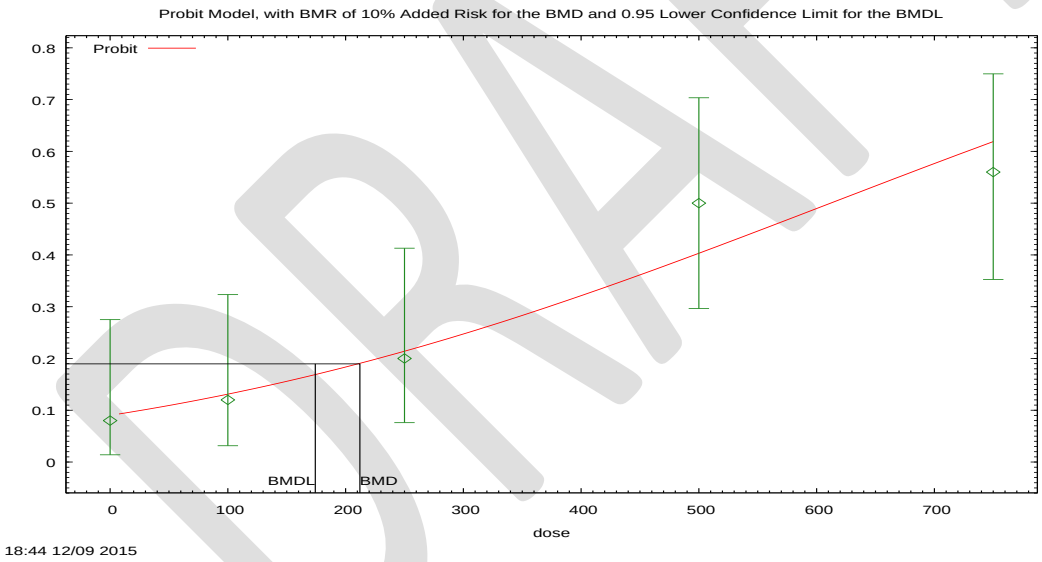
Dose (ppm)	Number of animals	Incidence
0	25	2
100	25	3
250	25	5
500	24	12
750	25	14

The BMD modeling results for vacuolization of renal pelvic mineralization are summarized in Table_Apx P-13. The best fitting model was the LogProbit based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. For the best fitting model a plot of the model is shown in Figure_Apx P-6. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below.

Table_Apx P-13 BMD Modeling Results for Renal Pelvic Mineralization in Female F_0 Rats Following Inhalation Exposure to 1-BP in a Two-Generation Study

Model[a]	Goodness of fit		$BMD_{10PctAdd}$ (ppm)	$BMDL_{10PctAdd}$ (ppm)	Basis for model selection
	p-value	AIC			
Probit	**0.708**	**130.24**	**212**	**174**	**Probit model was selected based on the lowest AIC, highest goodness of fit *p*-value and adequate fit by visual inspection.**
Quantal-Linear	0.703	130.32	113	79.3	
Logistic	0.664	130.43	228	186	
LogProbit	0.735	131.49	195	70.4	
LogLogistic	0.728	131.51	187	69.9	
Gamma	0.683	131.63	182	82.8	
Weibull	0.662	131.70	174	82.5	
Multistage 2°	0.610	131.86	164	81.6	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 100, 250, 500, and 750 ppm were -0.17, -0.15, -0.16, 0.99, -0.58, respectively.



Figure_Apx P-6 Plot of Mean Response by Dose with Fitted Curve for the Selected Model (Probit) for Renal Pelvic Mineralization in Female Rats Exposed to 1-BP Via Inhalation in ppm; BMR 10% Added Risk.

Probit Model. (Version: 3.3; Date: 2/28/2013)
The form of the probability function is: P[response] = CumNorm(Intercept+Slope*Dose), where CumNorm(.) is the cumulative normal distribution function
Slope parameter is not restricted

Benchmark Dose Computation.
BMR = 10% Added risk
BMD = 212.127
BMDL at the 95% confidence level = 174.256

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	n/a	0
intercept	-1.3432E+00	-1.3433E+00
slope	0.00218661	0.00218429

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	*p*-value
Full model	-62.44	5			
Fitted model	-63.12	2	1.36613	3	0.71
Reduced model	-74.7	1	24.5328	4	<.0001

AIC: = 130.239

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0896	2.24	2	25	-0.17
100	0.1304	3.26	3	25	-0.15
250	0.2129	5.321	5	25	-0.16
500	0.4013	9.632	12	24	0.99
750	0.6167	15.417	14	25	-0.58

Chi^2 = 1.39 d.f = 3 *p*-value = 0.7082

P-2-6 Decreased Seminal Vesicle Weight

Decreased relative and absolute seminal vesicle weights were observed in (Ichihara et al., 2000b). Continuous models were used to fit dose-response data for both absolute and relative seminal vesicle weights. A BMR 1 standard deviation was choosen per EPA Benchmark Dose Technical Guidance (U.S. EPA, 2012a). Both absolute and relative organ weights may be relevant for reproductive organs like the seminal vesicle as described in EPA's Guidelines for Reproductive Toxicity Risk Assessment (U.S. EPA, 1996). In this case by coincidence the BMDL was the same (38 ppm) for both absolute and relative seminal vesicle weights and therefore this endpoint is refered to as absolute/relative seminal vesicle weight in Table 3- and the

following text and tables. The doses, response data and BMD modeling results are presented for relative and then absolute seminal vesicle weights below.

P-2-6-1 Decreased Relative Seminal Vesicle Weight

The doses and response data used for relative seminal vesicle weight are presented in Table_Apx P-14.

Table_Apx P-14 Relative Seminal Vesicle Weight Data Selected for Dose-Response Modeling for 1-BP

Dose (ppm)	Number of animals	Relative Weight (mg/g BW)	Standard Deviation
0	8	4.35	0.62
200	9	3.23	0.55
400	9	3.17	0.67
800	9	2.62	0.87

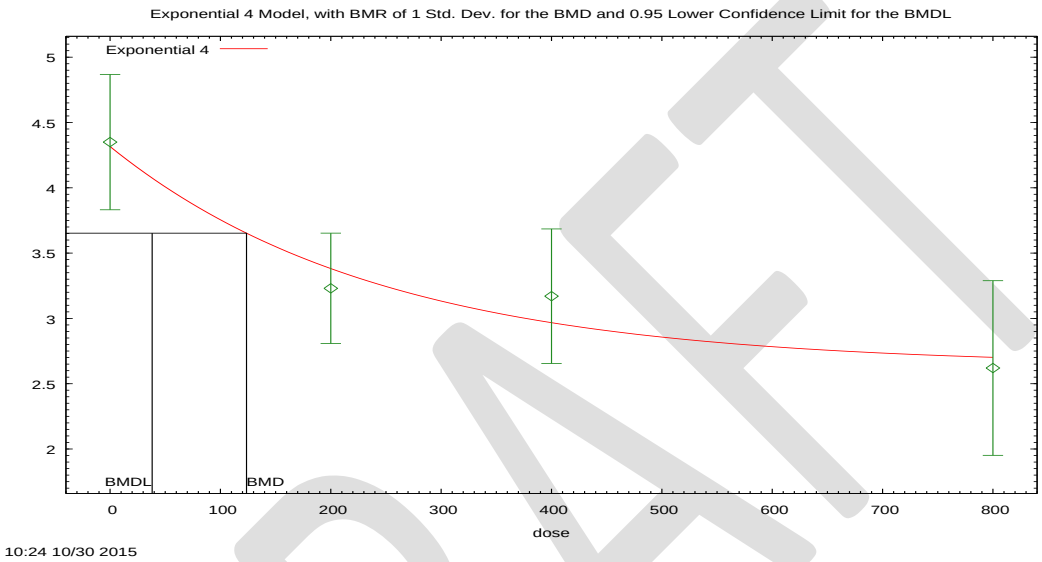
Comparisons of model fits obtained are provided in Table_Apx P-15. Models with homogeneous variance were used because the BMDS Test 2 *p*-value was 0.543. The Hill model was excluded because the BMD to BMDL ratio was 7.34. Of the remaining models the best fitting model (Exponential (M4)) was selected based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. The Exponential (M4) model had an acceptable BMD to BMDL ratio of 3.2 and is indicated in bold. For the best fitting model a plot of the model is shown in Figure_Apx P-7. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below.

Table_Apx P-15 Summary of BMD Modeling Results for Relative Seminal Vesicle Weight in Rats Exposed to 1-BP by Inhalation

Model[a]	Goodness of fit		BMD_{10RD} (ppm)	$BMDL_{10RD}$ (ppm)	BMD_{1SD} (ppm)	$BMDL_{1SD}$ (ppm)	Basis for model selection
	p-value	AIC					
Hill	0.298	13.857	57.2	6.72	101	13.7	**For models with BMD to BMDL ratios less than 5 (this excludes the Hill model), the Exponential (M4) model was selected based on the lowest AIC, highest goodness of fit *p*-value and adequate fit by visual inspection.**
Exponential (M4) **Exponential (M5)[b]**	**0.221**	**14.274**	73.1	21.4	**124**	**38.1**	
Exponential (M2) Exponential (M3)[c]	0.107	15.240	170	123	301	199	
Power[d] Polynomial 2°[e] Linear[f]	0.0604	16.386	213	165	376	267	
Polynomial 3°[g]	0.0604	16.386	213	165	376	267	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.543), selected model in bold; scaled residuals for selected model for doses 0, 200, 400, and 800 ppm were 0.15, -0.68, 0.92, -0.37, respectively.
[b] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

[c] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.
[d] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.
[e] For the Polynomial 2° model, the *b2* coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[f] The Linear model may appear equivalent to the Polynomial 3° model, however differences exist in digits not displayed in the table.
[g] The Polynomial 3° model may appear equivalent to the Power model, however differences exist in digits not displayed in the table. This also applies to the Polynomial 2° model. This also applies to the Linear model.



Figure_Apx P-7 Plot of Mean Response by Dose in ppm with Fitted Curve for Exponential (M4) Model with Constant Variance for Relative Seminal Vesicle Weight; BMR = 1 Standard Deviation Change from Control Mean.

Exponential Model. (Version: 1.10; Date: 01/12/2015)
The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]
A constant variance model is fit

Benchmark Dose Computation.
BMR = 1.0000 Estimated standard deviations from control
BMD = 123.644
BMDL at the 95% confidence level = 38.1407

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-0.820732	-0.863617
rho	n/a	0
a	4.31581	4.5675
b	0.00406673	0.00345735
c	0.611025	0.546303
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	8	4.35	4.32	0.62	0.66	0.1458
200	9	3.23	3.38	0.55	0.66	-0.6845
400	9	3.17	2.97	0.67	0.66	0.9177
800	9	2.62	2.7	0.87	0.66	-0.3705

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-2.386703	5	14.77341
A2	-1.313327	8	18.62665
A3	-2.386703	5	14.77341
R	-13.55019	2	31.10038
4	-3.137185	4	14.27437

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	24.47	6	0.0004272
Test 2	2.147	3	0.5425
Test 3	2.147	3	0.5425
Test 6a	1.501	1	0.2205

P-2-6-2 Decreased Absolute Seminal Vesicle Weight

The doses and response data used for the modeling are presented in Table_Apx P-16.

Table_Apx P-16 Absolute Seminal Vesicle Weight Data Selected for Dose-Response Modeling for 1-BP

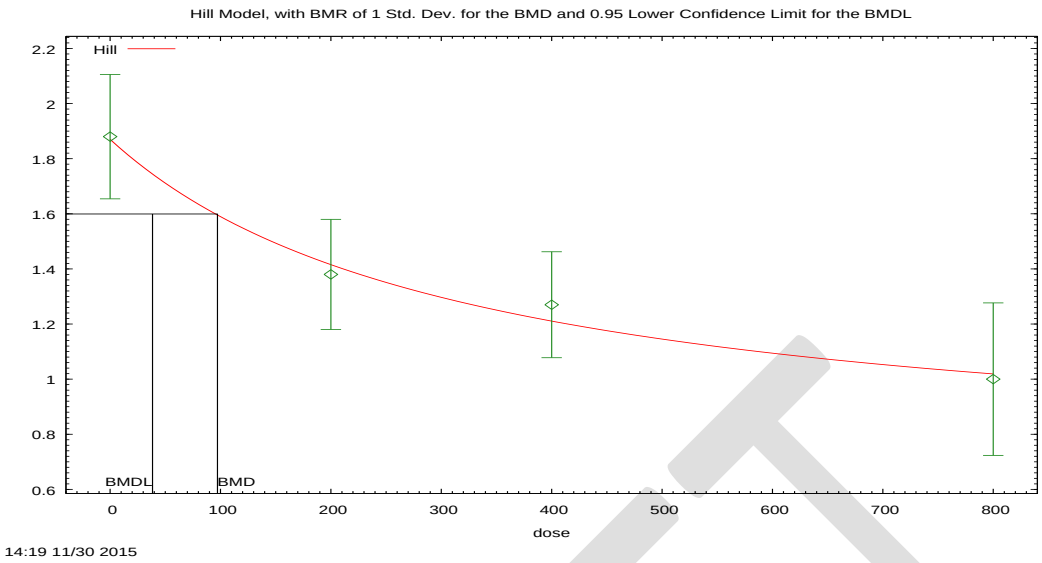
Dose (ppm)	Number of animals	Seminal Vesicle Absolute Weight (mg)	Standard Deviation
0	8	1.88	0.27
200	9	1.38	0.26
400	9	1.27	0.25
800	9	1.00	0.36

Comparisons of model fits obtained are provided in Table_Apx P-17. Models with homogeneous variance were used because the BMDS Test 2 *p*-value was 0.653. The best fitting model (Hill) was selected based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. The Hill model had an acceptable BMD to BMDL ratio of 2.5 and is indicated in bold. For the best fitting model a plot of the model is shown in Figure_Apx P-8. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below.

Table_Apx P-17 Summary of BMD Modeling Results for Seminal Vesicle Absolute Weight in Rats Exposed to 1-BP by Inhalation

Model[a]	Goodness of fit		BMD_{1SD} (ppm)	$BMDL_{1SD}$ (ppm)	Basis for model selection
	p-value	AIC			
Hill	**0.429**	**-47.533**	**97.3**	**38.4**	**The Hill model was selected based on the lowest AIC, highest goodness of fit *p*-value and adequate fit by visual inspection**
Exponential (M4) Exponential (M5)[b]	0.337	-47.235	112	58.4	
Exponential (M2) Exponential (M3)[c]	0.159	-46.484	219	152	
Power[d] Polynomial 3°[e] Polynomial 2°[f] Linear	0.0576	-44.450	299	222	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.653), selected model in bold; scaled residuals for selected model for doses 0, 200, 400, and 800 ppm were 0.07, -0.43, 0.61, -0.24, respectively.
[b] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.
[c] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.
[d] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.
[e] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[f] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.



Figure_Apx P-8 Plot of Mean Response by Dose in ppm with Fitted Curve for Hill Model with Constant Variance for Seminal Vesicle Absolute Weight; BMR = 1 Standard Deviation Change from Control Mean.

Hill Model. (Version: 2.17; Date: 01/28/2013)
The form of the response function is: Y[dose] = intercept + v*dose^n/(k^n + dose^n)
A constant variance model is fit

Benchmark Dose Computation.
BMR = 1 Estimated standard deviations from the control mean
BMD = 97.2583
BMDL at the 95% confidence level = 38.4029

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.0752711	0.0834806
rho	n/a	0
intercept	1.87362	1.88
v	-1.2008	-0.88
n	1	1.5698
k	328.422	176

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	8	1.88	1.87	0.27	0.27	0.0658
200	9	1.38	1.42	0.26	0.27	-0.428
400	9	1.27	1.21	0.25	0.27	0.61
800	9	1	1.02	0.36	0.27	-0.244

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	28.078773	5	-46.157546
A2	28.894036	8	-41.788073
A3	28.078773	5	-46.157546
fitted	27.766532	4	-47.533065
R	13.387326	2	-22.774652

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	31.0134	6	<0.0001
Test 2	1.63053	3	0.6525
Test 3	1.63053	3	0.6525
Test 4	0.624482	1	0.4294

P-2-7 Decreased Percent Normal Sperm Morphology

Decreased percent normal sperm morphology was observed in the F_0 generation of the reproductive and developmental study by WIL Laboratories (2001). The doses and response data used for the modeling are presented in Table_Apx P-18.

Table_Apx P-18 Sperm Morphology Data Selected for Dose-Response Modeling for 1-BP

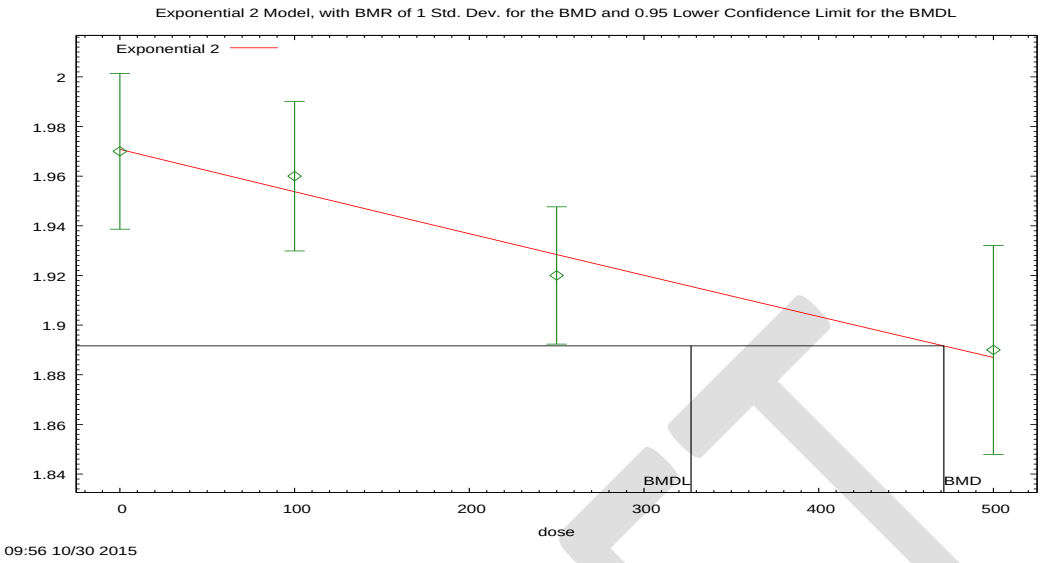
Dose (ppm)	Number of animals	% normal	Standard Deviation
0	25	99.7	0.6
100	25	99.7	0.52
250	25	99.3	0.83
500	24	98.2	2.59
750	24	90.6	8.74

Comparisons of model fits obtained are provided in Table_Apx P-19. The best fitting model (Exponential (M2) with homogeneous variance because the BMDS Test 2 *p*-value was 0.144) was selected based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. The best-fitting model is indicated in bold. For the best fitting model a plot of the model is shown in Figure_Apx P-9. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below.

Table_Apx P-19 Summary of BMD Modeling Results for Sperm Morphology in the F_0 Generation Exposed to 1-BP by Inhalation

Model[a]	Goodness of fit		BMD_{1SD} (ppm)	$BMDL_{1SD}$ (ppm)	Basis for model selection
	p-value	AIC			
Exponential (M2) **Exponential (M3)[b]**	**0.787**	**-401.21**	**472**	**327**	**The Exponential (M2) model was selected based on the lowest AIC, highest goodness of fit *p*-value and adequate fit by visual inspection.**
Power[c] Polynomial 3°[d] Polynomial 2°[e] Linear	0.780	-401.19	473	331	
Exponential (M4)	0.534	-399.30	459	230	
Hill	N/A[f]	-397.69	482	124	
Exponential (M5)	N/A[f]	-397.69	463	112	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.144), selected model in bold; scaled residuals for selected model for doses 0, 100, 250, and 500 ppm were -0.05, 0.39, -0.53, 0.19, respectively.
[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.
[c] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.
[d] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[e] For the Polynomial 2° model, the *b2* coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[f] No available degrees of freedom to calculate a goodness of fit value.



Figure_Apx P-9 Plot of Mean Response by Dose in ppm with Fitted Curve for Exponential (M2) Model with Constant Variance for Sperm Morphology in F_0 Rats Exposed to 1-BP by Inhalation; BMR = 1 Standard Deviation Change from Control Mean.

Exponential Model. (Version: 1.10; Date: 01/12/2015)
The form of the response function is: Y[dose] = a * exp(sign * b * dose)
A constant variance model is fit

Benchmark Dose Computation.
BMR = 1.0000 Estimated standard deviations from control
BMD = 471.627
BMDL at the 95% confidence level = 326.935

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-5.07205	-5.07685
rho	n/a	0
a	1.97082	1.89939
b	0.0000869453	0.000086769
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	25	1.97	1.97	0.08	0.08	-0.05174
100	25	1.96	1.95	0.07	0.08	0.3941
250	25	1.92	1.93	0.07	0.08	-0.5332
500	25	1.89	1.89	0.1	0.08	0.1908

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	203.8426	5	-397.6852
A2	206.5452	8	-397.0903
A3	203.8426	5	-397.6852
R	196.2377	2	-388.4753
2	203.6027	3	-401.2054

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	20.62	6	0.002151
Test 2	5.405	3	0.1444
Test 3	5.405	3	0.1444
Test 4	0.4799	2	0.7867

P-2-8 Decreased Percent Motile Sperm

A decrease in motile sperm was observed in the F_0 generation in the reproductive and developmental study by WIL Laboratories (2001). The doses and response data used for the modeling are presented in Table_Apx P-20.

Table_Apx P-20 Sperm Motility Data Selected for Dose-Response Modeling for 1-BP

Dose (ppm)	Number of animals	Mean sperm motility (% motile)	Standard Deviation
0	25	86.8	11.90
100	25	88.8	7.22
250	25	83.4	10.41
500	23	71.9	9.27
750	15	53.2	19.59

The BMD modeling results for sperm motility with non-homogeneous variance (BMDS test 2 *p*-value = 0.0001749) are summarized in Table_Apx P-21. Although the means are sufficiently fit for some models (e.g. the Polynomial 2° model has *p*-value of 0.516) the variances are not well modeled BMDS Test 3 *p*-value = 0.0426. This result suggests that due to the poor variance modeling for the data it is not reasonable to use BMDS for this endpoint. Instead the NOAEL of 250 ppm was used.

Table_Apx P-21 BMD Modeling Results for Sperm Motility F_0 Male Rats Following Inhalation Exposure to 1-BP

Model[a]	Goodness of fit		BMD_{1SD} (ppm)	$BMDL_{1SD}$ (ppm)	Basis for model selection
	p-value	AIC			
Polynomial 2°	0.516	657.83	386	346	**Due to unacceptable fitting of the variances no model was selected**.
Power	0.334	659.73	399	313	
Polynomial 3°	0.330	659.76	397	315	
Exponential (M3)	0.324	659.80	402	317	
Hill	0.139	661.73	400	323	
Polynomial 4°	0.137	661.76	397	314	
Exponential (M5)	0.133	661.80	402	317	
Linear	0.00132	671.22	237	192	
Exponential (M2) Exponential (M4)[b]	2.10E-04	675.10	226	178	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 1.75E-04, BMDS Test 3 *p*-value = 0.0426), no model was selected as a best-fitting model.
[b] For the Exponential (M4) model, the estimate of c was 0 (boundary). The models in this row reduced to the Exponential (M2) model.

To investigate the effect of the poor modeling of the variances on the BMDL the observed standard deviations were considered and the standard deviation at the highest dose is much larger than at the other dose groups. The data set was investigated with the highest dose dropped. The model fits with non-homogeneous variance (BMDS test 2 *p*-value = 0.0966) are summarized in Table_Apx P-22. Although the means are sufficiently fit for some models (e.g. the Polynomial 2° model has *p*-value of 0.676) the variances are not well modeled BMDS Test 3 *p*-value = 0.0426.

Table_Apx P-22 BMD Modeling Results for Sperm Motility F_0 Male Rats Following Inhalation Exposure to 1-BP with the Highest Dose Dropped

Model[a]	Goodness of fit		BMD_{1SD} (ppm)	$BMDL_{1SD}$ (ppm)	Basis for model selection
	p-value	AIC			
Polynomial 3°	0.676	551.25	394	345	**Due to unacceptable fitting of the variances no model was selected.**
Polynomial 2°	0.676	551.25	394	302	
Hill	0.529	552.86	271	255	
Exponential (M3)	0.386	553.22	391	294	
Power	0.376	553.25	395	296	
Exponential (M5)	N/A[b]	554.86	267	253	
Linear	0.107	554.94	315	241	
Exponential (M2)[c]	0.0743	555.67	310	231	
Exponential (M4)[d]	0.0743	555.67	310	231	
Polynomial 4°	error	error	error[e]	error[e]	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.0966, BMDS Test 3 *p*-value = 0.0426), no model was selected as a best-fitting model.
[b] No available degrees of freedom to calculate a goodness of fit value.
[c] The Exponential (M2) model may appear equivalent to the Exponential (M4) model, however differences exist in digits not displayed in the table.
[d] The Exponential (M4) model may appear equivalent to the Exponential (M2) model, however differences exist in digits not displayed in the table.
[e] BMD or BMDL computation failed for this model.

P-2-9 Decreased Left Cauda Epididymis Weight

A decrease in left cauda epididymis absolute weight was observed in the F_0 generation in the reproductive and developmental study by (WIL Research, 2001). The absolute weights are used for BMD modeling of the epididymis as described in EPA's Guidelines for Reproductive Toxicity Risk Assessment (U.S. EPA, 1996). The doses and response data used for the modeling are presented in Table_Apx P-23.

Table_Apx P-23 Left Cauda Epididymis Absolute Weight Data Selected for Dose-Response Modeling for 1-BP

Dose (ppm)	Number of animals	Left Cauda Epididymis Weight (mg)	Standard Deviation
0	25	0.3252	0.03673
100	25	0.3242	0.03149
250	25	0.3050	0.03556
500	23	0.2877	0.03170
750	22	0.2401	0.03529

The BMD modeling results for left cauda epididymis absolute weight with homogeneous variance (BMDS test 2 *p*-value =0.911) are summarized in Table_Apx P-24. The best fitting model (Polynomial 4°) was selected based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. The Polynomial 4° model had an acceptable BMD to BMDL ratio of 1.4 and is indicated in bold. For the best fitting model a plot of the model is shown in Figure_Apx P-10. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below.

Table_Apx P-24 BMD Modeling Results for Left Cauda Epididymis Absolute Weight F_0 Male Rats Following Inhalation Exposure to 1-BP

Model[a]	Goodness of fit		BMD_{1SD} (ppm)	$BMDL_{1SD}$ (ppm)	Basis for model selection
	p-value	AIC			
Polynomial 4°	**0.622**	**-714.88**	**438**	**313**	**The Polynomial 4° model was selected based on the lowest AIC, highest goodness of fit *p*-value and adequate fit by visual inspection.**
Polynomial 3°	0.565	-714.69	440	316	
Polynomial 2°	0.47	-714.32	437	315	
Power	0.430	-714.14	444	317	
Exponential (M3)	0.382	-713.91	446	320	
Linear	0.133	-712.23	307	256	
Hill	0.193	-712.14	444	317	
Exponential (M5)	0.166	-711.91	446	320	
Exponential (M2)	0.0636	-710.55	289	236	
Exponential (M4)	0.0636	-710.55	289	235	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.911), selected model in bold; scaled residuals for selected model for doses 0, 100, 250, 500, and 750 ppm were -0.21, 0.64, -0.65, 0.26, -0.04, respectively.

Figure_Apx P-10 Plot of Mean Response by Dose in ppm with Fitted Curve for Polynomial 4° Model with Constant Variance for Left Cauda Epididymis Absolute Weight; BMR = 1 Standard Deviation Change from Control Mean.

Polynomial Model. (Version: 2.20; Date: 10/22/2014)
The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …
A constant variance model is fit

Benchmark Dose Computation.
BMR = 1 Estimated standard deviations from the control mean
BMD = 438.482
BMDL at the 95% confidence level = 313.325

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.00113284	0.0011711
rho	n/a	0
beta_0	0.326617	0.3252
beta_1	-0.0000672194	0
beta_2	0	-0.00000139519
beta_3	-6.09563E-33	0
beta_4	-1.13164E-13	-2.44944E-12

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	25	0.32	0.33	0.04	0.03	-0.21
100	25	0.32	0.32	0.03	0.03	0.641
250	25	0.3	0.31	0.04	0.03	-0.649
500	25	0.29	0.29	0.03	0.03	0.262
750	25	0.24	0.24	0.04	0.03	-0.044

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	361.914605	6	-711.829209
A2	362.410744	10	-704.821488
A3	361.914605	6	-711.829209
fitted	361.438986	4	-714.877972
R	322.608827	2	-641.217655

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	79.6038	8	<0.0001
Test 2	0.992278	4	0.911
Test 3	0.992278	4	0.911
Test 4	0.951238	2	0.6215

P-2-10 Decreased Right Cauda Epididymis Weight

A decrease in right cauda epididymis absolute weight was observed in the F_0 generation in the reproductive and developmental study by (WIL Research, 2001). The absolute weights are used for BMD modeling of the epididymis as described in EPA's Guidelines for Reproductive Toxicity Risk Assessment (U.S. EPA, 1996). The doses and response data used for the modeling are presented in Table_Apx P-25.

Table_Apx P-25 Right Cauda Epididymis Absolute Weight Data Selected for Dose-Response Modeling for 1-BP

Dose (ppm)	Number of animals	Left Cauda Epididymis Weight (mg)	Standard Deviation
0	25	0.3327	0.03631
100	25	0.3311	0.04453
250	25	0.3053	0.04188
500	23	0.2912	0.05206
750	22	0.2405	0.04804

The BMD modeling results for right cauda epididymis absolute weight with homogeneous variance (BMDS test 2 *p*-value =0.455) are summarized in Table_Apx P-26. The best fitting model (Polynomial 4°) was selected based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. The Polynomial 4° model had an acceptable BMD to BMDL ratio of 1.4 and is indicated in bold. For the best fitting model a plot of the model is shown in Figure_Apx P-11. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below.

Table_Apx P-26 BMD Modeling Results for Right Cauda Epididymis Absolute Weight F_0 Male Rats Following Inhalation Exposure to 1-BP

Model[a]	Goodness of fit		BMD_{1SD} (ppm)	$BMDL_{1SD}$ (ppm)	Basis for model selection
	p-value	AIC			
Polynomial 4°	**0.493**	**-646.60**	**485**	**338**	**The Polynomial 4° model was selected based on the lowest AIC, highest goodness of fit *p*-value and adequate fit by visual inspection.**
Polynomial 3°	0.442	-646.38	480	334	
Linear	0.296	-646.32	371	303	
Polynomial 2°	0.376	-646.06	472	327	
Power	0.340	-645.86	474	323	
Exponential (M3)	0.304	-645.63	473	317	
Exponential (M2)	0.196	-645.33	350	277	
Exponential (M4)	0.196	-645.33	350	270	
Hill	0.142	-643.85	474	323	
Exponential (M5)	0.123	-643.63	473	317	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.455), selected model in bold; scaled residuals for selected model for doses 0, 100, 250, 500, and 750 ppm were -0.09, 0.63, -0.9, 0.44, -0.08, respectively.

Figure_Apx P-11 Plot of Mean Response by Dose in ppm with Fitted Curve for Polynomial 4° Model with Constant Variance for Right Cauda Epididymis Absolute Weight; BMR = 1 Standard Deviation Change from Control Mean.

Polynomial Model. (Version: 2.20; Date: 10/22/2014)
The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …
A constant variance model is fit

Benchmark Dose Computation.
BMR = 1 Estimated standard deviations from the control mean
BMD = 484.978
BMDL at the 95% confidence level = 338.42

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.00195609	0.00201467
rho	n/a	0
beta_0	0.333498	0.3327
beta_1	-0.0000793692	0
beta_2	-2.2991E-28	-0.00000198872
beta_3	-2.18866E-31	0
beta_4	-1.03676E-13	-3.6281E-12

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	25	0.33	0.33	0.04	0.04	-0.0902
100	25	0.33	0.33	0.04	0.04	0.627
250	25	0.3	0.31	0.04	0.04	-0.899
500	25	0.29	0.29	0.05	0.04	0.437
750	25	0.24	0.24	0.05	0.04	-0.0754

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	328.007576	6	-644.015151
A2	329.833395	10	-639.66679
A3	328.007576	6	-644.015151
fitted	327.300407	4	-646.600813
R	299.119376	2	-594.238753

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	61.428	8	<0.0001
Test 2	3.65164	4	0.4552
Test 3	3.65164	4	0.4552
Test 4	1.41434	2	0.493

P-2-11 Increased Estrus Cycle Length

An increase estrus cycle length was observed in the F_0 generation in the reproductive and developmental study by (WIL Research, 2001). The doses and response data used for the modeling are presented in Table_Apx P-27.

Table_Apx P-27 Estrus Cycle Length Data Selected for Dose-Response Modeling for 1-BP

Dose (ppm)	Number of animals	Estrus cycle Length (days)	Standard Deviation
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

The BMD modeling results for estrus cycle length with non-homogeneous variance (BMDS test 2 *p*-value = <0.0001) are summarized in Table_Apx P-28. The means are not adequately fit for any of the models as shown by the goodness of fit where the model with the highest *p*-value is 0.0065 for the Exponential M4 and M5 models (excluding the Hill model because a BMDL could not be calculated). This result suggests that due to the poor model fit to the data it is not reasonable to use BMDS for this endpoint. Instead the NOAEL of 250 ppm was used.

Table_Apx P-28 BMD Modeling Results for Estrus Cycle Length F_0 Female Rats Following Inhalation Exposure to 1-BP

Model[a]	Goodness of fit		BMD_{1SD} (ppm)	$BMDL_{1SD}$ (ppm)	Basis for model selection
	p-value	AIC			
Hill	0.00656	160.04	145	error[b]	**Due to inadequate fit of the models to the data means (shown by the goodness of fit *p*-value) no model was selected.**
Exponential (M4) Exponential (M5)[c]	0.00650	160.05	157	79.5	
Power[d] Polynomial 4°[e] Polynomial 3°[f] Polynomial 2°[g] Linear	0.00169	163.13	300	205	
Exponential (M2) Exponential (M3)[h]	7.68E-04	164.81	344	244	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001, BMDS Test 3 *p*-value = 0.506), no model was selected as a best-fitting model.
[b] BMD or BMDL computation failed for this model.
[c] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.
[d] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.
[e] For the Polynomial 4° model, the b4 and b3 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 4° model, the b4, b3, and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[f] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[g] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[h] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.

P-2-12 Decreased Antral Follical Count

A decreased antral follicle count was observed in the study of female reproductive function by (Yamada et al., 2003). The doses and response data used for the modeling are presented in Table_Apx P-29. The highest dose was not included for modeling because all the rats in the highest dose group (800 ppm) were seriously ill and were sacrificed during the 8th week of the 12 week study.

Table_Apx P-29 Antral Follicle Count Data Selected for Dose-Response Modeling for 1-BP

Dose (ppm)	Number of animals	Antral Follicle Count	Standard Deviation
0	8	30.1	22.4
200	9	12.6	4.82
400	9	7.44	6.52

The BMD modeling results for antral follical count with non-homogeneous variance (BMDS test 2 *p*-value = <0.0001) are summarized in Table_Apx P-30. The means are not adequately fit for any of the models as shown by the goodness of fit where the model with the highest *p*-value is 0.0404 for the Exponential M2 model. This result suggests that due to the poor model fit to the data it is not reasonable to use BMDS for this endpoint. Instead the LOAEL of 200 ppm was used.

Table_Apx P-30 BMD Modeling Results for Antral Follical Count in Female Rats Following Inhalation Exposure to 1-BP

Model[a]	Goodness of fit		BMD_{1SD} (ppm)	$BMDL_{1SD}$ (ppm)	Basis for model selection
	p-value	AIC			
Exponential (M4)	N/A[b]	148.31	189	0.651	**Due to inadequate fit of the models to the data means (shown by the goodness of fit *p*-value) no model was selected.**
Exponential (M2)	0.0404	150.51	270	117	
Power[c] Linear[d]	0.00496	154.21	410	233	
Polynomial 2°[e]	0.00496	154.21	410	233	
Exponential (M3)	N/A[b]	179.12	1.8E+05	754	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = <0.0001, BMDS Test 3 *p*-value = 0.0545), no model was selected as a best-fitting model.
[b] No available degrees of freedom to calculate a goodness of fit value.
[c] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.
[d] The Linear model may appear equivalent to the Polynomial 2° model, however differences exist in digits not displayed in the table.
[e] The Polynomial 2° model may appear equivalent to the Power model, however differences exist in digits not displayed in the table. This also applies to the Linear model.

P-2-13 Decreased Male and Female Fertility Index

A decrease in the male and female fertility index was observed in the F_0 generation in the reproductive and developmental study by WIL Laboratories (2001). The doses and response data are presented in Table_Apx P-31 as a percentage and incidence. The incidence represents the number of males that did not sire a litter which is equal to the number of nongravid females. The incidence was used for modeling as a dichotomous endpoint.

Table_Apx P-31 Fertility Index Data Selected for Dose-Response Modeling for 1-BP

Dose (ppm)	Number of animals	Fertility Index (%)	Number Nongravid Females = Males that did not Sire a Litter
0	25	92	2
100	25	100	0
250	25	88	3
500	23	52	12
750	22	0	25

The BMD modeling results for the fertility index are summarized in Table_Apx P-32. The best fitting models were the LogLogistic and Dichotomous-Hill based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. Dichotomous-Hill model had a warning about the BMDL computation and the LogLogistic model did not so the LogLogistic model was selected. The LogLogistic and Dichotomous-Hill models had nearly the same BMDLs with LogLogistic slightly lower (356 ppm) than Dichotomous-Hill (363 ppm). For the best fitting model a plot of the model is shown in Figure_Apx P-12. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below.

Table_Apx P-32 BMD Modeling Results for Fertility Index of F_0 Rats Following Inhalation Exposure of Parental Rats to 1-BP in a Two-Generation Study

Model[a]	Goodness of fit		BMD_{10Pct} (ppm)	$BMDL_{10Pct}$ (ppm)	Basis for model selection
	p-value	AIC			
LogLogistic	**0.388**	**75.396**	**448**	**356**	The Dichotomous-Hill and LogLogistic models had the lowest AIC, highest goodness of fit *p*-value and adequate fit by visual inspection. The Dichotomous-Hill model had a warning about the BMDL computation and the LogLogistic model did not so the LogLogistic model was selected.
Dichotomous-Hill	0.388	75.396	448	363	
Multistage 4°	0.355	75.682	306	219	
Weibull	0.253	77.024	361	252	
Gamma	0.256	77.045	361	260	
LogProbit	0.223	77.357	461	352	
Multistage 3°	0.161	78.153	250	202	
Logistic	0.0103	80.981	238	182	
Probit	0.0031	82.358	208	159	
Multistage 2°	0.0152	85.979	173	143	
Quantal-Linear	0	106.73	68.4	52.1	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 100, 250, 500, and 750 ppm were 0.27, -1.34, 1.07, -0.01, 0.14, respectively.

Figure_Apx P-12 Plot of Mean Response by Dose with Fitted Curve for the Selected Model (LogLogistic) for Fertility Index in Rats Exposed to 1-BP Via Inhalation in ppm BMR 10% Extra Risk.

Logistic Model. (Version: 2.14; Date: 2/28/2013)
The form of the probability function is: P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]
Slope parameter is restricted as slope >= 1

Benchmark Dose Computation.
BMR = 10% Extra risk
BMD = 448.13
BMDL at the 95% confidence level = 356.183

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
background	0.0666427	0.08
intercept	-1.1209E+02	-2.1668E+01
slope	18	3.62868

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	*p*-value
Full model	-33.45	5			
Fitted model	-35.7	2	4.4943	3	0.21
Reduced model	-79.79	1	92.6846	4	<.0001

AIC: = 75.3964

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.0666	1.666	2	25	0.27
100	0.0666	1.666	0	25	-1.34
250	0.0666	1.666	3	25	1.07
500	0.4809	12.022	12	25	-0.01
750	0.9992	24.98	25	25	0.14

Chi^2 = 3.02 d.f = 3 *p*-value = 0.3884

P-2-14 Decreased Implantations Sites

A decrease in the number of implantations sites was observed in the F_0 generation in the reproductive and developmental study by (WIL Research, 2001). The doses and response data used for modeling are presented in Table_Apx P-33. The highest dose group was not included because none of the dams had implantations sites.

Table_Apx P-33 Implantations Site Data Selected for Dose-Response Modeling for 1-BP

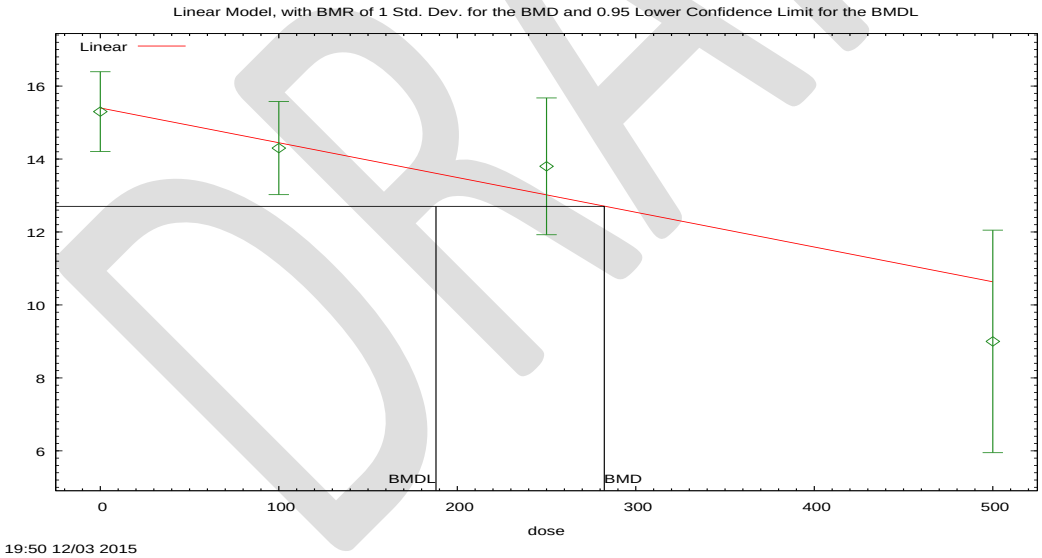
Dose (ppm)	Number of animals	Average Numer of Sites	Standard Deviation
0	23	15.3	2.53
100	25	14.3	3.09
250	22	13.8	4.23
500	11	9.0	4.54

The BMD modeling results for the number of implantations sites are summarized in Table_Apx P-34. The best fitting models were the Linear and Power based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. Based on the parameter estimate for the Power model it reduced to the Linear, so the Linear model was selected. For the best fitting model a plot of the model is shown in Figure_Apx P-13. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below.

Table_Apx P-34 BMD Modeling Results for Implantations Sites in F_0 Rats Following Inhalation Exposure of Parental Rats to 1-BP in a Two-Generation Study

Model[a]	Goodness of fit		BMD_{5RD} (ppm)	$BMDL_{5RD}$ (ppm)	BMD_{1SD} (ppm)	$BMDL_{1SD}$ (ppm)	Basis for model selection
	p-value	AIC					
Linear Power[b]	**0.936**	**284.66**	80.8	56.1	**282**	**188**	**Linear and Power models were selected based on the lowest AIC, highest goodness of fit *p*-value and adequate fit by visual inspection.**
Exponential (M2)	0.901	284.74	74.1	48.1	270	166	
Exponential (M4)	0.901	284.74	74.1	37.3	270	138	
Polynomial 3°	0.741	286.64	85.5	56.2	295	188	
Polynomial 2°	0.724	286.66	84.3	56.1	289	188	
Hill	0.715	286.67	80.6	55.8	282	195	
Exponential (M3)	0.669	286.71	82.3	48.2	278	167	
Exponential (M5)	N/A[c]	288.71	82.3	48.2	278	167	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.0493), selected model in bold; scaled residuals for selected model for doses 0, 100, 250, and 500 ppm were -0.17, -0.23, 1, -1, respectively.
[b] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.
[c] No available degrees of freedom to calculate a goodness of fit value.



Figure_Apx P-13 Plot of Mean Response by Dose with Fitted Curve for the Selected Model (Linear) for Implantation Sites in Rats Exposed to 1-BP Via Inhalation in ppm BMR 1 Standard Deviation.

Polynomial Model. (Version: 2.20; Date: 10/22/2014)
The form of the response function is: Y[dose] = beta_0 + beta_1*dose
A modeled variance is fit

Benchmark Dose Computation.
BMR = 1 Estimated standard deviations from the control mean
BMD = 282.359
BMDL at the 95% confidence level = 188.047

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lalpha	12.2915	2.51459
rho	-3.77194	0
beta_0	15.393	15.7286
beta_1	-0.00952791	-0.01237

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	23	15.3	15.4	2.53	2.69	-0.166
100	25	14.3	14.4	3.09	3.03	-0.231
250	22	13.8	13	4.23	3.69	1
500	11	9	10.6	4.54	5.41	-0.999

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-140.289933	5	290.579865
A2	-136.366566	8	288.733132
A3	-138.26616	6	288.532319
fitted	-138.332408	4	284.664816
R	-151.740933	2	307.481866

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	30.7487	6	<0.0001
Test 2	7.84673	3	0.04929
Test 3	3.79919	2	0.1496
Test 4	0.132497	2	0.9359

P-2-15 Decreased Pup Body Weight

Decreased pup body weight was observed in the 2-generation reproductive and developmental study by (WIL Research, 2001). Statistically significant decreases in pup body weight were noted for males in the F_1 generation at PND 28 and in the F_2 generation in both sexes at PNDs 14 and 21. Continuous models were used to fit-dose response data for decreased pup body weights. A BMR of 5% was used because this is a developmental endpoint (Kavlock et al., 1995). A BMR of 1 standard deviation is also shown for comparison per EPA Benchmark Dose Technical Guidance (U.S. EPA, 2012a). The doses, response data and BMD modeling results for decreased pup body weight are presented below at each time point.

P-2-15-1 Decreased Body Weight in F1 Male Pups at PND 28

The doses and response data from the WIL Laboratories (WIL Research, 2001) study were used for the modeling and are presented in Table_Apx P-35.

Table_Apx P-35 Pup Body Weight Data in F_1 Males at PND 28 for Dose-Response Modeling

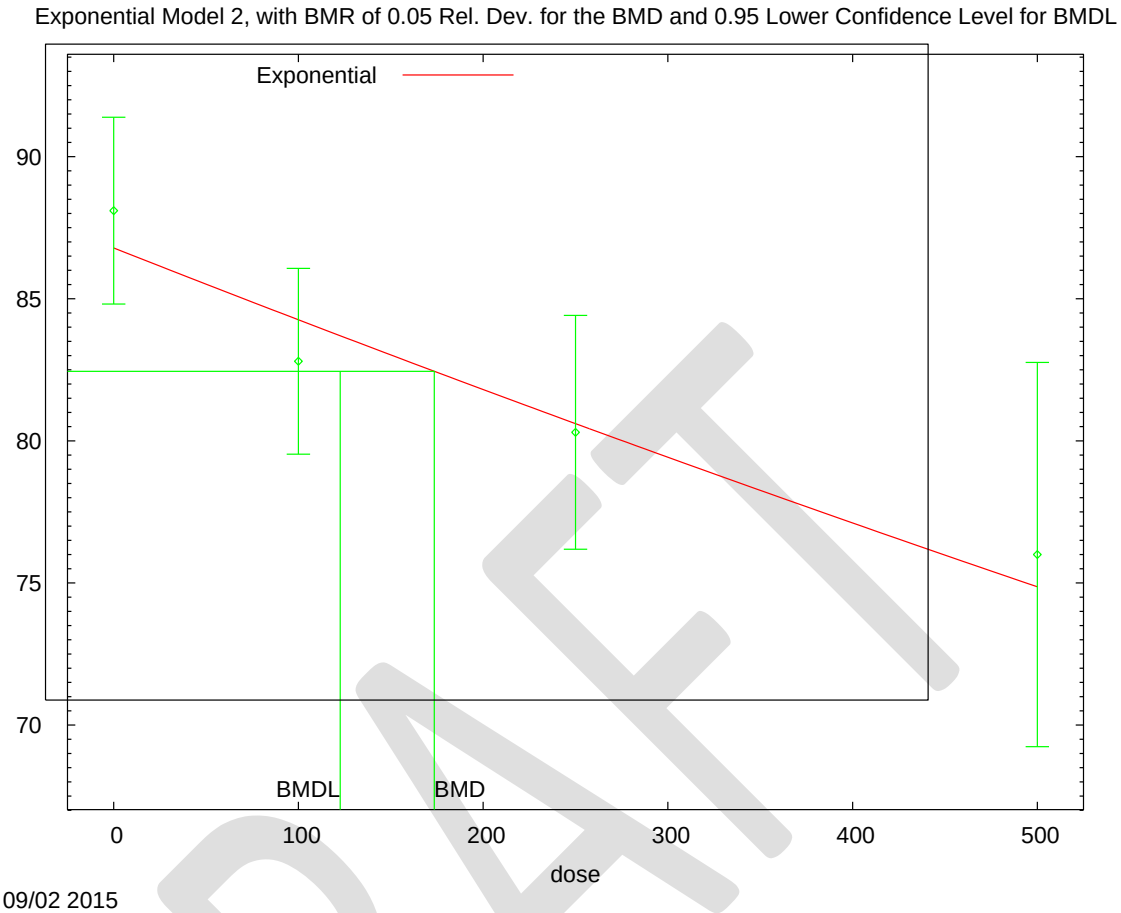
	Concentration (ppm)			
	0	**100**	**250**	**500**
Number of litters	23	24	21	10
Mean pup wt (g)	88.1	82.8	80.3	76.0
Standard deviation (g)	7.60	7.74	9.04	9.45

A comparison of the model fits obtained for pup body weight changes is provided in Table_Apx P-36. The best fitting model was selected based on Akaike information criterion (AIC; lower values indicates a better fit), visual inspection and comparison with the BMD/BMDLs among the data for decreased pup weights at other time points. There is a large spread in BMC/L values among the models and EPA procedures allow for selecting the lowest BMDL is this case (the Hill model) however the Exponential (M2) was selected because it is in line with the results from the pup body weight decreases observed at the other time points in this data set. The best-fitting model is indicated in bold. For the best fitting model a plot of the model is shown in Figure_Apx P-14. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below.

Table_Apx P-36 BMD Modeling Results for Body Weight of F_1 Male Rat Pups on PND 28 Following Inhalation Exposure of Parental Rats to 1-BP in a Two-Generation Study

Model[a]	Goodness of fit		BMD_{1SD} (ppm)	$BMDL_{1SD}$ (ppm)	BMD_{5RD} (ppm)	$BMDL_{5RD}$ (ppm)	Basis for model selection
	p-value	AIC					
Exponential (M2) Exponential (M3)[b]	**0.449**	**411.46**	334.07	228.77	**174**	**123**	**The Exponential (M2) model was selected based on the lowest AIC.**
Power[c] Polynomial 3°[d] Polynomial 2°[e] Linear	0.406	411.66	345.22	242.64	183	133	
Hill	0.578	412.17	234.74	85.21	92.2	23.2	
Exponential (M4) Exponential (M5)[f]	0.512	412.29	238.92	95.80	101	36.8	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.785), selected model in bold; scaled residuals for selected model for doses 0, 100, 250, and 500 ppm were 0.77, -0.88, -0.17, 0.44, respectively.
[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.
[c] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.
[d] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[e] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[f] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.



Figure_Apx P-14 Plot of Mean Response by Dose with Fitted Curve for the Selected Model (Exponential (M2)) for Pup Body Weight in Rats Exposed to 1-BP Via Inhalation in ppm BMR 5% Relative Deviation.

Exponential Model. (Version: 1.10; Date: 01/12/2015)
The form of the response function is: Y[dose] = a * exp(sign * b * dose)
A constant variance model is fit

Benchmark Dose Computation.
BMR = 5% Relative deviation
BMD = 173.561
BMDL at the 95% confidence level = 122.612

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	4.19824	4.17769
rho	n/a	0
a	86.7871	78.9392
b	0.000295534	0.000288601
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	23	88.1	86.79	7.6	8.16	0.7717
100	24	82.8	84.26	7.74	8.16	-0.8765
250	21	80.3	80.61	9.04	8.16	-0.1719
500	10	76	74.87	9.45	8.16	0.4398

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-201.9297	5	413.8595
A2	-201.395	8	418.7901
A3	-201.9297	5	413.8595
R	-210.4356	2	424.8712
2	-202.7313	3	411.4626

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	18.08	6	0.006033
Test 2	1.069	3	0.7845
Test 3	1.069	3	0.7845
Test 4	1.603	2	0.4486

P-2-15-2 Decreased Body Weight in F_2 Female Pups at PND 14

The doses and response data used for the modeling are presented in Table_Apx P-37.

Table_Apx P-37 Pup Body Weight Data in F_2 Females at PND 14 from Selected for Dose-Response Modeling

	Concentration (ppm)			
	0	**100**	**250**	**500**
Number of litters	22	17	15	15
Mean pup wt (g)	27.6	26.9	27.3	23.7
Standard deviation (g)	2.29	2.11	3.87	3.70

The BMD modeling results for decreased pup weight in F_2 females at PND 14 with non-homogeneous variance (BMDS test 2 *p*-value = 0.0218) are summarized in Table_Apx P-38. Although the variances are non-homogeneous and not well modeled for any of the non-homogeneous variance models the means were well-modeled (the highest *p*-value is 0.904 for the linear model with non-homogeneous variances).

Table_Apx P-38 BMD Modeling Results for Body Weight of F_2 Female Rat Pups on PND 14 Following Inhalation Exposure of Parental Rats to 1-BP in a Two-Generation Study

Model[a]	**Goodness of fit**		**BMD_{5RD} (ppm)**	**$BMDL_{5RD}$ (ppm)**
	***p*-value**	**AIC**		
Linear	0.904	221.02	228	145
Exponential (M2)	0.893	221.05	224	138
Exponential (M4)	0.893	221.05	224	104
Exponential (M3)	0.715	222.96	244	139
Power	0.708	222.96	245	146
Polynomial 3°[b]	0.687	222.98	245	145
Polynomial 2°[c]	0.687	222.98	245	145
Exponential (M5)	N/A[d]	224.82	228	107
Hill	N/A[d]	224.82	226	105
Polynomial 4°	error	error	error[e]	error[e]

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.0218, BMDS Test 3 *p*-value = 0.0438), no model was selected as a best-fitting model.
[b] The Polynomial 3° model may appear equivalent to the Polynomial 2° model, however differences exist in digits not displayed in the table.
[c] The Polynomial 2° model may appear equivalent to the Polynomial 3° model, however differences exist in digits not displayed in the table.
[d] No available degrees of freedom to calculate a goodness of fit value.
[e] BMD or BMDL computation failed for this model.

To investigate the effect of the poor modeling of the variances on the BMDL, the models were run using the smallest dose standard deviation (2.29), highest (3.87) and pooled (2.89) for all dose levels and the modeling results are summarized in Table_Apx P-39.

Table_Apx P-39 BMD Modeling Results for Body Weight of F2 Female Rat Pups on PND 14 Following Inhalation Exposure of Parental Rats to 1-BP in a Two-Generation Study with Variances Fixed at Smallest, Pooled and Highest Values.

Model[a]	Smallest Standard Deviation				Pooled Standard Deviation				Largest Standard Deviation				Ratio BMDLs Smallest to Largest Std Dev
	Goodness of fit		BMD_{5RD} (ppm)	$BMDL_{5RD}$ (ppm)	Goodness of fit		BMD_{5RD} (ppm)	$BMDL_{5RD}$ (ppm)	Goodness of fit		BMD_{5RD} (ppm)	$BMDL_{5RD}$ (ppm)	
	p-value	AIC			*p*-value	AIC			*p*-value	AIC			
Polynomial 3°	0.518	186.54	360	274	0.661	218.16	360	183	0.793	258.09	360	145	1.9
Polynomial 2°	0.318	187.51	304	199	0.485	218.78	304	260	0.667	258.44	304	140	1.4
Power	0.331	188.16	465	247	0.441	219.93	465	200	0.564	259.96	460	148	1.7
Exponential (M3)	0.331	188.16	473	249	0.441	219.93	470	202	0.564	259.96	473	143	1.7
Hill	N/A[b]	190.16	466	248	N/A[b]	221.93	465	200	N/A[b]	261.96	442	138	1.8
Exponential (M5)	N/A[b]	190.16	470	249	N/A[b]	221.93	470	202	N/A[b]	261.96	473	139	1.8
Linear	0.0533	191.08	193	146	0.154	221.07	193	138	0.348	259.74	193	127	1.1
Exponential (M2)	0.0443	191.45	188	139	0.137	221.31	188	131	0.325	259.88	188	119	1.2
Exponential (M4)	0.0443	191.45	188	131	0.137	221.31	188	115	0.325	259.88	188	90.2	1.5

[a] Constant variance case presented (BMDS Test 2 *p*-value = 1., BMDS Test 3 *p*-value = 1.), no model was selected as a best-fitting model.
[b] No available degrees of freedom to calculate a goodness of fit value.

A comparison across the full suite of BMD models shows the BMDL is sensitive to the adjustment of the variances and for the model that fit the constant variance data best, the Polynomial 3° model the ratio of BMDLs was 1.9. This result suggests that due to the poor variance modeling for the original data it is not reasonable to use BMDS for this endpoint. Instead the NOAEL of 250 ppm was used.

P-2-15-3 Decreased Body Weight in F_2 Female Pups at PND 21

The doses and response data used for the modeling are presented in Table_Apx P-40.

Table_Apx P-40 Pup Body Weight Data in F_2 Females at PND 21 from Selected for Dose-Response Modeling

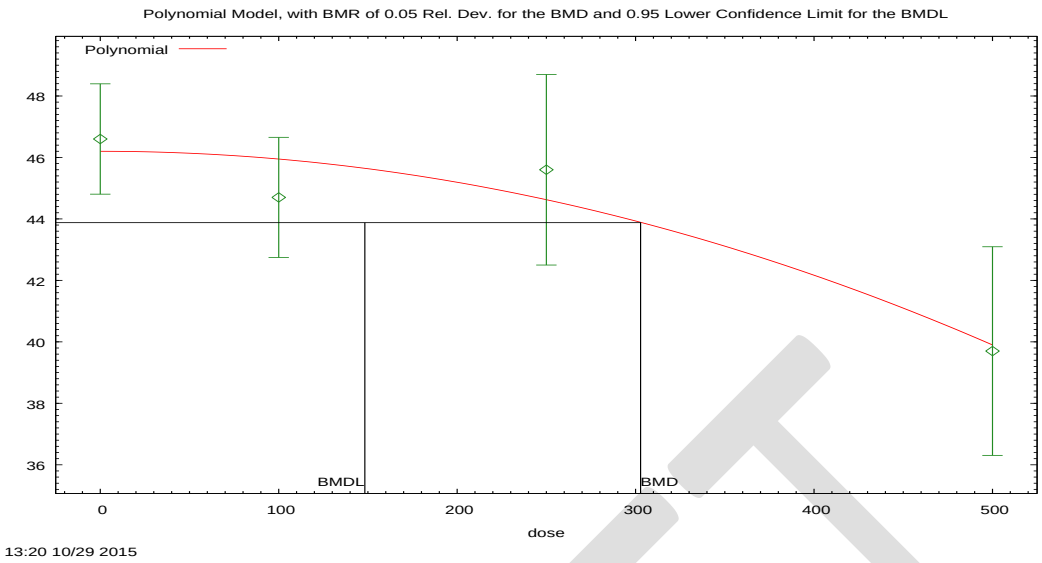
	Concentration (ppm)			
	0	**100**	**250**	**500**
Number of litters	22	17	15	15
Mean pup wt (g)	46.6	44.7	45.6	39.7
Standard deviation (g)	4.05	3.80	5.60	6.13

Comparisons of model fits obtained are provided in Table_Apx P-41. The best fitting model (Polynomial 2° with constant variance) was selected based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. The best-fitting model is indicated in bold. For the best fitting model a plot of the model is shown in Figure_Apx P-15. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below.

Table_Apx P-41 BMD Modeling Results for Body Weight of F_2 Females on PND 21 Following Inhalation Exposure of Parental Rats to 1-BP in a Two-Generation Study

Model[a]	Goodness of fit		BMD_{1SD} (ppm)	$BMDL_{1SD}$ (ppm)	BMD_{5RD} (ppm)	$BMDL_{5RD}$ (ppm)	Basis for model selection
	p-value	AIC					
Polynomial 2°	**0.372**	**291.28**	436.24	299.79	**303**	**148**	**The Polynomial 2° model was selected based on the lowest AIC, highest goodness of fit *p*-value and adequate fit by visual inspection.**
Linear	0.176	292.77	386.50	269.95	187	135	
Power	0.216	292.83	475.29	314.36	407	155	
Exponential (M3)	0.216	292.83	474.45	316.27	406	152	
Polynomial 3°	0.213	292.85	449.22	313.20	336	154	
Exponential (M2)	0.160	292.97	385.88	261.10	181	127	
Exponential (M4)	0.160	292.97	385.88	250.91	181	105	
Exponential (M5)	N/A[b]	294.83	474.45	316.27	406	152	
Hill	N/A[b]	294.83	475.10	314.77	406	150	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.144), selected model in bold; scaled residuals for selected model for doses 0, 100, 250, and 500 ppm were 0.4, -1.06, 0.8, -0.15, respectively.
[b] No available degrees of freedom to calculate a goodness of fit value.



Figure_Apx P-15 Plot of Mean Response by Dose with Fitted Curve for the Selected Model (Polynomial 2°) for Pup Body Weight in Rats Exposed to 1-BP Via Inhalation in ppm BMR = 5% Relative Deviation.

Polynomial Model. (Version: 2.20; Date: 10/22/2014)
The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …
A constant variance model is fit

Benchmark Dose Computation.
BMR = 5% Relative deviation
BMD = 302.794
BMDL at the 95% confidence level = 148.282

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	22.9776	23.7017
rho	n/a	0
beta_0	46.1877	45.9942
beta_1	0	0
beta_2	-0.0000251884	-0.000029911

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	46.6	46.2	4.05	4.79	0.403
100	17	44.7	45.9	3.8	4.79	-1.06
250	15	45.6	44.6	5.6	4.79	0.797
500	15	39.7	39.9	6.13	4.79	-0.154

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-141.651019	5	293.302038
A2	-138.944287	8	293.888574
A3	-141.651019	5	293.302038
fitted	-142.640988	3	291.281976
R	-150.681267	2	305.362534

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	23.474	6	0.0006523
Test 2	5.41346	3	0.1439
Test 3	5.41346	3	0.1439
Test 4	1.97994	2	0.3716

P-2-15-4 Decreased Body Weight in F_2 Male Pups at PND 14

The doses and response data used for the modeling are presented in Table_Apx P-42.

Table_Apx P-42 Pup Body Weight Data in F_2 Males at PND 14 from Selected for Dose-Response Modeling

	Concentration (ppm)			
	0	**100**	**250**	**500**
Number of litters	22	17	15	16
Mean pup wt (g)	29.2	28.1	28.4	24.5
Standard deviation (g)	2.77	2.43	3.65	4.14

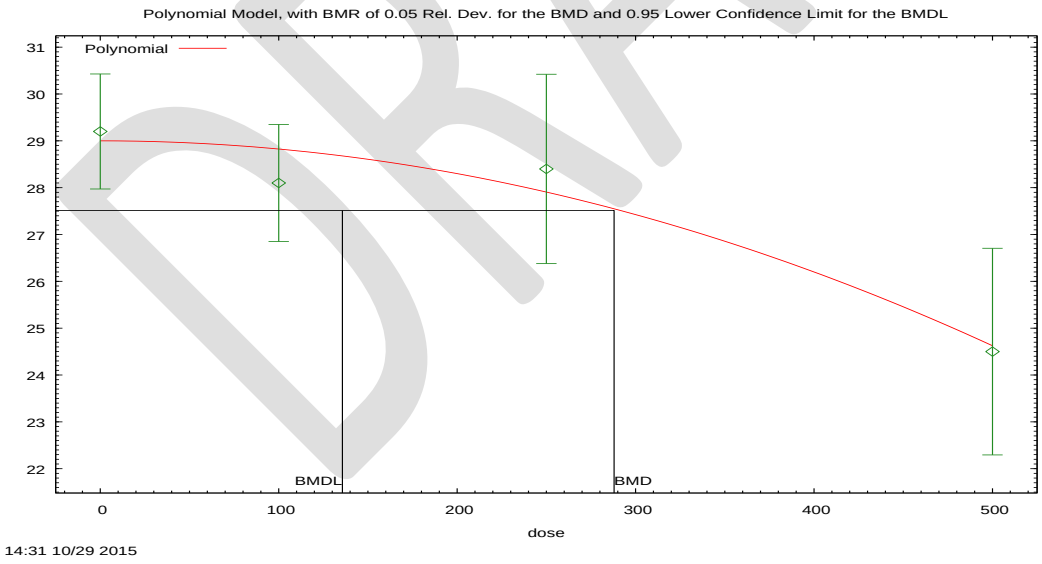
Comparisons of model fits obtained are provided in Table_Apx P-43. The best fitting model (Polynomial 2° with constant variance) was selected based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. The best-fitting model is indicated in bold. For the best fitting model a plot of the model is shown in Figure_Apx P-16. The model version number, model

form, benchmark dose calculation, parameter estimates and estimated values are shown below.

Table_Apx P-43 BMD Modeling Results for Body Weight of F_2 Male Rat Pups on PND 14 Following Inhalation Exposure of Parental Rats to 1-BP in a Two-Generation Study

Model[a]	Goodness of fit		BMD_{1SD} (ppm)	$BMDL_{1SD}$ (ppm)	BMD_{5RD} (ppm)	$BMDL_{5RD}$ (ppm)	Basis for model selection
	p-value	AIC					
Polynomial 2°	**0.509**	**238.45**	427.44	290.47	**288**	**136**	**The Polynomial 2° model was selected based on the lowest AIC, highest goodness of fit *p*-value and adequate fit by visual inspection.**
Linear	0.236	239.99	367.99	261.73	168	124	
Polynomial 3°	0.316	240.11	439.96	300.66	314	140	
Power	0.290	240.22	457.39	297.00	358	138	
Exponential (M3)	0.289	240.23	456.58	297.67	358	134	
Exponential (M2)	0.209	240.23	365.77	251.63	161	115	
Exponential (M4)	0.209	240.23	365.77	241.42	161	95.6	
Hill	N/A[b]	242.22	457.31	296.92	358	138	
Exponential (M5)	N/A[b]	242.23	456.58	297.67	358	134	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.116), selected model in bold; scaled residuals for selected model for doses 0, 100, 250, and 500 ppm were 0.35, -0.89, 0.64, -0.12, respectively.
[b] No available degrees of freedom to calculate a goodness of fit value.



Figure_Apx P-16 Plot of Mean Response by Dose with Fitted Curve for the Selected Model (Polynomial 2°) for Pup Body Weight in Rats Exposed to 1-BP Via Inhalation in ppm BMR = 5% Relative Deviation.

Polynomial Model. (Version: 2.20; Date: 10/22/2014)
The form of the response function is: Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + …

A constant variance model is fit

Benchmark Dose Computation.
BMR = 5% Relative deviation
BMD = 287.938
BMDL at the 95% confidence level = 135.688

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	10.1836	10.5942
rho	n/a	0
beta_0	28.9615	28.8658
beta_1	0	0
beta_2	-0.000017466	-0.000019675

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	29.2	29	2.77	3.19	0.35
100	17	28.1	28.8	2.43	3.19	-0.887
250	15	28.4	27.9	3.65	3.19	0.643
500	16	24.5	24.6	4.14	3.19	-0.119

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-115.551371	5	241.102743
A2	-112.600048	8	241.200097
A3	-115.551371	5	241.102743
fitted	-116.227119	3	238.454239
R	-125.255153	2	254.510306

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	25.3102	6	0.0002991
Test 2	5.90265	3	0.1164
Test 3	5.90265	3	0.1164
Test 4	1.3515	2	0.5088

P-2-15-5 Decreased Body Weight in F_2 Male Pups at PND 21

The doses and response data from the WIL Laboratories (2001) study was used for the modeling and are presented in Table_Apx P-44.

Table_Apx P-44 Pup Body Weight Data in F_2 Males at PND 21

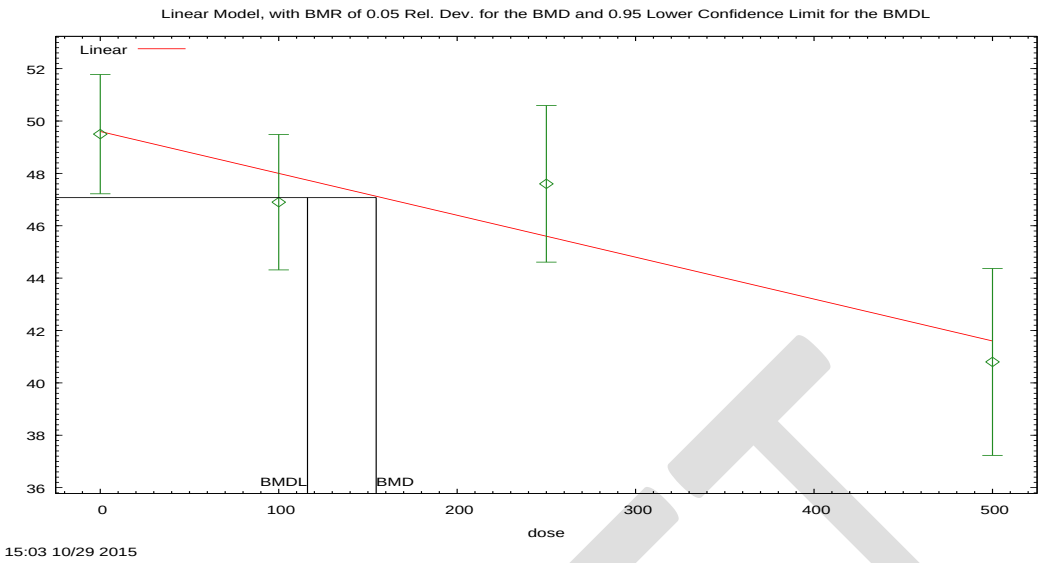
	Concentration (ppm)			
	0	**100**	**250**	**500**
Number of litters	22	17	15	16
Mean pup wt (g)	49.5	46.9	47.6	40.8
Standard deviation (g)	5.14	5.03	5.40	6.70

Comparisons of model fits obtained are provided in Table_Apx P-45. The best fitting model (Linear with homogeneous variance) was selected based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. The best-fitting model is indicated in bold. For the best fitting model a plot of the model is shown in Figure_Apx P-17. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below.

Table_Apx P-45 BMD Modeling Results for Body Weight of F_2 Male Rat Pups on PND 21 Following Inhalation Exposure of Parental Rats to 1-BP in a Two-Generation Study

Model[a]	Goodness of fit		BMD_{1SD} (ppm)	$BMDL_{1SD}$ (ppm)	BMD_{5RD} (ppm)	$BMDL_{5RD}$ (ppm)	Basis for model selection
	p-value	AIC					
Linear	**0.218**	**315.14**	**344.43**	**249.00**	**155**	**116**	**The Linear model was selected based on the lowest AIC, highest goodness of fit *p*-value and adequate fit by visual inspection.**
Exponential (M2)	0.194	315.38	339.42	237.32	147	107	
Exponential (M4)	0.194	315.38	339.42	220.01	147	84.8	
Polynomial 3°	0.194	315.78	418.75	271.24	273	125	
Polynomial 2°	0.153	316.14	404.48	264.17	252	122	
Power	0.150	316.17	435.13	263.67	313	122	
Exponential (M3)	0.148	316.19	436.20	257.18	318	115	
Hill	N/A[b]	318.17	435.26	262.98	314	121	
Exponential (M5)	N/A[b]	318.19	436.20	257.18	318	115	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.614), selected model in bold; scaled residuals for selected model for doses 0, 100, 250, and 500 ppm were -0.04, -0.78, 1.44, -0.54, respectively.
[b] No available degrees of freedom to calculate a goodness of fit value.



Figure_Apx P-17 Plot of Mean Response by Dose with Fitted Curve for the Selected Model (Linear) for Pup Body Weight in Rats Exposed to 1-BP Via Inhalation in ppm BMR = 5% Relative Deviation.

Polynomial Model. (Version: 2.20; Date: 10/22/2014)
The form of the response function is: Y[dose] = beta_0 + beta_1*dose
A constant variance model is fit

Benchmark Dose Computation.
BMR = 5% Relative deviation
BMD = 154.623
BMDL at the 95% confidence level = 116.114

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	30.4578	30.9275
rho	n/a	0
beta_0	49.5516	49.615
beta_1	-0.0160234	-0.0160705

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	49.5	49.6	5.14	5.52	-0.0439
100	17	46.9	47.9	5.03	5.52	-0.784
250	15	47.6	45.5	5.4	5.52	1.44
500	16	40.8	41.5	6.7	5.52	-0.536

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-153.048201	5	316.096402
A2	-152.146228	8	320.292456
A3	-153.048201	5	316.096402
fitted	-154.572024	3	315.144048
R	-163.858303	2	331.716606

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	23.4241	6	0.0006662
Test 2	1.80395	3	0.6141
Test 3	1.80395	3	0.6141
Test 4	3.04765	2	0.2179

P-2-16 Decreased Brain Weight

Decreased brain weights were observed in the 2-generation reproductive and developmental study by (WIL Research, 2001). Statistically significant decreases in brain weights were noted for both sexes in the F_0 generation, F_1 generation as adults and in the F_2 generation at PNDs 21. Continuous models were used to fit-dose response data for decreased brain weights. A BMR of 5% was used because this is a developmental endpoint (Kavlock et al., 1995). A BMR of 1 standard deviation is also shown for comparison per EPA Benchmark Dose Technical Guidance (U.S. EPA, 2012a). The doses, response data and BMD modeling results for decreased pup brain weight are presented below at each time point.

P-2-16-1 Decreased Brain Weight in F_0 Females

The doses and response data from the WIL Laboratories (2001) study was used for the modeling and are presented in Table_Apx P-46.

Table_Apx P-46 Brain Weight Data in F_0 Females for Dose-Response Modeling

	Concentration (ppm)				
	0	**100**	**250**	**500**	**750**
Number of animals	25	25	25	25	25
Brain wt (g)	1.96	1.92	1.94	1.89	1.86
Standard deviation (g)	0.078	0.094	0.084	0.105	0.072

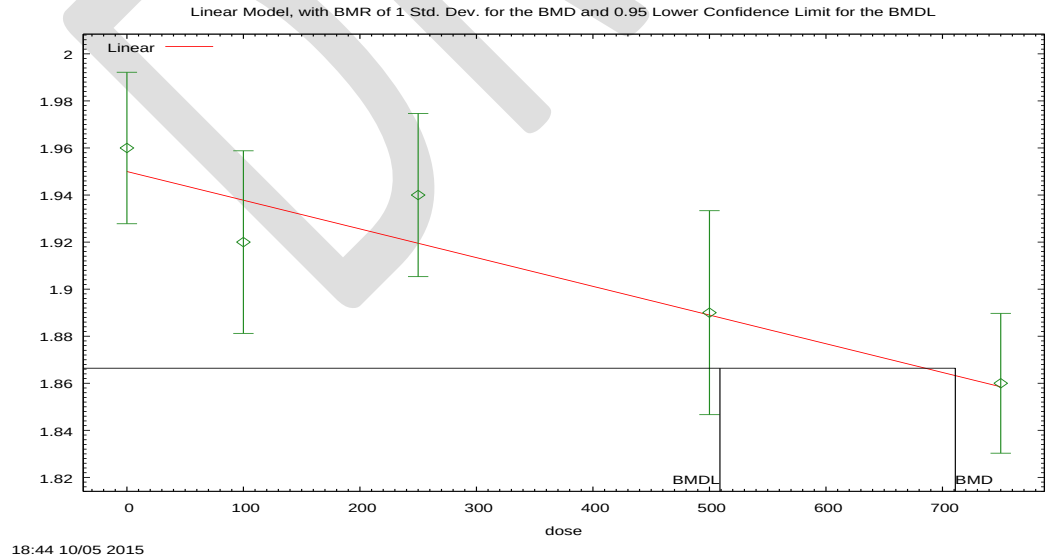
Comparisons of model fits obtained are provided in Table_Apx P-47. The best fitting model (Linear with homogeneous variance) was selected based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a

better fit) and visual inspection. The best-fitting model is indicated in bold. For the best fitting model a plot of the model is shown in Figure_Apx P-18. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below.

Table_Apx P-47 BMD Modeling Results for Brain Weight of F_0 Females Following Inhalation Exposure to 1-BP

Model[a]	Goodness of fit		BMD_{1SD} (ppm)	$BMDL_{1SD}$ (ppm)	Basis for model selection
	p-value	AIC			
Linear	**0.444**	**-480.77**	**711**	**509**	**The Linear model was selected based on the lowest AIC, highest goodness of fit *p*-value and adequate fit by visual inspection.**
Exponential (M2)	0.441	-480.75	711	504	
Exponential (M4)	0.441	-480.75	711	434	
Polynomial 4°[b] Polynomial 3°	0.273	-478.85	717	511	
Polynomial 2°	0.271	-478.84	718	511	
Power	0.263	-478.77	715	509	
Exponential (M3)	0.261	-478.76	716	504	
Exponential (M5)	0.101	-476.76	716	504	
Hill	0.100	-476.75	error[c]	error[c]	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.340), selected model in bold; scaled residuals for selected model for doses 0, 100, 250, 500, and 750 ppm were 0.41, -1.2, 1.01, -0.12, -0.1, respectively.
[b] For the Polynomial 4° model, the b4 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 3° model.
[c] BMD or BMDL computation failed for this model.



Figure_Apx P-18 Plot of Mean Response by Dose with Fitted Curve for the Selected Model (Linear) for Brain Weight in F_0 Female Rats Exposed to 1-BP Via Inhalation in ppm BMR = 1 Standard Deviation.

Polynomial Model. (Version: 2.20; Date: 10/22/2014)
The form of the response function is: Y[dose] = beta_0 + beta_1*dose
A constant variance model is fit

Benchmark Dose Computation.
BMR = 1 Estimated standard deviations from the control mean
BMD = 711.056
BMDL at the 95% confidence level = 508.985

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.00749034	0.007637
rho	n/a	0
beta_0	1.95295	1.95295
beta_1	-0.000121716	-0.000121716

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	25	1.96	1.95	0.08	0.09	0.407
100	25	1.92	1.94	0.09	0.09	-1.2
250	25	1.94	1.92	0.08	0.09	1.01
500	25	1.89	1.89	0.1	0.09	-0.121
750	25	1.86	1.86	0.07	0.09	-0.096

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	244.723276	6	-477.446552
A2	246.984613	10	-473.969225
A3	244.723276	6	-477.446552
fitted	243.383815	3	-480.76763
R	234.782134	2	-465.564268

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	24.405	8	0.001959
Test 2	4.52267	4	0.3399
Test 3	4.52267	4	0.3399
Test 4	2.67892	3	0.4438

P-2-16-2 Decreased Brain Weight in F_0 Males

The doses and response data from the WIL Laboratories (2001) study was used for the modeling and are presented in Table_Apx P-48.

Table_Apx P-48 Brain Weight Data in F_0 Males for Dose-Response Modeling

	Concentration (ppm)				
	0	**100**	**250**	**500**	**750**
Number of animals	25	25	25	25	25
Brain wt (g)	2.19	2.15	2.08	2.1	2.05
Standard deviation (g)	0.091	0.114	0.087	0.177	0.091

The BMD modeling results for decreased brain weight in F_0 males with non-homogeneous variance (BMDS test 2 *p*-value = 0.000386) are summarized in Table_Apx P-49. Although the variances are non-homogeneous and not well modeled for any of the non-homogeneous variance models the means were well-modeled (the highest *p*-value is 0.618 for the Exponential (M4) model with non-homogeneous variances).

Table_Apx P-49 BMD Modeling Results for Brain Weight of F_0 Males Following Inhalation Exposure to 1-BP

Model[a]	Goodness of fit		BMD_{5RD} (ppm)	$BMDL_{5RD}$ (ppm)
	p-value	AIC		
Exponential (M4)	0.618	-408.61	372	159
Hill	0.340	-406.66	354	107
Exponential (M5)	0.152	-405.52	115	102
Exponential (M2) Exponential (M3)[b]	0.0868	-405.00	636	453
Power[c] Polynomial 4°[d] Polynomial 2°[e] Linear[f]	0.0804	-404.83	644	463
Polynomial 3°[g]	0.0804	-404.83	644	463

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 3.86E-04, BMDS Test 3 *p*-value = 5.66E-04), no model was selected as a best-fitting model.
[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.
[c] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.
[d] For the Polynomial 4° model, the b4 and b3 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 4° model, the b4, b3, and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[e] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[f] The Linear model may appear equivalent to the Polynomial 3° model, however differences exist in digits not displayed in the table.
[g] The Polynomial 3° model may appear equivalent to the Power model, however differences exist in digits not displayed in the table. This also applies to the Polynomial 4° model. This also applies to the Polynomial 2° model. This also applies to the Linear model.

To investigate the effect of the poor modeling of the variances on the BMDL, the models were run using the smallest dose standard deviation (0.091), highest (0.177) and the pooled (0.0907) for all dose levels and the modeling results are summarized in Table_Apx P-50.

Table_Apx P-50 BMD Modeling Results for Brain Weight of F_0 Male Rats Following Inhalation Exposure to 1-BP in a Two-Generation Study with Variances Fixed at Smallest, Pooled and Highest Values.

Model[a]	Smallest Standard Deviation				Pooled Standard Deviation				Largest Standard Deviation				Ratio BMDLs Smallest to Largest Std Dev
	Goodness of fit		BMD_{5RD} (ppm)	$BMDL_{5RD}$ (ppm)	Goodness of fit		BMD_{5RD} (ppm)	$BMDL_{5RD}$ (ppm)	Goodness of fit		BMD_{5RD} (ppm)	$BMDL_{5RD}$ (ppm)	
	p-value	AIC			*p*-value	AIC			*p*-value	AIC			
Exponential (M4)	0.0893	-477.73	375	164	0.108	-467.70	375	159	0.553	-303.82	375	78.7	2.1
Hill	0.0423	-476.44	289	106	0.0513	-466.35	289	106	0.315	-302.00	289	70.4	1.5
Exponential (M5)	0.0398	-476.34	246	104	0.0484	-466.26	246	103	0.309	-301.97	246	82.4	1.3
Exponential (M2)	0.0238	-475.11	669	515	0.0332	-465.43	669	510	0.503	-304.65	669	420	1.2
Exponential (M3)	0.0238	-475.11	669	515	0.0332	-465.43	669	510	0.503	-304.65	669	420	1.2
Power	0.0223	-474.96	674	523	0.0312	-465.29	674	518	0.496	-304.62	674	430	1.2
Polynomial 4°	0.0223	-474.96	674	523	0.0312	-465.29	674	518	0.496	-304.62	674	430	1.2
Polynomial 2°	0.0223	-474.96	674	523	0.0312	-465.29	674	518	0.496	-304.62	674	430	1.2
Linear	0.0223	-474.96	674	523	0.0312	-465.29	674	518	0.496	-304.62	674	430	1.2
Polynomial 3°	0.0223	-474.96	674	523	0.0312	-465.29	674	518	0.496	-304.62	674	430	1.2

[a] Constant variance case presented (BMDS Test 2 *p*-value = 1., BMDS Test 3 *p*-value = 1.), no model was selected as a best-fitting model.

A comparison across the full suite of BMD models shows the BMDL is sensitive to the adjustment of the variances and for the model that fit the constant variance data best, the Exponential (M4) model the ratio of BMDLs was 2.1. This result suggests that due to the poor variance modeling for the original data it is not reasonable to use BMDS for this endpoint. Instead the NOAEL of 100 ppm was used.

P-2-16-3 Decreased Brain Weight in F_1 Females as Adults

The doses and response data used for the modeling are presented in Table_Apx P-51.

Table_Apx P-51 Brain Weight Data in F_1 Females as Adults from Selected for Dose-Response Modeling

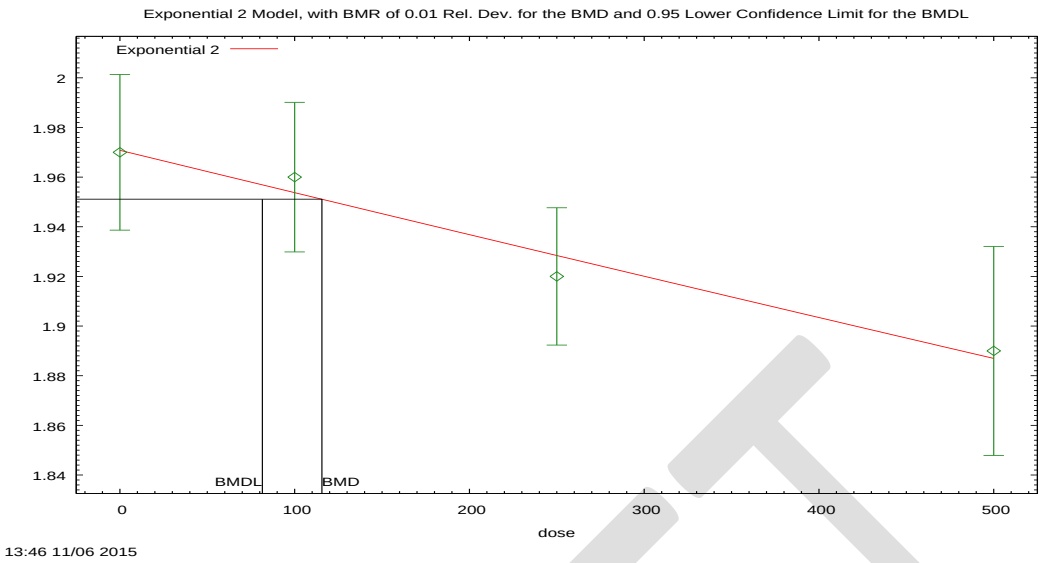
	Concentration (ppm)			
	0	**100**	**250**	**500**
Number of animals	25	25	25	25
Brain wt (g)	1.97	1.96	1.92	1.89
Standard deviation (g)	0.076	0.073	0.067	0.102

Comparisons of model fits obtained are provided in Table_Apx P-52. The best fitting model (Exponential (M2) with homogeneous variance) was selected based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. The best-fitting model is indicated in bold. For the best fitting model a plot of the model is shown in Figure_Apx P-19. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below.

Table_Apx P-52 BMD Modeling Results for Brain Weight of F_1 Female Rats as Adults Following Inhalation Exposure of Parental Rats to 1-BP in a Two-Generation Study

Model[a]	Goodness of fit		BMD_{1SD} (ppm)	$BMDL_{1SD}$ (ppm)	BMD_{5RD} (ppm)	$BMDL_{5RD}$ (ppm)	BMD_{1RD} (ppm)	$BMDL_{1RD}$ (ppm)	Basis for model selection
	p-value	AIC							
Exponential (M2) **Exponential (M3)[b]**	**0.787**	**-401.21**	472	327	590	416	**116**	**81.5**	**The Exponential (M2) model was selected based on the lowest AIC, highest goodness of fit *p*-value and adequate fit by visual inspection.**
Power[c] Polynomial 3°[d] Polynomial 2°[e] Linear	0.780	-401.19	473	331	589	419	118	83.8	
Exponential (M4)	0.534	-399.30	459	230	619	363	94.7	35.1	
Hill	N/A[f]	-397.69	482	230	error[g]	error[g]	138	33.1	
Exponential (M5)	N/A[f]	-397.69	463	112	error[g]	0	141	37.6	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.144), selected model in bold; scaled residuals for selected model for doses 0, 100, 250, and 500 ppm were -0.05, 0.39, -0.53, 0.19, respectively.
[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.
[c] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.
[d] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[e] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[f] No available degrees of freedom to calculate a goodness of fit value.
[g] BMD or BMDL computation failed for this model.



Figure_Apx P-19 Plot of Mean Response by Dose with Fitted Curve for the Selected Model (Exponential (M2)) for Brain Weight in F_1 Female Rats as Adults Exposed to 1-BP Via Inhalation in ppm BMR = 1% Relative Deviation.

Exponential Model. (Version: 1.10; Date: 01/12/2015)
The form of the response function is: Y[dose] = a * exp(sign * b * dose)
A constant variance model is fit

Benchmark Dose Computation.
BMR = 1% Relative deviation
BMD = 115.594
BMDL at the 95% confidence level = 81.5083

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-5.07205	-5.07685
rho	n/a	0
a	1.97082	1.89939
b	0.0000869453	0.000086769
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	25	1.97	1.97	0.08	0.08	-0.05174
100	25	1.96	1.95	0.07	0.08	0.3941
250	25	1.92	1.93	0.07	0.08	-0.5332
500	25	1.89	1.89	0.1	0.08	0.1908

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	203.8426	5	-397.6852
A2	206.5452	8	-397.0903
A3	203.8426	5	-397.6852
R	196.2377	2	-388.4753
2	203.6027	3	-401.2054

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	20.62	6	0.002151
Test 2	5.405	3	0.1444
Test 3	5.405	3	0.1444
Test 4	0.4799	2	0.7867

P-2-16-4 Decreased Brain Weight in F_1 Males as Adults

The doses and response data used for the modeling are presented in Table_Apx P-53.

Table_Apx P-53 Brain Weight Data in F_1 Males as Adults from Selected for Dose-Response Modeling

	Concentration (ppm)			
	0	**100**	**250**	**500**
Number of animals	24	25	25	24
Brain wt (g)	2.21	2.11	2.12	2.01
Standard deviation (g)	0.092	0.111	0.109	0.079

The data were not adequately fit by any of the models, the means goodness of fit *p*-values were less than 0.05 for all of the models. Comparisons of model fits obtained are provided in Table_Apx P-54. Since no model was selected a plot of the model, BMD and BMDL calculations and other output are not presented. BMRs other than 5% relative deviation are not shown because the fit to the means are not different and therefore also inadequate. Instead the LOAEL

of 100 ppm was used because there was no NOAEL observed in the WIL Laboratories (2001) study.

Table_Apx P-54 BMD Modeling Results for Brain Weight of F_1 Male Rats as Adults Following Inhalation Exposure of Parental Rats to 1-BP in a Two-Generation Study

Model[a]	Goodness of fit		BMD_{5RD} (ppm)	$BMDL_{5RD}$ (ppm)
	p-value	AIC		
Exponential (M2) Exponential (M3)[b]	0.0320	-346.71	308	245
Power[c] Polynomial 3°[d] Polynomial 2°[e] Linear	0.0312	-346.66	314	252
Hill	0.00968	-344.90	265	112
Exponential (M4) Exponential (M5)[f]	0.00932	-344.84	279	144

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.310, BMDS Test 3 *p*-value = 0.310), no model was selected as a best-fitting model.
[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.
[c] For the Power model, the power parameter estimate was 1. The models in this row reduced to the Linear model.
[d] For the Polynomial 3° model, the b3 coefficient estimates was 0 (boundary of parameters space). The models in this row reduced to the Polynomial 2° model. For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[e] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[f] For the Exponential (M5) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M4) model.

P-2-16-5 Decreased Brain Weight in F_2 Females at PND 21

The doses and response data used for the modeling are presented in Table_Apx P-55.

Table_Apx P-55 Brain Weight Data in F_2 Females at PND 21 from Selected for Dose-Response Modeling

	Concentration (ppm)			
	0	**100**	**250**	**500**
Number of animals	22	17	15	15
Brain wt (g)	1.3957	1.3903	1.3673	1.3089
Standard deviation (g)	0.06491	0.08882	0.12231	0.1004

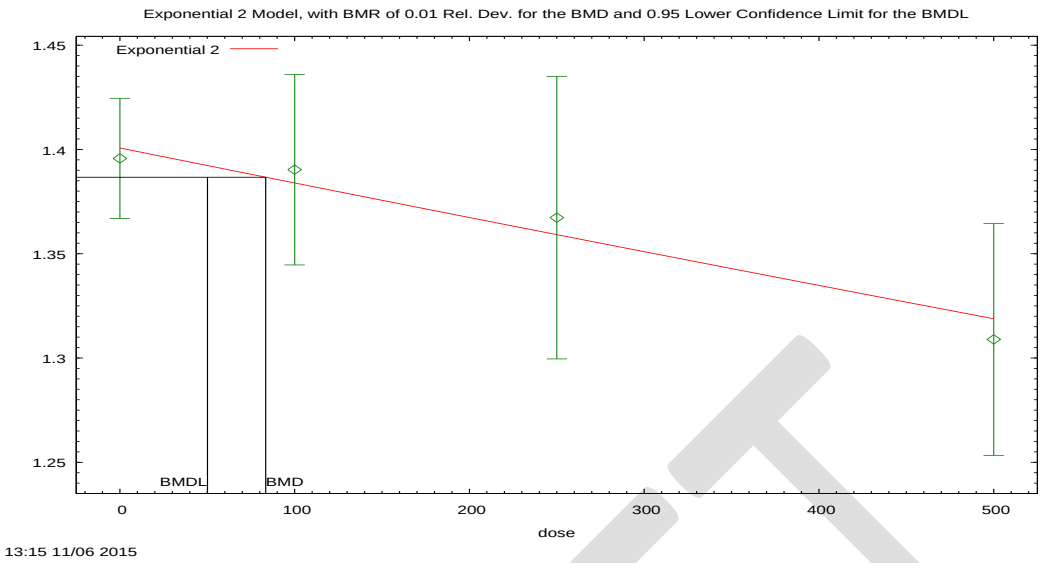
Comparisons of model fits obtained are provided in Table_Apx P-56. The best fitting model (Exponential (M2) with non-homogeneous variance) was selected based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. The best-fitting model is indicated in bold. For the best fitting model a plot of the model is shown in Figure_Apx P-20. The model version

number, model form, benchmark dose calculation, parameter estimates and estimated values are shown below.

Table_Apx P-56 BMD Modeling Results for Brain Weight of F_2 Female Rats at PND 21 Following Inhalation Exposure of Parental Rats to 1-BP in a Two-Generation Study

Model[a]	Goodness of fit		BMD_{1SD} (ppm)	$BMDL_{1SD}$ (ppm)	BMD_{5RD} (ppm)	$BMDL_{5RD}$ (ppm)	BMD_{1RD} (ppm)	$BMDL_{1RD}$ (ppm)	Basis for model selection
	p-value	AIC							
Exponential (M2) Exponential (M3)[b]	**0.634**	**-257.31**	454	260	426	256	**83.4**	**50.1**	**The Exponential (M2) model was selected based on the lowest AIC and adequate fit by visual inspection.**
Power	0.621	-257.27	456	266	427	261	85.3	52.1	
Polynomial 3°[c] Linear[d]	0.566	-257.27	456	266	427	261	85.3	52.1	
Polynomial 2°[e]	0.566	-257.27	456	266	427	261	85.3	52.1	
Exponential (M4)	0.702	-256.08	643	130	1149	170	48.5	12.6	
Hill	N/A[f]	-254.41	error[g]	error[g]	error[g]	error[g]	85.7	6.27	
Exponential (M5)	N/A[f]	-254.41	error[g]	0	error[g]	0	81.2	14.9	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.0643), selected model in bold; scaled residuals for selected model for doses 0, 100, 250, and 500 ppm were -0.31, 0.32, 0.34, -0.32, respectively.
[b] For the Exponential (M3) model, the estimate of d was 1 (boundary). The models in this row reduced to the Exponential (M2) model.
[c] For the Polynomial 3° model, the b3 and b2 coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[d] The Linear model may appear equivalent to the Polynomial 2° model, however differences exist in digits not displayed in the table.
[e] The Polynomial 2° model may appear equivalent to the Polynomial 3° model, however differences exist in digits not displayed in the table. This also applies to the Linear model.
[f] No available degrees of freedom to calculate a goodness of fit value.
[g] BMD or BMDL computation failed for this model.



Figure_Apx P-20 Plot of Mean Response by Dose with Fitted Curve for the Selected Model (Exponential (M2)) for Brain Weight in F_2 Female Exposed to 1-BP Via Inhalation in ppm BMR = 1% Relative Deviation.

Exponential Model. (Version: 1.10; Date: 01/12/2015)
The form of the response function is: Y[dose] = a * exp(sign * b * dose)
A modeled variance is fit

Benchmark Dose Computation.
BMR = 1% Relative deviation
BMD = 83.4282
BMDL at the 95% confidence level = 50.1098

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-0.0282712	-1.99881
rho	-15.3239	-8.92906
a	1.40066	1.33604
b	0.000120467	0.000129477
c	n/a	0
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	1.4	1.4	0.06	0.07	-0.3121
100	17	1.39	1.38	0.09	0.08	0.3231
250	15	1.37	1.36	0.12	0.09	0.3377
500	15	1.31	1.32	0.1	0.12	-0.3236

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	131.2578	5	-252.5155
A2	134.8828	8	-253.7656
A3	133.1137	6	-254.2275
R	126.819	2	-249.638
2	132.6574	4	-257.3148

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	16.13	6	0.01309
Test 2	7.25	3	0.06434
Test 3	3.538	2	0.1705
Test 4	0.9127	2	0.6336

P-2-16-6 Decreased Brain Weight in F_2 Males at PND 21

The doses and response data from the WIL Laboratories (2001) study was used for the modeling are presented in Table_Apx P-57.

Table_Apx P-57 Brain Weight Data in F_2 Males at PND 21 for Dose-Response Modeling

	Concentration (ppm)			
	0	**100**	**250**	**500**
Number of animals	22	17	15	16
Brain wt (g)	1.4728	1.4253	1.4668	1.3629
Standard deviation (g)	0.07836	0.07679	0.05971	0.09581

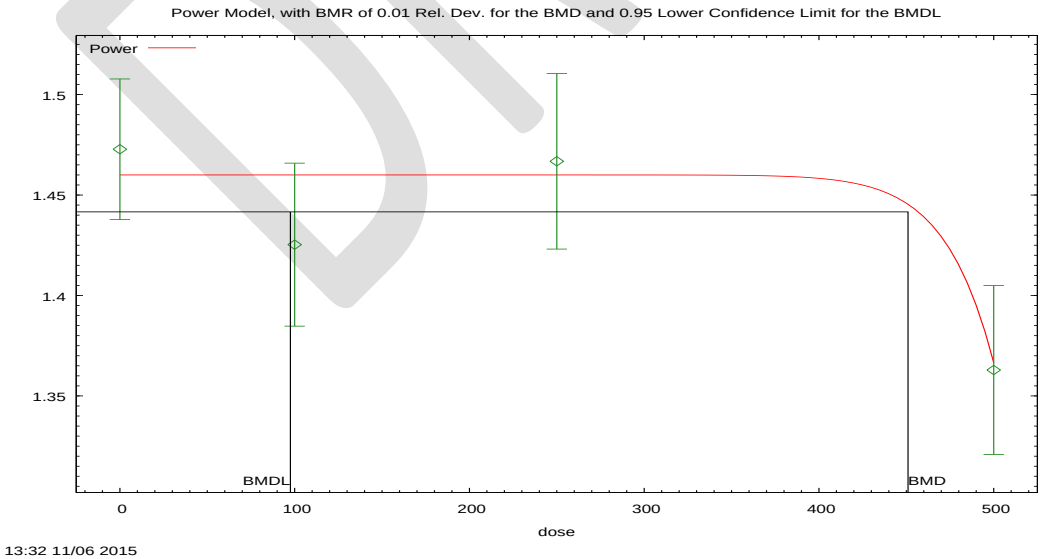
Comparisons of model fits obtained are provided in Table_Apx P-58. The best fitting model (Power with homogeneous variance) was selected based on Akaike information criterion (AIC; lower values indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit) and visual inspection. The best-fitting model is indicated in bold. For the best fitting model a plot of the model is shown in Figure_Apx P-21. The model version number, model

form, benchmark dose calculation, parameter estimates and estimated values are shown below.

Table_Apx P-58 BMD Modeling Results for Brain Weight of F_2 Male Rats as Adults Following Inhalation Exposure of Parental Rats to 1-BP in a Two-Generation Study

Model[a]	Goodness of fit		BMD_{1SD} (ppm)	$BMDL_{1SD}$ (ppm)	BMD_{5RD} (ppm)	$BMDL_{5RD}$ (ppm)	BMD_{1RD} (ppm)	$BMDL_{1RD}$ (ppm)	Basis for model selection
	p-value	AIC							
Power	**0.137**	**-279.68**	495	395	493	374	**451**	**97.6**	**The Power model was selected based on the lowest AIC, highest goodness of fit *p*-value and adequate fit by visual inspection**
Polynomial 3°	0.0961	-278.97	472	353	459	331	269	67.1	
Polynomial 2°	0.0647	-278.18	459	383	440	370	197	166	
Exponential (M3)	0.0463	-277.68	495	396	493	376	450	102	
Hill	0.0463	-277.68	495	281	493	error[b]	450	error[b]	
Linear	0.0306	-276.68	430	293	393	274	78.6	54.8	
Exponential (M2)	0.0294	-276.60	431	289	393	269	76.9	52.8	
Exponential (M4)	0.0294	-276.60	431	278	393	250	76.9	36.9	
Exponential (M5)	N/A[c]	-275.68	495	272	493	376	449	102	

[a] Constant variance case presented (BMDS Test 2 *p*-value = 0.337), selected model in bold; scaled residuals for selected model for doses 0, 100, 250, and 500 ppm were 0.99, -1.62, 0.52, 0, respectively.
[b] BMD or BMDL computation failed for this model.
[c] No available degrees of freedom to calculate a goodness of fit value.



Figure_Apx P-21 Plot of Mean Response by Dose with Fitted Curve for the Selected Model (Power) for Brain Weight in Rats Exposed to 1-BP Via Inhalation in ppm BMR = 1% Relative Deviation.

Power Model. (Version: 2.18; Date: 05/19/2014)
The form of the response function is: Y[dose] = control + slope * dose^power
A constant variance model is fit

Benchmark Dose Computation.
BMR = 1% Relative deviation
BMD = 450.983
BMDL at the 95% confidence level = 97.5507

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
alpha	0.00621258	0.00622577
rho	n/a	0
control	1.45618	1.3629
slope	-2.44527E-50	0.0048117
power	18	-9999

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	22	1.47	1.46	0.08	0.08	0.989
100	17	1.43	1.46	0.08	0.08	-1.62
250	15	1.47	1.46	0.06	0.08	0.522
500	16	1.36	1.36	0.1	0.08	-0.00000182

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	144.826466	5	-279.652932
A2	146.516124	8	-277.032248
A3	144.826466	5	-279.652932
fitted	142.841294	3	-279.682588
R	135.116612	2	-266.233223

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	22.799	6	0.0008667
Test 2	3.37932	3	0.3368
Test 3	3.37932	3	0.3368
Test 4	3.97034	2	0.1374

P-2-17 Decreased Hang Time

EPA/OPPT selected decreased time hanging from a suspended bar from the (Honma et al., 2003) study as a relevant endpoint for calculating risks associated with chronic worker scenarios. Since this is a continuous endpoint and in the absence of a basis for selecting a BMR a default selection of 1 standard deviation was used in accordance with EPA Benchmark Dose Technical Guidance (U.S. EPA, 2012a). The doses and response data used for the modeling are presented in Table_Apx P-59.

Table_Apx P-59 Hang Time from a Suspended Bar Data for Dose-Response Modeling for 1-BP

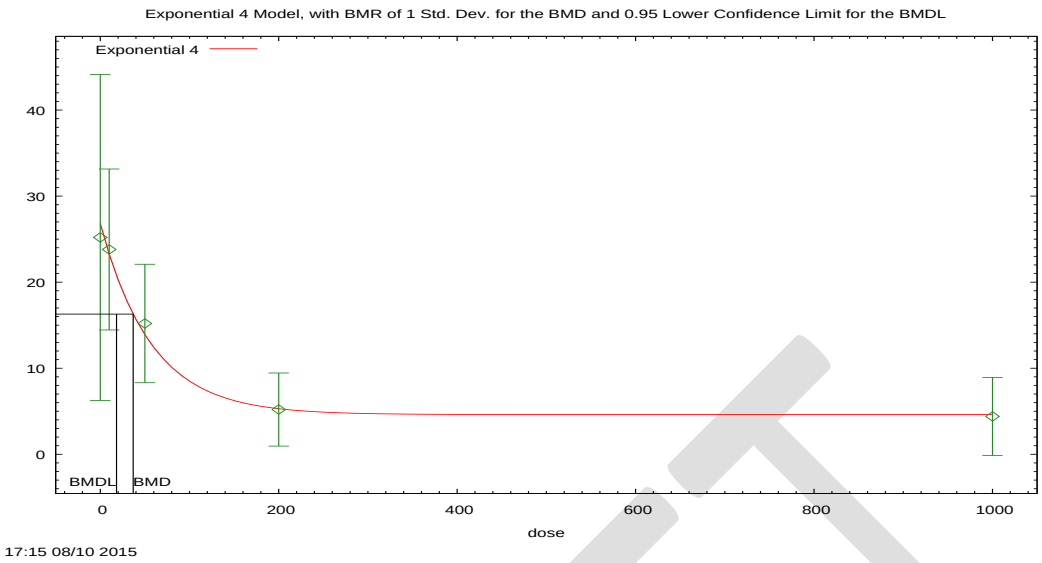
Dose (ppm)	Number of animals	Mean traction time (sec)	Standard Deviation
0	5	25.2	15.25
10	5	23.8	7.53
50	5	15.2	5.54
200	5	5.2	3.42
1000	5	4.4	3.65

The best fitting model was selected based on Akaike information criterion (AIC; lower value indicates a better fit), chi-square goodness of fit *p*-value (higher value indicates a better fit), ratio of the BMC:BMCL (lower value indicates less model uncertainty) and visual inspection. Comparisons of model fits obtained are provided in
Table_Apx P-60. The best-fitting model (Exponential M4), based on the criteria described above, is indicated in bold. For the best fitting model a plot of the model is shown in Figure_Apx P-22. The model version number, model form, benchmark dose calculation, parameter estimates and estimated values are shown.

Table_Apx P-60 Summary of BMD Modeling Results for Hang Time from a Suspended Bar; BMR = 1 std. dev. change from control mean

Model[a]	Goodness of fit		BMD_{1SD} (ppm)	$BMDL_{1SD}$ (ppm)	Basis for model selection
	p-value	AIC			
Exponential (M4)	**0.955**	**122.13**	**36.9**	**18.2**	**The Exponential (M4) model was selected based on the lowest AIC, highest goodness of fit *p*-value and adequate fit by visual inspection.**
Exponential (M5)	0.766	124.12	37.7	18.2	
Hill	0.467	124.57	45.0	error[b]	
Exponential (M2)[c]	0.00443	133.13	47.4	20.8	
Exponential (M3)[d]	0.00443	133.13	47.4	20.8	
Power[e]	2.22E-04	139.47	799	525	
Polynomial 2°[f] Linear[g]	2.22E-04	139.47	799	525	
Polynomial 3°	<0.0001	188.00	-9999	error[b]	
Polynomial 4°	N/A[h]	192.45	-9999	error[b]	

[a] Modeled variance case presented (BMDS Test 2 *p*-value = 0.00293), selected model in bold; scaled residuals for selected model for doses 0, 10, 50, 200, and 1000 ppm were -0.34, 0.12, 0.44, -0.07, -0.17, respectively.
[b] BMD or BMDL computation failed for this model.
[c] The Exponential (M2) model may appear equivalent to the Exponential (M3) model, however differences exist in digits not displayed in the table.
[d] The Exponential (M3) model may appear equivalent to the Exponential (M2) model, however differences exist in digits not displayed in the table.
[e] The Power model may appear equivalent to the Polynomial 2° model, however differences exist in digits not displayed in the table. This also applies to the Linear model.
[f] For the Polynomial 2° model, the b2 coefficient estimate was 0 (boundary of parameters space). The models in this row reduced to the Linear model.
[g] The Linear model may appear equivalent to the Power model, however differences exist in digits not displayed in the table.
[h] No available degrees of freedom to calculate a goodness of fit value.



Figure_Apx P-22 Plot of Mean Response by Dose in ppm with Fitted Curve for Exponential (M4) Model with Modeled Variance for Hang Time from a Suspended Bar; BMR = 1 Standard Deviation Change from Control Mean.

Exponential Model. (Version: 1.10; Date: 01/12/2015)
The form of the response function is: Y[dose] = a * [c-(c-1) * exp(-b * dose)]
A modeled variance is fit

Benchmark Dose Computation.
BMR = 1.0000 Estimated standard deviations from control
BMD = 36.9173
BMDL at the 95% confidence level = 18.2429

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
lnalpha	-0.107405	0.415293
rho	1.46448	1.29675
a	26.8244	26.46
b	0.0174245	0.00510395
c	0.172048	0.15837
d	n/a	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Resid
0	5	25.2	26.82	15.25	10.54	-0.3447
10	5	23.8	23.27	7.53	9.5	0.1241
50	5	15.2	13.91	5.54	6.51	0.4434
200	5	5.2	5.3	3.42	3.21	-0.0668
1000	5	4.4	4.62	3.65	2.9	-0.1656

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-62.64066	6	137.2813
A2	-54.60856	10	129.2171
A3	-56.01777	7	126.0355
R	-73.64274	2	151.2855
4	-56.06343	5	122.1269

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	*p*-value
Test 1	38.07	8	<0.0001
Test 2	16.06	4	0.002934
Test 3	2.818	3	0.4205
Test 6a	0.09133	2	0.9554

P-3 Benchmark Dose Modeling of Tumors

EPA/OPPT selected 1-BP-induced tumors observed in mice and rats in the chronic inhalation bioassay by NTP (2011) for BMD modeling with EPA's BMDS. The three tumor sites were selected for modeling were alveolar/bronchiolar adenomas and carcinomas (i.e. lung tumors) in female mice (Section P-3-1), adenomas of the large intestine in female rats (Section P-3-2), and keratoacanthoma and squamous cell carcinomas of the skin in male rats (Section P-3-3). All of the models in the BMDS suite of dichotomous models were applied the gamma, logistic, log-logistic, multistage, probit, log-probit, quantal-linear and Weibull models. A BMR of 0.1% (1 in 1,000) added risk was used and the 95% lower confidence limit was calculated. Models were determined to be adequate or not in a manner consistent with EPA Benchmark Dose Technical Guidance (U.S. EPA, 2012a). Briefly the AIC, goodness of fit *p*-values (0.1 or greater) and a visual assessment of fit are important criteria. The data were further modeled by using a model-averaging (MA) technique with the Model Averaging for Dichotomous Response Benchmark Dose (MADr-BMD) software as described in Wheeler and Bailer (2008). The models in the averaging technique are weighted on the basis of model fit. The models selected for averaging

are the multistage, log-probit and Weibull based on the observation that this 3 model suite performed better in bias and coverage in the analysis by Wheeler and Bailer (2007). Confidence limits in the model were determined with a bootstrapping method. The doses, tumor incidence data, BMD modeling results and model averaging results are presented below for each tumor site. Further a sensitivity analysis by quantitatively comparing the impact of alternative model selections is presented for each of the tumor data sets.

P-3-1 Lung Tumors in Female Mice

The doses and response data from the NTP (2011) study that were used for the modeling are presented in Table_Apx P-61.

Table_Apx P-61 Incidence of Lung Tumors in Female Mice

Dose (ppm)	Number of animals	Number of Animals with Tumors
0	50	1
62.5	50	9
125	50	8
250	50	14

Comparisons of model fits obtained from BMD modeling of the NTP (2011) study are provided in Table_Apx P-62. The loglogistic, gamma, Weibull, quantal-linear, multistage and logprobit all had acceptable fits to the data by *p*-value, visual inspection and similar AIC values. A summary of the model average results are shown for comparison with the BMDS results in Table_Apx P-62. Detailed output of the model average run are shown below. The model average result was selected because the model has an adequate *p*-value and model-averaging has been shown to have reduced bias and better coverage in some cases (Wheeler and Bailer, 2007). In a sensitivity analysis alternative model selections include the single best benchmark dose model based on *p*-value, visual inspection and lowest AIC the loglogistic model or the multistage model per EPA Benchmark Dose Technical Guidance for cancer datasets (U.S. EPA, 2012a). The BMDL of the loglogistic model is 0.42 ppm and multistage model is 0.522 ppm, both are similar (within a factor of 2) of the the model average BMDL of 0.63 ppm.

Table_Apx P-62 Summary of BMD Modeling Results for Lung Tumors in Female Mice

Model	Goodness of fit		$BMD_{0.1PctAdd}$ (ppm)	$BMDL_{0.1PctAdd}$ (ppm)
	p-value	AIC		
LogLogistic	0.283	166.52	0.649	0.423
Gamma[b]	0.218	166.97	0.772	0.522
Weibull[c] Quantal-Linear[b]	0.218	166.97	0.772	0.522
Multistage 3°[d] Multistage 2°[b]	0.218	166.97	0.772	0.522

LogProbit	0.343	167.13	0.0391	error[e]
Probit	0.0956	169.23	1.94	1.47
Logistic	0.0889	169.51	2.16	1.64
Model average (multistage, log-probit and Weibull)	**0.1298**		**0.849**	**0.634**

[b] The Gamma model may appear equivalent to the Weibull model, however differences exist in digits not displayed in the table. This also applies to the Multistage 3° model. This also applies to the Multistage 2° model. This also applies to the Quantal-Linear model.
[c] For the Weibull model, the power parameter estimate was 1. The models in this row reduced to the Quantal-Linear model.
[d] For the Multistage 3° model, the beta coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Multistage 2° model.
[e] BMD or BMDL computation failed for this model.

Summary of Model Averaging Fit Statistics

Model	Weight	-2log(L)	AIC	BIC
Multistage, 3°	0.245	162.97	170.97	184.16
Weibull	0.665	162.97	168.97	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):0.400888479370
BMDL(Percentile):0.634308392327
Acceleration: 0.043517
Bootstrap Resamples: 5000
Random Seed: 102210

Average-Model Goodness of Fit Test
Test Statistic: 3.274559
Bootstrap *p*-value: 0.129800

Parameter Estimates

Model	Parameter	Estimate	Standard Error
Multistage, 3°	gamma	0.03348013	0.02882729
	beta(1)	0.001340506	0.0003669969
	beta(2)	0	N/A
	beta(3)	0	N/A
Weibull	gamma	0.033480	0.028840
	alpha	1.0	N/A

	beta	0.001341	0.000367
Log-Probit	gamma	0.079419089201	0.034577
	alpha	-6.191081	0.272037
	beta	1.0	N/A

P-3-2 Large Intestine Adenomas in Female Rats

The doses and response data from the NTP (2011) study that were used for the modeling are presented in Table_Apx P-63.

Table_Apx P-63 Incidence of Large Intestine Adenomas in Female Rats

Dose (ppm)	Number of animals	Number of Animals with Tumors
0	50	0
125	50	1
250	50	2
500	50	5

Comparisons of model fits obtained from BMD modeling of the NTP (2011) study are provided in Table_Apx P-64. All of the models tested had acceptable fits to the data acceptable by *p*-value and visual inspection. The quantal-linear model had the lowest AIC value. A summary of the model average results are shown for comparison with the BMDS results in Table_Apx P-64. Detailed output of the model average run are shown below. The model average result was selected because the model has an adequate *p*-value and model-averaging has been shown to have reduced bias and better coverage in some cases (Wheeler and Bailer, 2007). In a sensitivity analysis alternative model selections include the single best benchmark dose model based on *p*-value, visual inspection and lowest AIC the quantal-linear model or the multistage model per EPA Benchmark Dose Technical Guidance for cancer datasets (U.S. EPA, 2012a). The BMDL of the quantal-linear model is 3.1 ppm and multistage model is 3.14 ppm, both are similar (within a factor of 2) of the the model average BMDL of 5.005 ppm.

Table_Apx P-64 Summary of BMD Modeling Results for Large Intestine Adenomas in Female Rats

Model	Goodness of fit		$BMD_{0.1PctAdd}$ (ppm)	$BMDL_{0.1PctAdd}$ (ppm)
	p-value	AIC		
Quantal-Linear	0.989	61.234	5.27	3.10
Multistage 3°	0.999	63.109	6.56	3.14
Multistage 2°	0.996	63.115	7.44	3.14
Weibull	0.991	63.126	11.8	3.13
Gamma	1.0	63.1	12.2	3.1
LogLogistic	0.989	63.128	12.5	2.97
LogProbit	0.979	63.150	22.5	3.05E-10

Probit	0.758	63.982	20.4	10.3
Logistic	0.722	64.145	21.9	11.4
Model average (multistage, log-probit and Weibull)	**0.824**		**13.5**	**5.005**

Summary of Model Averaging Fit Statistics

Model	Weight	-2log(L)	AIC	BIC
Multistage, 3°	0.191	59.11	67.11	80.30
Weibull	0.514	59.13	65.13	75.02
Log-Probit	0.295	60.24	66.24	76.13

Average-Model Benchmark Dose Estimate:
Nominally Specified Confidence Level:0.950
Weighting Criterion: AIC
BMD Calculation: Added Risk
BMR: 0.001000
BMD: 13.472617282689
BMDL(BCa): 2.445277845095
BMDL(Percentile): 5.005030327500
Acceleration: -0.149668
Bootstrap Resamples: 5000
Random Seed: 331201

Average-Model Goodness of Fit Test
Test Statistic: 0.139777
Bootstrap *p*-value: 0.824400

Parameter Estimates

Model	Parameter	Estimate	Standard Error
Multistage, 3°	gamma	0.0	N/A
	beta(1)	0.0001525544	0.00006655318
	beta(2)	0	N/A
	beta(3)	2.307482E-10	N/A
Weibull	gamma	0.0	N/A
	alpha	1.238098	0.739784
	beta	0.000047	0.000206
Log-Probit	gamma	0.006136953057	0.011787
	alpha	-7.449471	0.263198
	beta	1.0	N/A

P-3-3 Keratoacanthoma and Squamous Cell Carcinomas in Male Rats

The doses and response data from the NTP (2011) study that were used for the modeling are presented in Table_Apx P-65.

Table_Apx P-65 Incidence of Keratoacanthoma and Squamous Cell Carcinomas in Male Rats

Dose (ppm)	Number of animals	Number of Animals with Tumors
0	50	1
125	50	4
250	50	6
500	50	8

Comparisons of model fits obtained from BMD modeling of the NTP (2011) study are provided in Table_Apx P-66. All of the models tested had acceptable fits to the data acceptable fits to the data by *p*-value and visual inspection. The quantal-linear had the lowest AIC value. A summary of the model average results are shown for comparison with the BMDS results in Table_Apx P-66. Detailed output of the model average run are shown below. The model average result was selected because the model has an adequate *p*-value and model-averaging has been shown to have reduced bias and better coverage in some cases (Wheeler and Bailer, 2007). In a sensitivity analysis alternative model selections include the single best benchmark dose model based on *p*-value, visual inspection and lowest AIC the loglogistic model or the multistage model per EPA Benchmark Dose Technical Guidance for cancer datasets (U.S. EPA, 2012a). The BMDL of the loglogistic model is 1.58 ppm and multistage model is 1.78 ppm, both are similar (within a factor of 2) of the the model average BMDL of 2.26 ppm.

Table_Apx P-66 Summary of BMD Modeling Results for Keratoacanthoma and Squamous Cell Carcinomas in Male Rats

Model	Goodness of fit		$BMD_{0.1PctAdd}$ (ppm)	$BMDL_{0.1PctAdd}$ (ppm)
	p-value	AIC		
LogLogistic	0.843	122.68	2.72	1.58
Gamma[b]	0.802	122.78	2.96	1.78
Multistage 3°[c] Multistage 2°[b]	0.802	122.78	2.96	1.78
Weibull[d] Quantal-Linear[b]	0.802	122.78	2.96	1.78
Probit	0.503	123.82	6.80	4.76
Logistic	0.471	123.99	7.54	5.31
LogProbit	0.913	124.35	1.25	error[e]

Model average (multistage, log-probit and Weibull)	**0.7077**		**3.73**	**2.26**

[b] The Gamma model may appear equivalent to the Weibull model, however differences exist in digits not displayed in the table. This also applies to the Multistage 3° model. This also applies to the Multistage 2° model. This also applies to the Quantal-Linear model.
[c] For the Multistage 3° model, the beta coefficient estimates were 0 (boundary of parameters space). The models in this row reduced to the Multistage 2° model.
[d] For the Weibull model, the power parameter estimate was 1. The models in this row reduced to the Quantal-Linear model.
[e] BMD or BMDL computation failed for this model.

Summary of Model Averaging Fit Statistics

Model	Weight	-2log(L)	AIC	BIC
Multistage, 3°	0.213	118.78	126.78	139.97
Weibull	0.580	118.78	124.78	134.67
Log-Probit	0.207	120.84	126.84	136.74

Average-Model Benchmark Dose Estimate:
Nominally Specified Confidence Level:0.950
Weighting Criterion: AIC
BMD Calculation: Added Risk
BMR: 0.001000
BMD: 3.732432783338
BMDL(BCa): 1.505273123061
BMDL(Percentile): 2.260265766150
Acceleration: 0.030873
Bootstrap Resamples: 5000
Random Seed: 257515

Average-Model Goodness of Fit Test
Test Statistic: 0.707725
Bootstrap *p*-value: 0.586800

Parameter Estimates

Model	Parameter	Estimate	Standard Error
Multistage, 3°	gamma	0.02541313	0.02238034
	beta(1)	0.0003467654	0.0001309450
	beta(2)	0	N/A
	beta(3)	0	N/A
Weibull	gamma	0.025414	0.022401
	alpha	1.0	N/A
	beta	0.000347	0.000131
Log-Probit	gamma	0.050387778679	0.025518
	alpha	-7.271630	0.311627
	beta	1.0	N/A