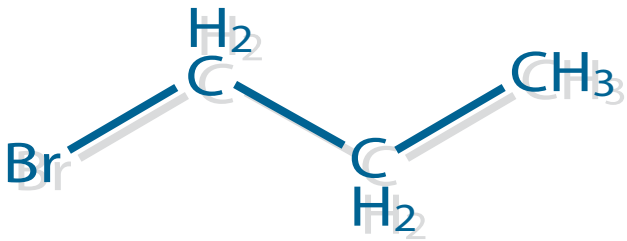
National Toxicology Program
U.S. Department of Health and Human Services

Report on Carcinogens
Monograph on 1-Bromopropane

September 2013



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

Report on Carcinogens
Monograph on 1-Bromopropane

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Office of the Report on Carcinogens
Division of the National Toxicology Program
National Institute of Environmental Health Sciences
U.S. Department of Health and Human Services

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FOREWORD

The National Toxicology Program (NTP) is an interagency program within the Public Health Service (PHS) of the Department of Health and Human Services (HHS) and is headquartered at the National Institute of Environmental Health Sciences of the National Institutes of Health (NIEHS/NIH). Three agencies contribute resources to the program: NIEHS/NIH, the National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention (NIOSH/CDC), and the National Center for Toxicological Research of the Food and Drug Administration (NCTR/FDA). Established in 1978, the NTP is charged with coordinating toxicological testing activities, strengthening the science base in toxicology, developing and validating improved testing methods, and providing information about potentially toxic substances to health regulatory and research agencies, scientific and medical communities, and the public.

The Report on Carcinogens (RoC) is prepared in response to Section 301 of the Public Health Service Act, as amended. The RoC contains a list of identified substances (i) that either are *known to be human carcinogens* or are *reasonably anticipated to be human carcinogens* and (ii) to which a significant number of persons residing in the United States are exposed. The Secretary, Department of HHS, has delegated responsibility for preparation of the RoC to the NTP, which prepares the report with assistance from other Federal health and regulatory agencies and nongovernmental institutions. The most recent RoC, the 12th Edition (2011), is available at http://ntp.niehs.nih.gov/go/roc12.

Nominations for (1) listing a new substance, (2) reclassifying the listing status for a substance already listed, or (3) removing a substance already listed in the RoC are evaluated in a scientific review process (http://ntp.niehs.nih.gov/go/rocprocess) with multiple opportunities for scientific and public input using established listing criteria (http://ntp.niehs.nih.gov/go/15209). A list of candidate substances under consideration for listing in (or delisting from) the RoC can be obtained by accessing http://ntp.niehs.nih.gov/go/37893.

INTRODUCTION

1-Bromopropane (*n*-propyl bromide, CASRN 106-94-5) is a brominated hydrocarbon that is currently used as a solvent in a variety of industrial and commercial applications. Exposure to workers has been increasing in the past few years due to several new applications in which 1-bromopropane has been substituted for substances identified as suspect carcinogens or ozone-depleting chemicals. The available occupational exposure data indicate that workers can be exposed to high levels of 1-bromopropane.

1-Bromopropane was selected as a candidate substance for the Report on Carcinogens (RoC) due to the potential for substantial human exposure to 1-bromopropane in the United States, and an adequate database to evaluate its potential carcinogenicity. 1-Bromopropane has been tested for carcinogenicity in rodents in a 2-year inhalation study (NTP 2011a). In addition, 1-bromopropane causes toxicity in people and experimental animals. Structurally related haloalkanes are carcinogenic in experimental animals.

Monograph contents

The *RoC Monograph on 1-Bromopropane* consists of the following components: (Part 1) the cancer evaluation component that reviews the relevant scientific information, assesses its quality, applies the RoC listing criteria to the scientific information, and gives the RoC listing status for 1-bromopropane, and (Part 2) the RoC monograph's substance profile containing the NTP's listing status decision, a summary of the scientific evidence considered key to reaching that decision, and data on properties, use, production, exposure, and Federal regulations and guidelines to reduce exposure to 1-bromopropane.

The cancer evaluation component for 1-bromopropane provides information on the following topics: human exposure and properties (Section 1), disposition and toxicokinetics (Section 2), cancer studies in experimental animals (Section 4), and studies of mechanisms and other related effects (Section 5), including relevant toxicological effects, genetic toxicology, and mechanisms of carcinogenicity. When human cancer studies are reviewed, they are discussed in Section 3; however, no cancer studies in humans with exposure specifically to 1-bromopropane were identified. The information in Sections 2 through 5 is synthesized in Section 6.

The information reviewed in Sections 2 through 5 (and synthesized in Section 6) came from publicly available, peer-reviewed sources. Information in Section 1, including chemical and physical properties, analytical methods, production, use, and occurrence came from publicly available, published or unpublished sources.

The cancer evaluation for 1-bromopropane focuses on the evaluation of the cancer studies in experimental animals and mechanistic data, and also whether there is any evidence that the potential modes of action by which 1-bromopropane might cause cancer are not relevant to humans.

Process for preparation of the cancer evaluation component

The process for preparing the cancer evaluation component of the monograph included approaches for obtaining public and scientific input and using systematic methods (e.g., standardized methods for identifying the literature, inclusion/exclusion criteria, extraction of data and evaluation of study quality using specific guidelines [see Appendix A], and assessment of the level of evidence for carcinogenicity using established criteria).

The Office of the Report on Carcinogens (ORoC) followed the approaches outlined in the concept document, which discusses the scientific issues and questions relevant to the evaluation of 1-bromopropane carcinogenicity, the scope and focus of the monograph, and the approaches to obtain scientific and public input to address the key scientific questions and issues, for preparing the cancer evaluation component of the draft monograph. The ORoC presented the draft concept document on 1-bromopropane to the NTP Board of Scientific Counselors (BSC) at the June 21–22, 2012 meeting that provided opportunity for written and oral public comments; the concept document is available on the RoC website (http://ntp.niehs.nih.gov/go/37896). The draft monograph was peer reviewed in a public forum in March 2013 (see 'Peer Review of the *Draft RoC Monograph on 1-Bromopropane*' below), revised accordingly, and presented to the BSC at a June 2013 meeting.

Key scientific questions and issues relevant for the cancer evaluation

The cancer evaluation component of the monograph focuses on studies of 1-bromopropane in experimental animals and mechanistic data. It also identifies and discusses human and animal studies of non-cancer endpoints, such as neurological or reproductive/developmental toxicity, immunosuppression, and studies of structurally related compounds and metabolites, to determine whether this information can inform mechanisms of carcinogenicity of 1-bromopropane.

The key scientific questions identified in the concept, which concern the results in experimental animals and mechanisms of carcinogenicity are:

- What is the level of evidence (sufficient or not sufficient) for the carcinogenicity of 1-bromopropane from studies in experimental animals? What are the tissue sites?
- What are potential mechanisms by which 1-bromopropane may cause cancer?
  - Do the mechanistic data in experimental animals support the cancer findings in humans?
  - Are there mechanistic data to suggest that the cancer findings in experimental animals are not relevant to humans?
  - Does immunomodulation play a role in 1-bromopropane carcinogenicity?

Approach for obtaining scientific and public input

Additional scientific input was obtained for exposure and disposition and toxicokinetics of 1-bromopropane. (Technical advisors are identified on the "CONTRIBUTORS" page.)

Public comments on scientific issues were requested on 1-bromopropane by Federal Register notices at several times prior to and during the development of the final RoC monograph, including a request for information on the nomination, and for comment on the draft concept document (which outlined the rationale and approach for conducting the scientific review) and comment on the draft RoC monograph. In addition, the NTP posted its preliminary literature search strategy and list of references for public input on the RoC webpage for 1-bromopropane (http://ntp.niehs.nih.gov/go/37896) several months prior to the release of the draft monograph. Four public comments were received in response to the Federal Register notices and are available at http://ntp.niehs.nih.gov/go/37663.

Methods for writing the cancer evaluation component of the monograph

The procedures by which relevant literature were identified, data were systematically extracted and summarized, and the monograph was written, together with the processes for scientific review, quality assurance, and assessment and synthesis of data, are described below.

The preparation of the *RoC Monograph on 1-Bromopropane* began with development of a literature search strategy for 1-bromopropane to obtain information relevant to the topics for monograph sections, as discussed above, using search terms developed in collaboration with a reference librarian (see Appendix A for a detailed description of the literature search strategy). The citations (N = 1,689) identified from these searches were uploaded to a web-based systematic review system for evaluation by two reviewers using inclusion/exclusion criteria, and 158 references were selected for final inclusion in the monograph using these criteria.

Information for the exposure, relevant cancer, and mechanistic sections was systematically extracted in tabular format and/or summarized in the text, following specific procedures developed by ORoC, from studies selected for inclusion in the monograph. All sections of the monograph underwent scientific review and quality assurance (QA) (i.e., assuring that all the relevant data and factual information extracted from the publications have been reported accurately) by a separate reviewer. Any discrepancies between the writer and the reviewer were resolved by mutual discussion in reference to the original data source.

Strengths, weaknesses, and data quality of the cancer studies for 1-bromopropane in experimental animals were assessed based on a series of questions related to characterization of the substance tested, the features of animal husbandry, the design of the study, the methods for clinical observations and necropsy, and the manner in which the data were reported (see Appendix C). Relevant genotoxicity and mechanistic studies were also assessed for their strengths and weaknesses.

Human exposure information was assessed to determine whether the evidence indicates that a significant number of persons residing in the United States are exposed to 1-bromopropane (see Foreword for information regarding the congressional mandate for the RoC). However, for many substances, this information is not available, and typically, U.S. exposure can be inferred from data on use, production volume, occupational monitoring, environmental (occurrence), estimated daily intake, and biomonitoring. Because cancer has a long latency period, past exposure is also considered in the assessment.

RoC listing criteria (see text box) were applied to the available database of carcinogenicity data to assess the level of evidence (sufficient or not sufficient) for the carcinogenicity of 1-bromopropane from studies in experimental animals. This initial conclusion does not integrate the experimental animal and mechanism data. The evaluation of the mechanistic data included a discussion and assessment of the strength of evidence for potential modes of action of 1-bromopropane–induced neoplasia, including metabolic activation, cytotoxicity, and genetic effects and immunosuppression. In addition, human and animal studies of non-cancerous endpoints, such as neurological or reproductive/developmental toxicity, as well as studies of structurally related compounds and metabolites, may be informative. The RoC listing criteria were then applied to the available body of knowledge for 1-bromopropane to reach a listing recommendation.

RoC Listing Criteria

Known To Be Human Carcinogen:

There is sufficient evidence of carcinogenicity from studies in humans*, which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer.

Reasonably Anticipated To Be Human Carcinogen:

There is limited evidence of carcinogenicity from studies in humans*, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded, OR

there is sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site, or type of tumor, or age at onset, OR

there is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals, but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

*This evidence can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues or cells from humans exposed to the substance in question that can be useful for evaluating whether a relevant cancer mechanism is operating in people.

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Peer Review of the *Draft RoC Monograph on 1-Bromopropane*

Peer review of the *Draft RoC Monograph on 1-Bromopropane* was conducted by an *ad hoc* expert panel at a public meeting held March 21–22, 2013, at the National Institute of Environmental Health Sciences, Keystone Building, Research Triangle Park, NC (see http://ntp.niehs.nih.gov/go/38854) for materials, minutes, and panel recommendations from the peer review meeting). The selection of panel members and conduct of the peer review were performed in accordance with the Federal Advisory Committee Act and Federal policies and regulations. The panel members served as independent scientists, not as representatives of any institution, company, or governmental agency.

In this capacity, panel members had the following major responsibilities in reviewing the draft RoC monograph: (1) to comment on the draft cancer evaluation components for 1-bromopropane, specifically, whether they are technically correct and clearly stated, whether the NTP has objectively presented and assessed the scientific evidence, and whether the scientific evidence is adequate for applying the RoC listing criteria, and (2) to comment on the draft substance profile for 1-bromopropane, specifically, whether the scientific justification presented in the substance profile supports the NTP's preliminary policy decision on the RoC listing status of 1-bromopropane. The panel was also asked to vote on the following questions: (1) whether the scientific evidence supports the NTP's conclusion on the level of evidence for carcinogenicity from experimental animal studies on 1-bromopropane and (2) whether the scientific evidence supports the NTP's preliminary listing decision for 1-bromopropane in the RoC. The panel agreed with the NTP conclusions that 1-bromopropane should be listed in the RoC based on sufficient evidence of carcinogenicity from studies in experimental animals, which found skin tumors in male rats, large intestine tumors in female and male rats, and lung tumors in female mice.

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Part 1

Cancer Evaluation

Properties and Human Exposure

Disposition (ADME) and Toxicokinetics

Human Cancer Studies

Studies in Experimental Animals

Mechanistic Data and Other Relevant Effects

Overall Cancer Evaluation

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1 Properties and Human Exposure

1-Bromopropane is a brominated hydrocarbon currently used as a solvent in several industrial sectors including adhesives, dry cleaning, vapor degreasing, and aerosol solvents. In recent years, occupational exposures to 1-bromopropane have increased due to new industrial and commercial applications for 1-bromopropane involving its use as a substitute for ozone-depleting chemicals or suspect carcinogens.

This section describes the chemical and physical properties of 1-bromopropane (Section 1.1); its uses and production (Section 1.2); biological indices of exposure (Section 1.3); characterization of exposure in the workplace (Section 1.4); potential for environmental exposure, including sources of release of 1-bromopropane to the environment, and its fate, occurrence, and exposure (Section 1.5); potential for exposure from other sources such as consumer products (Section 1.6); and exposure levels for people (Section 1.7). Section 1.8 summarizes the information in Sections 1.1 to 1.7. Data tables with occupational exposure to 1-bromopropane are provided in Appendix B, and include individual (e.g., personal breathing zone [PBZ], urinary biomarker, serum bromide, and exhaled breath) and area concentration measurements in various industrial sectors. U.S. regulations and guidelines that potentially limit exposure to 1-bromopropane are also reported in Appendix B.

1.1 Chemical identification and properties

1-Bromopropane (Figure 1-1) is a bromoalkane or alkyl bromide. Table 1-1 contains some chemical identification information for 1-bromopropane.

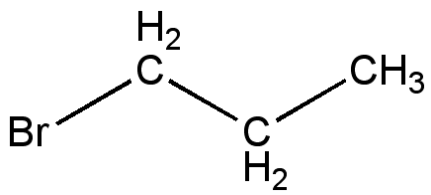

Figure 1-1. Chemical structure of 1-bromopropane

Table 1-1. Chemical identification of 1-bromopropane

Characteristic	Information
Chemical Abstracts index name	1-Bromopropane[a]
CAS Registry number	106-94-5[a]
Molecular formula	C_3H_7Br[b]
Synonyms	1-BP[b]; Propyl bromide[b]; *n*-Propyl bromide[b]; Propane, 1-bromo-[b]; *normal* propyl bromide[c]; nPB[d]

Sources: [a]NTP 2003a, [b]HSDB 2006, [c]UNEP 2001, [d]EPA 2007.

1-Bromopropane exists as a colorless to pale yellow liquid with a strong, characteristic odor (NTP 2011a). It is slightly soluble in water and in most organic solvents including acetone, ethanol, ether, benzene, chloroform, and carbon tetrachloride. It is less flammable than many other halogenated alkanes at room temperature. 1-Bromopropane's thermal decomposition produces hydrogen bromide. 1-Bromopropane can react with oxidizing agents to form hazardous flammable compounds and with water to produce acids. Some physical and chemical properties for 1-bromopropane are listed in Table 1-2.

Table 1-2. Physical and chemical properties of 1-bromopropane

Property	Information
Molecular weight	123.0[b]
Melting point	-110°C[b]
Boiling point	64.7°C[b]
Vapor pressure (mm Hg)	110.8 at 20°C[b]
Vapor density	4.25[a]
Specific gravity	1.353 at 20°C[b]
Solubility in water (20°C)	2,450 mg/L[a]
Octanol/water partition coefficient (log K_{ow})	2.10[a]
Henry's law constant	0.0073 atm-m^3/mol at 25°C[a]
Conversion factors (1-bromopropane in air) parts per million (ppm) to µg/m^3 µg/m^3 to parts per million (ppm)	 µg/m^3 = 5,030.7 × (ppm)[c] ppm = 1.988 × 10^{-4} × (µg/m^3)[c]

Sources: [a]HSDB 2006, [b]NTP 2003a, [c]SMARTe.org 2012.

1.2 Uses and production

1-Bromopropane is used primarily as a solvent cleaner in vapor and immersion degreasing operations to clean optics, electronics, and metals and as a solvent vehicle in industries using aerosol-applied adhesives such as foam cushion manufacturing; however, these uses might be impacted by an EPA proposed rule listing certain uses as unacceptable (see Appendix B, Table B-10). In recent years, 1-bromopropane usage has increased due to new industrial applications involving its use as a substitute for ozone-depleting chemicals or suspect carcinogens. For example, increased use of 1-bromopropane in the dry-cleaning industry has occurred in response to states considering and pursuing actions to ban the use of tetrachloroethylene (perchloroethylene or PERC) (Blando *et al.* 2010). 1-Bromopropane also has been reported to have other advantages as a replacement for other halogenated solvents, including lower energy costs due to lower boiling point and reduced drying time, low Global Warming Potential (GWP), and reduced water consumption (Craft 2013). 1-Bromopropane also has potential application as a spot remover in the textile industry, but an evaluation of 1-bromopropane as a substitute for trichloroethylene (TCE) concluded that chronic toxicity data were lacking and use of 1-bromopropane was not recommended until more data were available (Mirza *et al.* 2000). In the past, 1-bromopropane was used primarily as a solvent for fats, waxes, or resins and as an

intermediate in the synthesis of pharmaceuticals, insecticides, quaternary ammonium compounds, flavors, or fragrances in generally well-controlled, closed processes (Hanley *et al.* 2006a, NTP 2003a).

1-Bromopropane is produced by reacting *n*-propyl alcohol with hydrogen bromide and then removing the water that forms in the process. 1-Bromopropane can also be produced by dehydrating propanol with bromine or hydrogen bromide in the presence of sulfur catalyst (NTP 2003a). In 2012, 1-bromopropane was manufactured by at least 21 companies worldwide, including at least 1 company in the United States (SRI 2012). Production data for 1-bromopropane are listed in Table 1-3. Production data are based on Internet searches of sources dated as noted; data are subject to change.

Table 1-3. Production data for 1-bromopropane

Category	Years covered	Quantity in pounds[a]
U.S. EPA Chemical Data Reporting Rule[b]	2006 2002, 1998 1994 1990, 1986	> 1 million to 10 million 1 million to < 10 million > 500K to 1 million 10K to 500K
U.S. imports (recent)[c]	2011	10.3 million
U.S. imports (historical)[c]	2007	10.9 million
U.S. exports (recent)[c]	2011	15.1 million
U.S. exports (historical)[c]	2007	8.8 million

Sources: EPA 2012, SRI 2012, USITC 2012.
[a]From 10/2012 Internet searches; data subject to change.
[b]Formerly called Inventory Update Rule.
[c]Reported as brominated derivatives of acyclic hydrocarbons, which includes other chemicals in addition to 1-bromopropane.

1.3 Biological indices of exposure

Potential biological indices of exposure to 1-bromopropane include measurements of bromide ion ($Br^{(-)}$), *N*-acetyl-*S*-(*n*-propyl)-L-cysteine (AcPrCys) (see Section 2.2 for a description of the metabolism of 1-bromopropane), and 1-bromopropane in urine, and serum bromide levels (Eisenberg and Ramsey 2010, Hanley *et al.* 2006a, Hanley *et al.* 2009, Kawai *et al.* 2001, Valentine *et al.* 2007). Urinary 3-bromopropionic acid (3-BPA) was not found to be an effective urinary biomarker for occupational exposure to 1-bromopropane from spray adhesives, because it was not detected in heavily exposed workers at foam cushion manufacturers. However, AcPrCys and bromide ion were effective biomarkers (Mathias *et al.* 2012).

1.4 Characterization of exposure in the workplace

Occupational exposure to 1-bromopropane may occur through inhalation and dermal contact at workplaces where 1-bromopropane is produced or used (HSDB 2006), and extensive 1-bromopropane occupational exposure-monitoring data are available. Many of the data either

were submitted to the EPA under the Significant New Alternatives Policy (SNAP) program or collected during studies conducted under the NIOSH Health Hazard Evaluation (HHE) or Industrywide Studies Branch (IWSB) programs. (See Appendix B, Tables B-1 to B-8 for personal samples (e.g., personal breathing zone [PBZ], urinary biomarker, serum bromide, and exhaled breath) as well as area samples for 1-bromopropane concentrations in various industrial sectors.)

Based on the available occupational exposure (as described in Tables B-1 to B-8), 8- to 12-hr time-weighted average (TWA) 1-bromopropane air concentrations across all sectors ranged from not detected to 380 ppm. Jobs requiring workers to spray 1-bromopropane adhesives have the highest exposures and jobs requiring workers to clean and assemble small parts used in radio frequency and microwave communication instruments (vapor degreasing operations) have the lowest exposures. In extreme cases, 1-bromopropane air concentrations during vapor degreasing may be as much as four orders of magnitude lower than during adhesives use. This could be due in part to exposure to 1-bromopropane during only part of the workday. For example, Hanley *et al.* (2010) reported that parts were cleaned on an as-needed basis in the facilities that they sampled, and use of degreasers was limited to 90 minutes or less for an entire work shift. Figure 1-2 graphically depicts TWA 1-bromopropane air concentrations across industry sectors. The figure does not include all data for occupation exposure; thus, the highest air concentration shown is less than the maximum reported of 380 ppm.

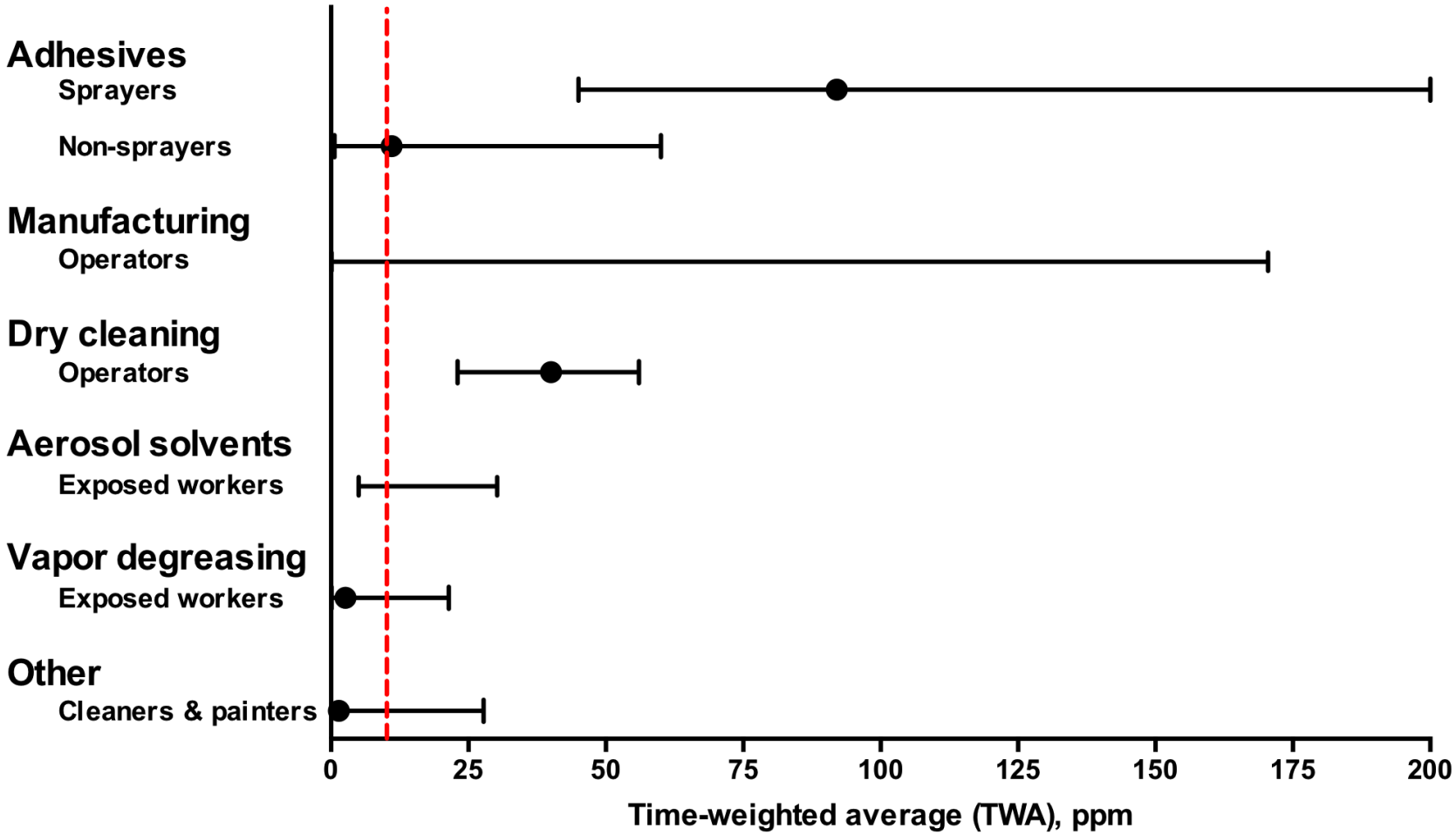

Figure 1-2. TWA 1-bromopropane air concentrations across industry sectors

From Eisenberg and Ramsey 2010, Graul 2012, Hanley *et al.* 2006b, Hanley *et al.* 2010, Ichihara *et al.* 2004a, Kawai *et al.* 2001. Time-weighted-average 1-bromopropane exposure levels as geometric means (Adhesives, Other, and Vap. Deg.); arithmetic mean (Dry Cln.); or not reported (Manuf. and Aer. Solv.). Note: the dashed, vertical line represents the ACGIH threshold limit value – time-weighted average (TLV-TWA) of 10 ppm.

The Occupational Safety and Health Administration (OSHA) Chemical Exposure Health Dataset contains OSHA compliance monitoring program industrial hygiene samples. 1-Bromopropane concentration sampling data are available for 1998 to 2011. Of the 164 total sample points for 1-bromopropane, 126 were personal breathing zone (PBZ) samples with detectable values from 18 facilities. PBZ samples with detectable values ranged from 0.0477 to 423 ppm. Sixty-two (62) samples from 9 of the facilities were above the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV) of 10 ppm. Most of those facilities (7 of 9) were in the vapor degreasing or adhesives use sector (OSHA 2011).

1.4.1 *Adhesives use*

1-Bromopropane–based adhesives are used most widely as spray adhesives for foam cushion manufacturing (e.g., the furniture industry) and to a lesser extent in laminate adhesives (FR 2007); however, no exposure data were identified for laminate adhesives. In furniture foam cushion manufacturing plants, cushions are generally assembled by gluing together pieces of cut flexible foam (Harney *et al.* 2002, Harney *et al.* 2003). Once the foam pieces are glued together, workers hand press the pieces to achieve a proper bond. The adhesive is spray-applied using a compressed air spray gun. Data were also identified for one adhesives and coatings manufacturer (Hanley *et al.* 2007, Hanley *et al.* 2010).

Personal samples (available data for personal breathing zone and exhaled breath concentrations for 1-bromopropane as well as urinary biomarker and serum bromide concentrations for the adhesives use sector) are provided in Appendix B, Table B-1. Eight- to twelve-hour TWA 1-bromopropane air concentrations for adhesives use ranged from 0.1 to 380 ppm. These data indicate that workers engaged in adhesive spraying are consistently exposed to higher concentrations than non-sprayers, in some cases by as much as three orders of magnitude. The higher exposures are reflected in higher levels of urinary biomarkers for both urinary $Br^{(-)}$ (Hanley *et al.* 2006a) and urinary AcPrCys concentrations (Hanley *et al.* 2009).

Pre- and post-shift 1-bromopropane breath concentrations have been measured for adhesives use. Available breath monitoring data indicate that post-shift 1-bromopropane concentrations were consistently higher than pre-shift concentrations, in many cases, more than 10 times higher. For example, Hanley *et al.* (2005) reported a pre-shift mean breath concentration of 0.96 ppm and a post-shift mean breath concentration of 15.4 ppm for a polyurethane seat cushion manufacturing plant. Further, breath concentrations for sprayers were consistently higher than concentrations for workers performing other jobs.

Serum bromide concentration data indicated that concentrations are highest in the adhesives sector, for which values as high as 1,700 mg/L have been reported (Majersik *et al.* 2007) (see Appendix B, Table B-1). Based on NIOSH HHE data for one facility, the average difference between end-of-week and start-of-week serum bromide concentrations for exposed workers was 23 mg/L compared with 3 mg/L for unexposed workers (Harney *et al.* 2003).

1-Bromopropane air concentrations differed considerably before and after engineering controls (i.e., ventilation improvements, enclosure of spray tables, etc.) were implemented at two facilities studied in the NIOSH HHE program. Figure 1-3 depicts 1-bromopropane air concentrations for first and second NIOSH facility surveys for the three known facilities in the adhesives use sector at which NIOSH conducted HHE assessments. In two cases (Custom Products and STN Cushion Company), the facilities adopted NIOSH recommendations concerning addition of engineering controls and TWAs decreased by 80% or greater. The results demonstrated reductions of mean TWA 1-bromopropane air concentration from 168.9 ppm (N = 69) to 19.0 ppm (N = 30) for all workers at Custom Products Inc. and from 65.9 ppm (N = 12) to 16.6 ppm (N = 11) for sprayers at STN Cushion Company (Reh *et al.* 2002).

NIOSH also recommended similar controls for the third facility (Marx Industries), but the agency reported that they were unaware of any changes in controls or employee use of personal protective equipment during the time interval between the first and second survey for this facility, and only slight change in exposure for sprayers occurred between the first and second surveys. The mean TWA 1-bromopropane air concentration for all sprayers for the first survey (N = 12) was 107.6 ppm, and the mean for the second survey (N = 8) was 101.4 ppm (Harney *et al.* 2003).

According to a summary of workplace exposure data for 1-bromopropane submitted to EPA for the SNAP program (Graul 2012), initially, fewer than half the personal breathing zone (PBZ) sample concentrations were below 50 ppm (8-hr TWA); however, after ventilation improvements, 97% of the PBZ samples were less than 50 ppm and 78% were ≤ 25 ppm. Further, the initial mean concentration was 141.7 ppm; after ventilation improvements, the mean concentration was 18.3 ppm (Graul 2012).

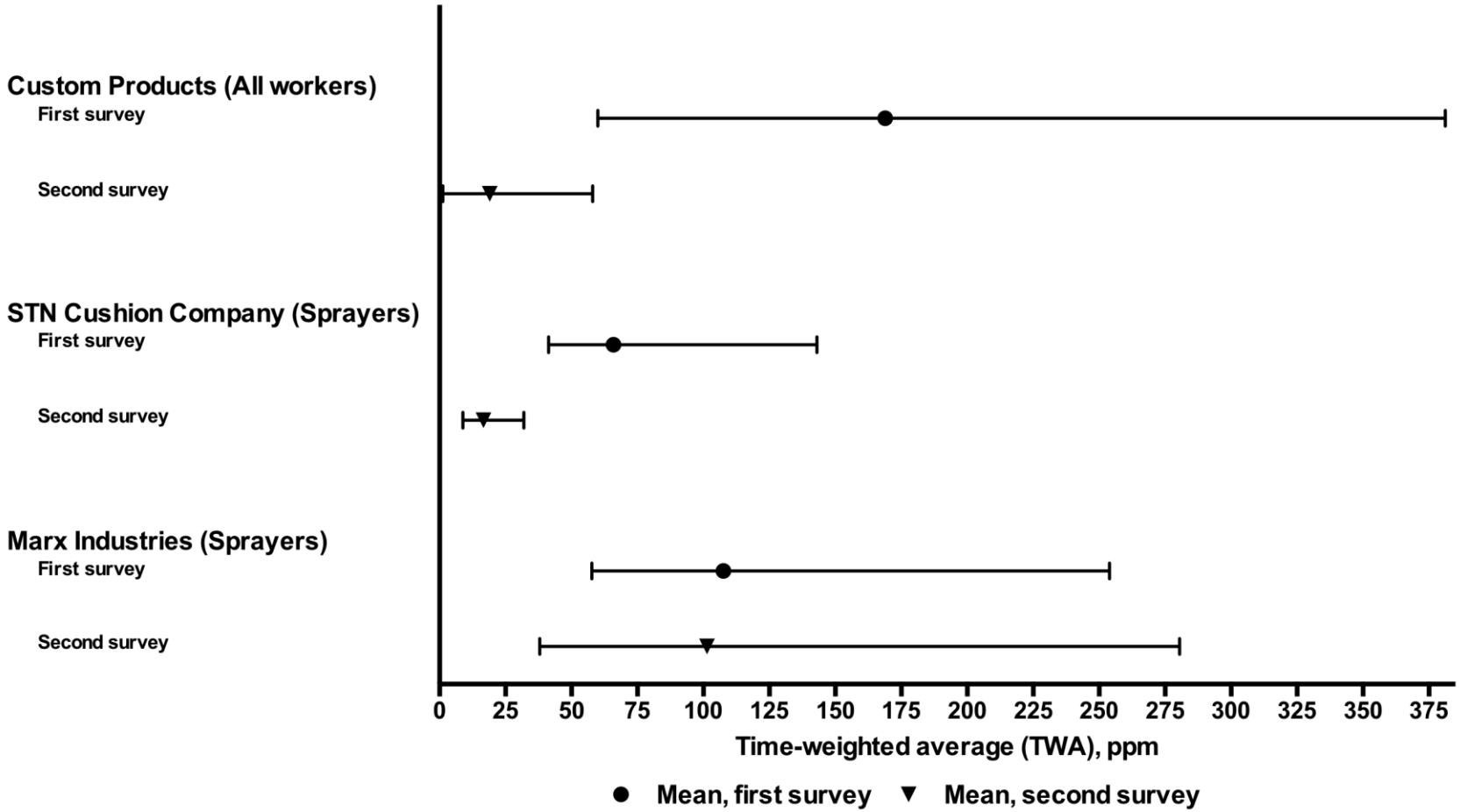

Figure 1-3. 1-Bromopropane air concentrations for first and second NIOSH facility surveys in the adhesives use sector
TWA concentrations reported for Custom Products, Inc. and STN Cushion Company are arithmetic means, and those reported for Marx Industries, Inc. are geometric means.

Concentration measurements for the adhesives use sector are shown in Appendix B, Table B-2. Area samples for 1-bromopropane for adhesives use ranged from 0.01 to 176 ppm. The range of area samples reflects variation between facilities; however, differences within a facility appear to vary only minimally for the same task.

1.4.2 *1-Bromopropane manufacturing*

Personal samples (from the available data for personal breathing zone concentrations of 1-bromopropane) for the manufacturing sector in China are provided in Appendix B, Table B-3. No 1-bromopropane air concentration data were identified for 1-bromopropane manufacturing plants in the United States, but Patent Number 5,773,672 (June 30, 1998), which is assigned to a U.S. manufacturer of 1-bromopropane, contains descriptions of numerous control processes to contain 1-bromopropane in contrast with the more open processes described below. Eight- to twelve-hour TWA 1-bromopropane air concentrations for these facilities ranged from not detected to 170 ppm. Worker exposure was reported to occur from (1) adding chemicals into reaction pots, (2) sitting close to reaction pots when observing and recording the temperature, (3) removing crude product, (4) adding hydrogen carbonate and stirring, and (5) pouring the product into 1000 L drums (Li *et al.* 2010b). In one plant, the highest concentrations were measured during the transfer of processed product into containers (Ichihara *et al.* 2004a).

Area sample concentrations of 1-bromopropane for 1-bromopropane manufacturing ranged from not detected to 90.2 ppm (see Appendix B, Table B-4).

One study also examined biomarkers of 1-bromopropane exposure. Valentine *et al.* (2007) measured globin *S*-propylcysteine (PrCys) adducts and urinary *N*-acetyl-*S*-propylcysteine (*N*-acetyl-*S*-(*n*-propyl)-L-cysteine or AcPrCys) for workers in a Chinese 1-bromopropane manufacturing facility and reported a significant ($P < 0.01$) increase in PrCys adducts on 1-bromopropane manufacturing workers' globin (1.52 pmol/mg globin) compared with control factory workers (0.11 pmol/mg globin) (N = 32 controls, N = 26 exposed). Further, Valentine *et al.* (2007) determined that urinary AcPrCys levels increased as 1-bromopropane ambient exposure levels increased (N = 47 exposed); the exposure levels ranged from 0 to 170.54 ppm.

1.4.3 *Dry cleaning*

The increased use of 1-bromopropane in the dry-cleaning industry has occurred in response to states considering and pursuing actions to ban the use of PERC (Blando *et al.* 2010). 1-Bromopropane has been reported to be the only PERC alternative that can be used in the original PERC machines with alterations; other cleaners would require the purchase of new machines (Eisenberg and Ramsey 2010).

Personal full- and partial-shift samples (available data for personal breathing zone concentrations of 1-bromopropane) for the dry-cleaning sector are provided in Appendix B, Table B-5. Eight- to twelve-hour TWA 1-bromopropane air concentration data identified in these dry-cleaning facilities ranged from < 0.004 to 56 ppm. Eisenberg and Ramsey (2010) reported a mean serum bromide concentration of 144 mg/L for a dry-cleaning facility owner who was converting his machine from PERC to 1-bromopropane (value reported as 144 mcg/mL). Worker exposure could occur from introduction of

solvent to the cleaning machine, machine maintenance, unloading and handling of recently cleaned clothes, interrupting the machine wash cycle, and "cooking" the solvent (i.e., boiling the solvent to remove impurities) (Blando *et al.* 2010, Eisenberg and Ramsey 2010). Further, exposure could occur due to leaks resulting from normal machine wear with time, poor maintenance, and incompatibility of 1-bromopropane with system gasket materials and poor ventilation (Blando *et al.* 2010).

Reduced exposure due to improved ventilation procedures also has been illustrated for dry-cleaning applications. For example, Blando *et al.* (2010) (see Appendix B, Table B-6) noted that building size, exhaust fan capacity and operation, and natural ventilation (i.e., opening doors and windows) were the determining factors for operator air concentrations in two of the three shops studied differing by as much as 4 orders of magnitude. Other studies have shown that dry cleaning operators often use natural ventilation (i.e., opening doors and windows) to control 1-bromopropane exposures. However, weather conditions may prevent use of natural ventilation (Eisenberg and Ramsey 2010), which typically is not as effective as mechanical ventilation.

Area sample concentrations for 1-bromopropane for dry cleaning ranged from < 0.004 to 170 ppm and differences were mainly explained by characteristics of the individual facilities (see Appendix B, Table B-6). Area samples at Facility 1 in Eisenberg and Ramsey (2010) varied between morning and afternoon measurements. Measurements taken in the morning were higher because the facility closed the doors and did not operate the ventilation system at this time; only the front windows were open. However, in the afternoon, the facility operated the ventilation system and opened the back door. Variation in area samples at Facility 4 in Eisenberg and Ramsey (2010) might have been due to machine leaks as the owner converted the machine himself and reported that he had difficulties finding the correct conversion materials. Further, opening the front door and operating the exhaust fan produced a marked decrease in solvent odor at this facility (Eisenberg and Ramsey 2010). Findings reported by Blando *et al.* (2010) for dry-cleaning Shops A, B, and C were discussed above.

1.4.4 *Aerosol solvents*

1-Bromopropane has been reported to be used as a solvent in aerosol lubricants, coatings, or cleaning fluids for electrical or electronic equipment or aircraft maintenance, or in spinnerette lubricants and cleaning sprays used in synthetic fiber production (FR 2007). Spray-can aerosol solvents are normally used intermittently and for short periods of time (i.e., 1 to 2 minutes). In some cases, aerosol products are used in confined spaces without ventilation or fans where short-term worker exposure can be high. Although emissions from aerosol solvents typically are not controlled via engineering controls, aerosol users can reduce exposure levels through use of fume hoods and improving ventilation (FR 2003). Eight- to twelve-hour TWA 1-bromopropane air concentration data identified for aerosol solvents ranged from 5 to 30.2 ppm (Graul 2012). Fifteen-minute STEL sample data ranged from 45.1 to 254 ppm.

1.4.5 *Vapor degreasing*

In general, vapor degreasers use a refrigerated cooling coil around the top of the interior of the vapor chamber to condense heated 1-bromopropane vapor into liquid droplets on

the cooler surface of parts to remove dirt, grease, and surface contaminants (Hanley and Dunn 2006). Excess 1-bromopropane drips back into the solvent sump and is recycled as the parts ascend from the vapor to condensing zones. Another function of the cooling coil is to control solvent vapor emissions by "capping" the heated vapor zone with a refrigerated air space.

For the vapor degreasing sector, personal samples of 1-bromopropane are provided in Appendix B, Table B-7. Eight- to twelve-hour GM TWA 1-bromopropane air concentration for vapor degreasing ranged from 0.077 to 21 ppm. In Hanley *et al.* (2010), workers near degreasers had personal breathing zone TWA 1-bromopropane concentrations higher (GM = 2.6 ppm) than workers away from degreasers (GM = 0.31 ppm), and urinary bromide and AcPrCys concentrations showed the same trend.

A NIOSH HHE was conducted at a facility that used 1-bromopropane below its boiling point as a vapor degreaser (Reh and Nemhauser 2001). Eight- to twelve-hour TWA 1-bromopropane air concentration data for this facility ranged from 0.01 to 0.63 ppm. Fifteen-minute sample data identified ranged from 2.3 to 8.4 ppm. This facility's cleaning system was located in a special, enclosed room with a local exhaust ventilation system (FR 2003). The design of most vapor degreasers reduces emissions from equipment because the solvent is boiled and subsequently condensed rather than allowing vapors to be emitted. In general, it is expected to be more difficult to control emissions from cleaning equipment in which the solvent is not boiled and condensed (FR 2003). Both cleaning methods could benefit from the installation of well-maintained, effective local exhaust ventilation systems as these are the preferred method of solvent emission control.

A summary of 500 personal samples for vapor degreasing by Graul (2012) reported that > 87% of the personal samples were below 25 ppm on an 8-hour TWA basis and approximately 75% of those samples were below 10 ppm on an 8-hour TWA basis.

1-Bromopropane emissions exposure to vapor degreasing workers can be reduced through changes in equipment and operating practices (FR 2003, Hanley and Dunn 2007). For example, additional condensation coils can be installed to prevent vapors from leaving the degreaser. Further, workers can tilt pieces to be cleaned to increase solvent drainage inside the vapor degreaser instead of leaving 1-bromopropane on the pieces to evaporate outside the degreaser where workers can inhale the vapors. A mechanical hoist operated at a controlled rate is also advantageous so that workers cannot raise the parts basket too quickly, which may circumvent effective vapor control of the condensing zone.

Area sample concentrations for 1-bromopropane for vapor degreasing ranged from 0.02 to 4.42 ppm (see Appendix B, Table B-8). These measurements indicate that the highest concentrations are found in areas near degreasers and lower concentrations are in areas away from degreasers.

1.4.6 *Cleaning and painting workshops*

In a study of 33 workers in a cleaning and painting workshop using 1-bromopropane cleaning solvents in a Japanese factory, Kawai *et al.* (2001) reported a geometric mean 1-bromopropane concentration of 1.42 ppm and a maximum concentration of 27.8 ppm.

1.5 Potential for environmental exposure

1.5.1 *Release of 1-bromopropane to the environment*

Based on the production and use of 1-bromopropane it may be released to the environment through various waste streams. 1-Bromopropane has also been detected in temperate marine macroalgae tissue and is believed to be transported from these algae to the marine environment. (HSDB 2006).

In a search of the National Response Center database for the time period of January 1, 1990 to the present, "1-bromopropane" identified three chemical spill incidents and "*n*-propyl bromide" identified one incident (NRC 2012). No Toxics Release Inventory (TRI) data for 1-bromopropane were identified, since 1-bromopropane is not included on the TRI list of toxic chemicals (EPA 2011).

1.5.2 *Fate, occurrence, and exposure*

No data have been identified indicating the measurement of 1-bromopropane in ambient air, drinking water, surface water, soil, or food. EPA has estimated 1-bromopropane concentrations in ambient air at a distance of 100 meters from average-adhesive use model facilities via air dispersion modeling to be 0.138 mg/m^3 [0.0274 ppm] and 1.38 mg/m^3 [0.274 ppm] for high-adhesive use facilities (Wolf *et al.* 2003). EPA also has estimated daily uptake from 1-bromopropane in the environment from inhalation for a person living 100 meters from average-adhesive use model facilities to be 0.0537 mg/kg-day and 0.537 mg/kg-day from high-adhesive use facilities.

Investigation of a wastewater tank leak at a Swiss alkyl halide factory that manufactured 1-bromopropane at quantities reported as greater than 5 tons/year did not identify any 1-bromopropane or its alcohol metabolite in groundwater after clean up (Schwarzenbach *et al.* 1985, as cited by NTP 2003a).

1.6 Potential for exposure from other sources: consumer products

No 1-bromopropane concentration measurement data for consumer products have been identified. Knöppel and Schauenburg (1989) analyzed VOC emissions of household wax, liquid pastes, and detergents, and 1-bromopropane was included in the list of analytes; however, 1-bromopropane was used as an internal standard in that study and the authors did not report it as being present in the consumer products (HSDB 2006).

1.7 Exposure levels for people

No data for non-occupational 1-bromopropane exposure levels for people have been identified.

1.8 Synthesis and summary

A significant number of people in the United States are exposed to 1-bromoproane as a result of widespread usage, high-production volume, and exposure to high levels of 1-bromopropane in commercial and industrial settings. The principal uses of 1-bromopropane are as a solvent cleaner in vapor and immersion degreasing operations to clean optics, electronics, and metals, as a solvent vehicle in industries that use aerosol-applied adhesives such as foam cushion manufacturing, and as a textile solvent in the

dry-cleaning industry. In recent years, certain 1-bromopropane uses have increased because it is an alternative to ozone-depleting chemicals or suspect carcinogens; e.g., 1-bromoprane has been used as an alternative to PERC (listed as *reasonably anticipated to be a human carcinogen* in the RoC) in the dry cleaning industry.

Inhalation is the primary route of human exposure; dermal exposure is also possible. 1-Bromopropane is a high-production-volume chemical with annual production ranging from 1 million to 10 million pounds as reported in 1998, 2002, and 2006. Based on occupational exposure data across several industrial sectors, 8- to 12-hour time-weighted average (TWA) 1-bromopropane air concentrations ranged from not detected to 380 ppm. 1-Bromopropane air concentrations are highest for adhesives use and lowest for vapor degreasing. In extreme cases, vapor degreasing 1-bromopropane air concentrations may be as much as four orders of magnitude lower than adhesives use concentrations.

No data have been identified indicating measurable levels of 1-bromopropane in ambient air, drinking water, surface water, soil, or food. However, the EPA has estimated via air dispersion modeling that 1-bromopropane may be present in ambient air, and daily intake from exposure in the environment may occur, particularly for people who live near industrial and commercial users of 1-bromopropane.

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2 Disposition and Toxicokinetics

This section describes the overall disposition of 1-bromopropane, i.e., how it can enter the body (absorption), what happens to it once it is in the body (distribution and metabolism), how it leaves the body (excretion), and the extent and/or rates of these processes. Section 2.1 discusses the absorption, distribution, and excretion of 1-bromopropane for both humans and experimental animals, and metabolism is discussed in Section 2.2. Toxicokinetics is the mathematical description (toxicokinetic model) of the time course of disposition of a chemical in the body; however, no toxicokinetic models of 1-bromopropane were identified.

Data on disposition of 1-bromopropane are important because they can help identify the various factors that affect the toxicity of the chemical. These factors include routes and rates of absorption, tissue concentrations and their temporal changes, reactive metabolites, toxification and detoxification reactions, routes of elimination, and species differences in these factors. The mechanistic implications of these data are discussed in Section 5.

2.1 Absorption, distribution, and excretion

2.1.1 *Absorption*

Studies in humans and laboratory animals indicate that 1-bromopropane can be absorbed following inhalation, ingestion, or dermal contact, and both inhalation and dermal exposure are likely to occur in the workplace (Cheever *et al.* 2009, Hanley *et al.* 2007). Occupational exposure studies consistently reported a correlation between ambient air levels of 1-bromopropane and levels of 1-bromopropane or metabolites in urine. (See Section 1 for a description of these exposure studies.) An *in vitro* study of absorption characteristics of 1-bromopropane using heat-separated human epidermal membranes demonstrated that dermal penetration of 1-bromopropane could be substantial but the actual absorption depended on the type and duration of exposure (Frasch *et al.* 2011).

The most relevant route of exposure for 1-bromopropane based on human exposures is inhalation, and metabolism studies in rats and mice show that 1-bromopropane is absorbed following inhalation (Garner *et al.* 2007, Garner *et al.* 2006, Ishidao *et al.* 2002) or oral exposure (Jones and Walsh 1979, Lee *et al.* 2010a). In male Wistar rats exposed to 1-bromopropane vapor at either 700 or 1,500 ppm, the concentration of 1-bromopropane in blood decreased linearly with time and was below the detection limit within 0.7 hours following the end of the exposure period (Ishidao *et al.* 2002). This study also reported that concentrations of bromide ion (a byproduct of 1-bromopropane metabolism) in rat blood decreased much more slowly, with a half-life of 4.7 to 15 days, depending on the exposure scenario (concentration and duration of treatment) while the half-life of bromide ion excreted in the urine was 5 to 7.5 days.

2.1.2 *Distribution*

No data on distribution of 1-bromopropane in humans was identified, and only one study (Garner *et al.* 2006) was found that reported limited data on distribution of radiolabeled [^{14}C]1-bromopropane in rats and mice after exposure by intravenous (i.v.) injection.

Exhaled air, urine, and feces were collected at various intervals up to 48 hours, and blood and tissue (reported as carcass) samples were collected 48 hours post-exposure. The total radioactivity recovered ranged from 83% to 103% with the largest percentages represented by volatile organic chemicals (VOCs) (25% to 71%), CO_2 (10% to 31%) and urine (13% to 23%). Much smaller amounts were recovered from the total carcass (2% to 6%) and feces (< 1% to 4%). Limited data were reported for radioactivity in liver, and no recovery data were reported for other individual tissues that might be potential tumor sites (see Section 4). The liver to blood tissue radioactivity ratios were similar (~3) regardless of dose, and dose-normalized 1-bromopropane ng equivalents/g of liver were inversely proportional to dose in both species.

2.1.3 *Excretion*

Once absorbed, the majority of 1-bromopropane is rapidly cleared from the blood by exhalation of the unchanged compound or as either CO_2 or VOCs, and by urinary excretion of metabolites of 1-bromopropane or the unmetabolized molecule. Only limited information is available for the excretion of 1-bromopropane in humans, but the presence of the unmetabolized molecule in urine has been described in studies of exposed workers (Ichihara *et al.* 2004a, Kawai *et al.* 2001). Excretion of unmetabolized 1-bromopropane in urine in these studies of exposed workers was significantly correlated with exposure to 1-bromopropane in air. No studies were identified that reported urinary excretion of unmetabolized 1-bromopropane in rodents. Bromide ion is also excreted, but the specificity of this ion as a biomarker for exposure to 1-bromopropane is limited because of a relatively high background from dietary sources, particularly seafood. As discussed below in the section on metabolism, several mercapturic acid derivatives of 1-bromopropane have been identified in urine from exposed humans and experimental animals. Many more metabolites or potential metabolites have been identified from experimental animal studies using labeled 1-bromopropane and these are discussed below.

Other studies in experimental animals have exposed rats or mice to radiolabeled [^{14}C]1-bromopropane by intraperitoneal (i.p.) injection (Jones and Walsh 1979) or i.v. administration through the tail vein or jugular vein (Garner *et al.* 2006). Jones and Walsh reported that 60% of a single dose of 200 mg/kg 1-bromopropane administered to rats was exhaled unchanged within 4 hours with only trace amounts detected after that time. Only 1.4% of the total dose was exhaled as CO_2 and about 45% of the metabolized dose was excreted in the urine after 100 hours. A much lower recovery of 3.3% of an i.p. dose of 200 mg/kg as urinary metabolites was reported by Walsh and Jones (1977) after 100 hours.

2.2 **Metabolism**

The metabolites identified in humans are limited to those recovered in the urine of factory workers after exposure to 1-bromopropane. Several studies have investigated 1-bromopropane metabolism in experimental animals, and the different metabolites identified in studies by different routes of exposure indicate that the metabolism is complex.

2.2.1 *Metabolites detected in humans*

Several studies have monitored urine samples from humans occupationally exposed to 1-bromopropane in order to establish biomarkers of exposure. The predominant metabolite detected in the urine of workers is *N*-acetyl-*S*-propylcysteine (AcPrCys), and levels increased with increasing 1-bromopropane ambient exposure levels (Hanley and Dunn 2006, Hanley *et al.* 2009, 2010, Valentine *et al.* 2007). In addition to AcPrCys, several other urinary mercapturic acid conjugates were identified from 1-bromopropane–exposed workers; these included *N*-acetyl-*S*-(*n*-propyl)-L-cysteine-*S*-oxide, *N*-acetyl-*S*-(2-carboxyethyl)-L-cysteine, and *N*-acetyl-*S*-(3-hydroxy-*n*-propyl)-L-cysteine (Cheever *et al.* 2009, Hanley *et al.* 2009). The oxidative metabolites that likely lead to the conjugates have not been reported in human studies, however no publications were identified that actually tested for them. Metabolism has been more extensively studied in experimental animals.

2.2.2 In vivo *studies in experimental animals*

Metabolism studies were conducted in rats and mice exposed by inhalation, oral, subcutaneous (s.c.), i.p., or i.v. administration and *in vitro* using rat liver microsomes (Barnsley *et al.* 1966, Garner *et al.* 2007, Garner *et al.* 2006, Jones and Walsh 1979). The four urinary mercapturic acid conjugates identified in exposed workers were also identified in experimental animals. AcPrCys was identified in the urine of rats, mice, guinea pigs, and rabbits exposed to 1-bromopropane via s.c. injection. The other metabolites were identified in the urine of rats following oral exposure. Additional urinary metabolites identified from studies in experimental animals are listed in Table 2-1, but the available studies do not agree completely with regard to metabolites detected, which might be due to differences in route of exposure, species tested, and detection methods. Overall, three major categories of metabolites have been identified: (1) brominated metabolites (Phase I), (2) debrominated metabolites (Phase I), and (3) glucuronide or glutathione conjugated metabolites (Phase II).

Table 2-1. 1-Bromopropane metabolites

Metabolite	Humans	Experimental animals			*In vitro*
		Inh.	Oral	Inj.	
N-acetyl-*S*-(*n*-propyl)-L-cysteine (AcPrCys, *n*-propyl mercapturic acid)	X [a]	X [b,c]	X [d]	X [e,f,g]	
N-Acetyl-3-(propylsulfinyl)alanine (*N*-acetyl-*S*-(*n*-propyl)-L-cysteine-*S*-oxide or *n*-propylmercapturic acid)	X [a]	X [b]	X [d]	X [f]	
N-Acetyl-*S*-(3-hydroxypropyl)cysteine	X [a]		X [d]		
N-Acetyl-*S*-(2-carboxyethyl)cysteine	X [a]		X [d]		
1-Bromo-2-propanol		X [b]			
Bromoacetone		X [b]			
α-Bromohydrin		X [b]			
Glycidol		X [h]			
N-Acetyl-*S*-(2-hydroxypropyl)cysteine (2-hydroxypropyl mercapturic acid)		X [b]	X [d]	X [f,g]	
N-Acetyl-*S*-(2-oxopropyl)cysteine		X [b]			
N-Acetyl-3-[(2-hydroxypropyl)sulfinyl]alanine		X [b]			
N-Acetyl-3-[(2-oxopropyl)sulfinyl]alanine		X [b]			
N-Acetyl-3-[(2-propenol)sulfinyl]alanine		X [b]			
2,3-Dihydroxypropylmercapturic acid				X [g]	
1-Bromo-2-hydroxypropane-*O*-glucuronide		X [b]			
3-Bromopropionic acid			X [d]	X [g]	X [d]
Propene					X [i]
n-Propanol					X [j]
1,2-Propanediol					X [i]
Propionic acid					X [i]
S-*n*-Propylglutathione					X [i]
S-(2-Hydroxypropyl)glutathione					X [i]
3-Hydroxypropionic acid					X [d]
S-(2-hydroxypropyl)cysteine					X [d]

Inh. = inhalation; Inj. = injection.
[a]Hanley *et al.* 2009.
[b]Garner *et al.* 2006.
[c]Valentine *et al.* 2007.
[d]Jones and Walsh 1979.
[e]Grenby and Young 1959, 1960.
[f]Barnsley *et al.* 1966.
[g]Walsh and Jones 1977.
[h]Ishidao *et al.* 2002.
[i]Tachizawa *et al.* 1982.
[j]Kaneko *et al.* 1997.

Garner *et al.* (2006) investigated the metabolism of 1-bromopropane in male F344 rats and $B6C3F_1$ mice following inhalation or tail vein injection. These routes were selected because they do not involve first-pass metabolism and the inhalation route, specifically, is more likely to be consistent with occupational or environmental exposures compared with the oral and i.p. routes used by Jones and Walsh (1979). Much of the administered dose (40% to 70%) was exhaled unchanged. Oxidation and glutathione conjugation were the primary metabolic pathways (Figure 2-1). In both rats and mice, hydroxylation at the C_2 position (forming 1-bromo-2-propanol) was the predominant pathway of oxidation. Although 1-bromo-2-propanol was not detected in the urine, resonances associated with unconjugated 1-bromo-2-propanol were detected in rat liver homogenates, and more than half of the urinary metabolites were derived from this metabolite. Although bromoacetone was not detected in the urine, its mercapturic acid conjugate, *N*-acetyl-*S*-(2-oxopropyl)cysteine, was detected in rats at levels approaching that of *N*-acetyl-*S*-(2-hydroxypropyl)cysteine, the mercapturic acid of 1-bromo-2-propanol. Another possible metabolite detected in rat liver homogenate was α-bromohydrin.

Urinary metabolites in rats exposed to 1-bromopropane by i.v. injection were affected by dose (Garner *et al.* 2006). At the low dose, AcPrCys was a relatively minor component compared with earlier eluting peaks that included *N*-acetyl-*S*-(2-hydroxypropyl)cysteine. However, the relative proportion of AcPrCys increased with dose and accounted for more than 80% of the urinary radioactivity in the high-dose group. AcPrCys is formed by direct conjugation with glutathione without oxidation (Figure 2-1). In contrast, in mice injected i.v. with 1-bromopropane, *N*-acetyl-*S*-(2-hydroxypropyl)cysteine was the single predominant metabolite at all dose levels.

A pathway overlapping in part with that described by Garner *et al.* (2006) was reported by Jones and Walsh (1979), who investigated the metabolism of 1-bromopropane in male Sprague-Dawley rats following five consecutive daily oral doses. Four possible metabolic pathways were identified (Figure 2-2). The first pathway involved direct conjugation with glutathione to produce the urinary metabolites AcPrCys and *N*-acetyl-*S*-propylcysteine-*S*-oxide. The second pathway involved oxidation at C_3 of 1-bromopropane to 3-bromo-1-propanol. Pathway 3 was based on oxidation of C_1 of 1-bromopropane to CO_2 (hydrolysis to *n*-propanol with rapid oxidation to propionic acid and decarboxylation to CO_2). Pathway 4 is the proposed mechanism for forming *N*-acetyl-*S*-(2-hydroxypropyl)cysteine; however, there was no direct evidence for this pathway *in vivo*. Several additional metabolites, including 3-bromopropionic acid and *n*-propanol, were identified by Jones and Walsh that were not described by Garner *et al.* However, as suggested by Garner *et al.*, the difference in the observed metabolites might be explained by the analytical methods used by Jones and Walsh, which included concentration steps that could have amplified several minor metabolites (see Section 2.2.5).

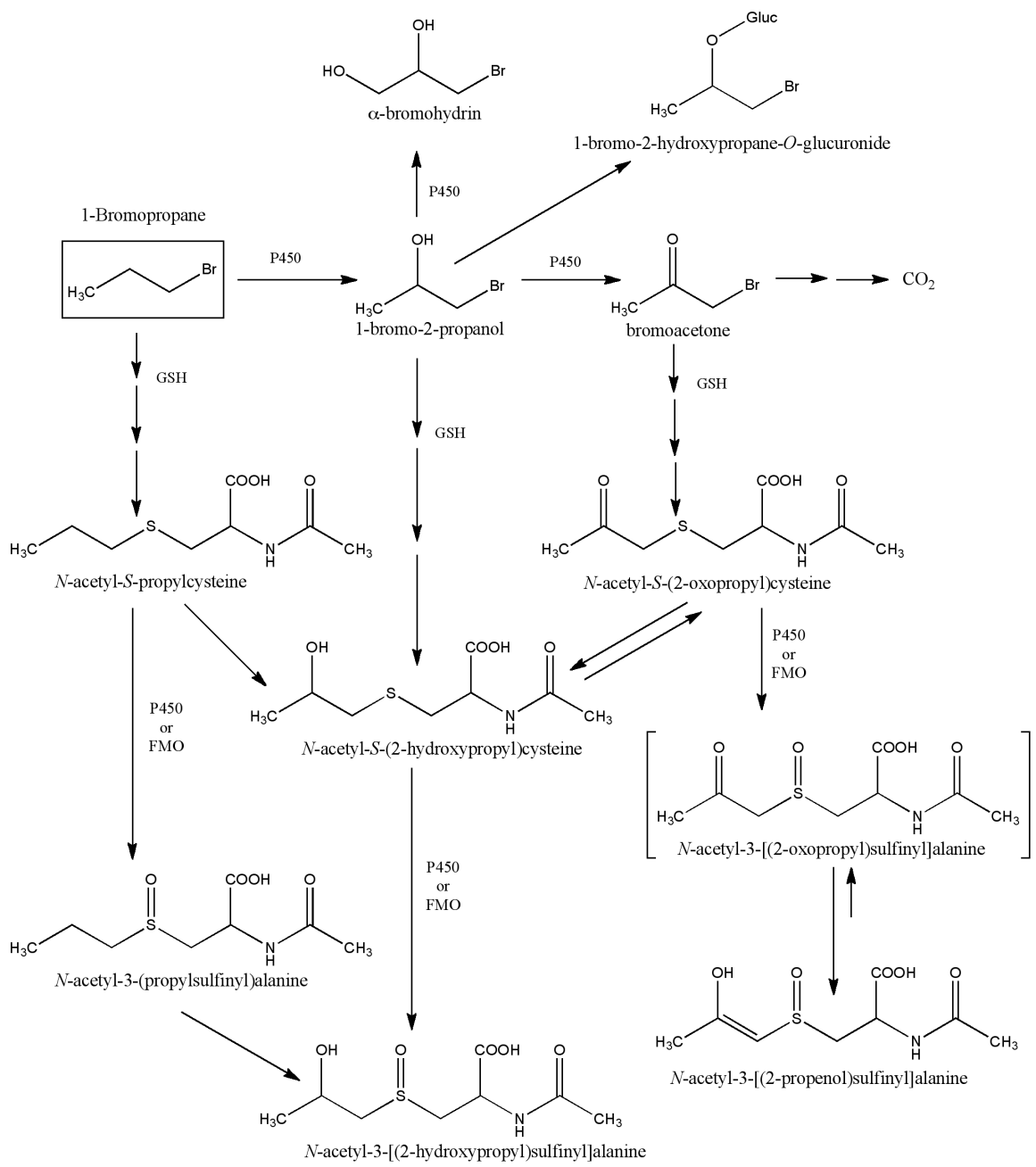

Figure 2-1. 1-Bromopropane metabolism in male F344 rats and B6C3F$_1$ mice following inhalation exposure

Source: Garner *et al.* 2007, Garner *et al.* 2006. Structure in brackets is a proposed intermediate and was not isolated. FMO = flavin-containing monooxygenase, GSH = glutathione, P450 = cytochrome P450.

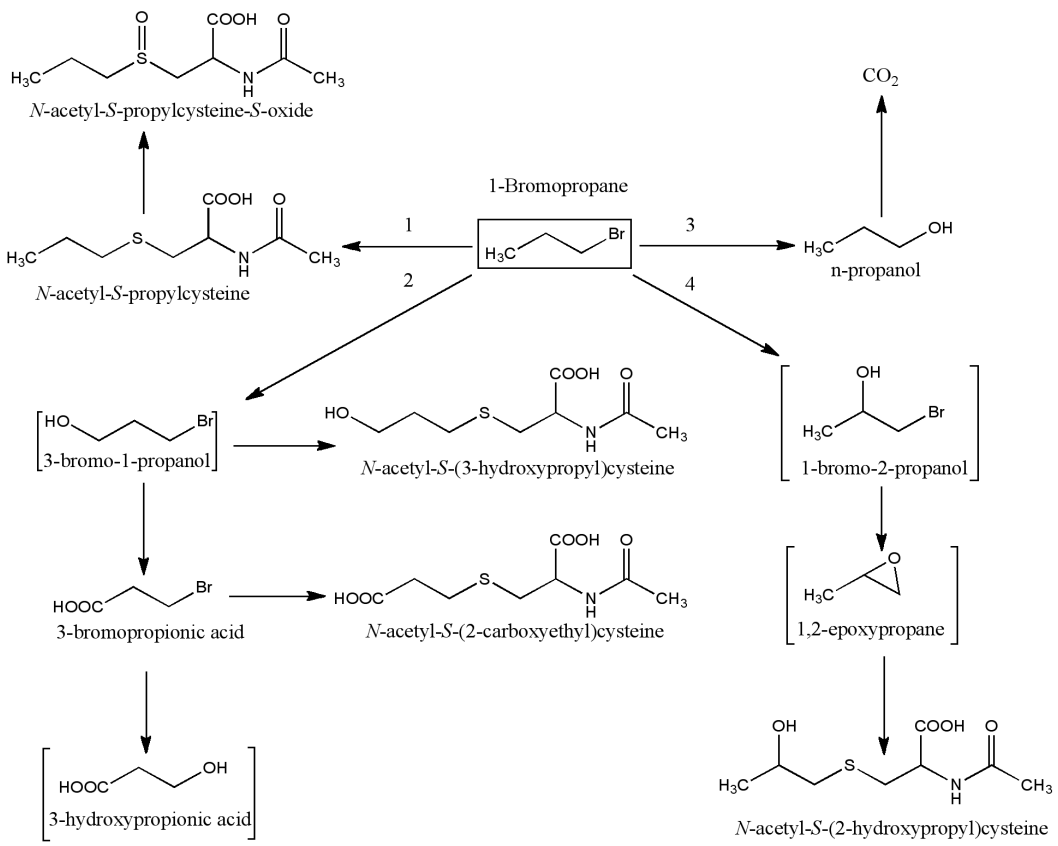

Figure 2-2. Metabolic pathways of 1-bromopropane in male Sprague-Dawley rats following oral exposure

Source: Jones and Walsh 1979. Compounds enclosed in brackets were not isolated from the urine. Pathway 1: direct conjugation with glutathione; Pathway 2: oxidation at C_3 to 3-bromo-1-propanol; Pathway 3: oxidation at C_1 to *n*-propanol and then to CO_2; Pathway 4: formation of *N*-acetyl-*S*-(2-hydroxypropyl)cysteine.

Possible reactive metabolites identified in these studies of 1-bromopropane metabolism include glycidol, α-bromohydrin, and propylene oxide (1,2-epoxypropane). Glycidol was identified in urine samples but not quantified by Ishidao *et al.* (2002) as a metabolite resulting from exposure of rats to 1-bromopropane by inhalation. Walsh and Jones (1977) did not detect glycidol in rats given an i.p. injection but proposed that it was a likely intermediate in formation of the urinary metabolite 2,3-dihydroxypropylmercapturic acid. Garner *et al.* (2007) identified α-bromohydrin as a metabolite. Propylene oxide was proposed as a likely metabolite by Ishidao *et al.* (2002) and by Jones and Walsh (1979), but neither group detected it in their studies. The genotoxicity and potential carcinogenicity of glycidol, α-bromohydrin, and propylene oxide are discussed in Section 5.

2.2.3 In vitro *studies*

Several debrominated metabolites of 1-bromopropane were identified only in studies *in vitro* using rat liver microsomes (see Table 2-1). Three metabolites of 1-bromopropane – propene, 1,2-propanediol, and propionic acid – were identified from the *in vitro* P450-catalyzed metabolism of 1-bromopropane by phenobarbital-induced rat liver microsomes;

when exogenous glutathione was added to the incubation mixture, S-(1'-propyl)glutathione and S-(2'-hydroxy-1'-propyl)glutathione were detected (Tachizawa *et al.* 1982). In another *in vitro* metabolism study of 1-bromopropane by rat liver microsomes reported by Kaneko *et al.* (1997) only *n*-propyl alcohol was reported as a metabolite, but the authors noted that differences between the rate of substrate disappearance and product formation suggested that there might be other metabolic pathways.

Jones and Walsh (1979) also conducted an *in vitro* metabolism study of 1-bromopropane. Oxidation of carbons 2 and 3 (C_2 and C_3) of 1-bromopropane was demonstrated *in vitro*. Metabolites oxidized at C_3 included 3-bromopropionate and 3-hydroxypropionate. Evidence for C_2 oxidation (i.e., formation of 1-bromo-2-propanol) was provided by the isolation of *S*-(2-hydroxypropyl)cysteine from the reaction mixture after it was reacted with cysteine in sodium hydroxide.

2.2.4 *Studies of metabolizing enzymes*

It is clear from the available studies that most of the metabolites of 1-bromopropane are formed following oxidation reactions and glutathione conjugation. The proportion of 1-bromopropane metabolized via oxidation relative to pathways dependent on direct glutathione conjugation was inversely proportional to dose in rats but independent of dose in mice (Garner *et al.* 2006). Garner *et al.* concluded that formation of AcPrCys results from release of a bromide ion without oxidation. Barnsley *et al.* (1966) also postulated formation of *S*-*n*-propylglutathione directly from 1-bromopropane with subsequent formation of *S*-*n*-propylcysteine and AcPrCys.

The importance of the cytochromes P450 (CYP) oxidative enzymes in the metabolism of 1-bromopropane has been confirmed by the severe reduction in formation of metabolites when NADPH was eliminated from the incubation mixture with phenobarbital-induced rat liver microsomes, effectively inactivating CYP oxidation (Tachizawa *et al.* 1982). Pretreatment of rats with 1-aminobenzotriazole (ABT), a general inhibitor of CYP, significantly reduced the number of metabolites from 10 to 1 major metabolite, AcPrCys, which accounted for more than 90% of the total radioactivity (Garner *et al.* 2006). Results from a study on the induction of liver CYP isozymes in male and female Sprague-Dawley rats exposed to 1-bromopropane indicated that the expression of the CYP2E1 isozyme was enhanced while the signals for the other isozymes (CYP1A/2 and CYP2B1/2) were not, suggesting that CYP2E1 is possibly responsible for 1-bromopropane metabolism (Kim *et al.* 1999b). Further evidence for the specific contribution of CYP2E1 to metabolism of 1-bromopropane was provided by studies with $Cyp2e1^{-/-}$ knockout and wild-type mice (Garner *et al.* 2007). Compared with wild-type mice exposed to 1-bromopropane by inhalation for 6 hours, the elimination half-life was more than twice as long in knockout mice (3.2 vs. 1.3 hours) exposed in the same way. In addition, the ratio of glutathione conjugation to 2-hydroxylation increased 5-fold, and the urinary concentration of *N*-acetyl-*S*-(2-hydroxypropyl)cysteine was reduced by about 50%. These data indicate that CYP2E1 is responsible for much, but not all, of the oxidative metabolism of 1-bromopropane since hydroxylated metabolites were significantly decreased, but not completely eliminated, in knockout mice.

The role of glutathione conjugation was also investigated using DL-buthionine(S,R)-sulfoximine 1-aminobenzotriazole (BSO), an inhibitor of GSH synthesis (Garner *et al.* 2006). Pretreatment with BSO did not significantly alter the metabolite profile for 1-bromopropane, although there was a moderate decrease in the level of AcPrCys with a concomitant increase in other metabolites compared with rats that were exposed to 1-bromopropane alone. The authors suggested that direct conjugation of 1-bromopropane might be a relatively minor pathway compared with oxidative metabolism in mammals.

2.2.5 *Differences in metabolic pathways*

Differences exist for the metabolites and metabolic pathways identified by various researchers. Possible explanations for these differences include the route of exposure, the location of the radiolabel, and other potential factors as discussed below.

The study by Jones and Walsh (1979) identified two mercapturic acid conjugates derived from metabolites oxidized at the C_3 position (3-bromo-1-propanol and 3-bromopropionic acid) that were not detected in other studies. Jones and Walsh confirmed formation of these molecules using Udenfriend's reagent (a mixture of iron, citric acid, EDTA, and oxygen) to oxidize 1-bromopropane *in vitro*; these conditions might have been too harsh and could reflect more of a chemical reaction than an *in vitro* metabolism study. In addition, Garner *et al.* (2006) proposed that Jones and Walsh (1979) might have artificially amplified these metabolites by pooling, acidifying, and concentrating a large volume of urine prior to analysis. Garner *et al.* (2006) also noted differences with the *in vitro* study of Tachizawa *et al.* (1982) (see Section 2.2.3). *In vitro* metabolism of 1-bromopropane by hepatic microsomes from phenobarbital-induced rats produced propene, 1,2-propanediol, and propionic acid; *S*-(1'-propyl)glutathione and *S*-(2'-hydroxy-1'-propyl)glutathione were detected when glutathione was added to the incubation mixture. However, none of these metabolites was detected in rat liver homogenate incubations or in experimental animal models. Garner *et al.* speculated that the use of phenobarbital as an inducer of CYP by Tachizawa *et al.* might have produced metabolites that are not normally generated by constitutively expressed CYPs.

The studies discussed here also reported large differences in the amounts of 1-bromopropane exhaled as CO_2. The reason for this apparent discrepancy is unclear but may be attributed to the particular carbon atom that was radiolabeled. Jones and Walsh (1979) concluded that oxidation of 1-bromopropane at the C_1 position with subsequent oxidation to propionate and decarboxylation to CO_2 was insignificant *in vivo*. However, Garner *et al.* (2007, 2006) concluded that a large portion of the administered dose was converted to CO_2 regardless of the exposure route and that 1-bromo-2-propanol was the ultimate source of CO_2 (via oxidation to bromoacetone, pyruvaldehyde, and pyruvate). This was supported by a significant drop in exhaled CO_2 in rats pretreated with the CYP inhibitor ABT and by a previous study (Bond *et al.* 1988) that reported that about 65% of an analogous molecule, 1-chloro-2-propanol, administered to rats was excreted as CO_2. Bond *et al.* (1988) demonstrated that about 30% of the CO_2 originated from C_3 and about 35% originated from C_2.

2.3 Synthesis and summary

Studies in humans and laboratory animals indicate that 1-bromopropane can be absorbed following inhalation, ingestion, or dermal exposure. Occupational exposure occurs primarily by inhalation and dermal contact and studies of workers show a good correlation between urinary concentrations of 1-bromopropane, bromide ion, and *N*-acetyl-*S*-(*n*-propyl)-L-cysteine (AcPrCys) with their 1-bromopropane breathing zone air concentrations. Several studies have monitored urine and blood samples in workers to establish biomarkers of exposure. These studies also indicate that unmetabolized 1-bromopropane is excreted in the urine in humans but has not been reported in animal studies. The four urinary mercapturic conjugates identified from 1-bromopropane–exposed workers have also been reported as urinary metabolites from studies in rodents, including AcPrCys, *N*-acetyl-*S*-(*n*-propyl)-L-cysteine-*S*-oxide, *N*-acetyl-*S*-(2-carboxyethyl)-L-cysteine, and *N*-acetyl-*S*-(3-hydroxy-*n*-propyl)-L-cysteine. The oxidative metabolites that likely lead to the conjugates have not been reported in human studies; however, no publications were identified that actually tested for them.

Experimental animal studies have shown that 1-bromopropane is absorbed, rapidly distributed, and predominantly eliminated by exhalation (approximately 40% to 70%), but is also excreted in the urine and feces. In rats and mice, most of the 1-bromopropane administered by i.v. injection was exhaled unchanged or as CO_2 within 4 hours of exposure. Urinary metabolites accounted for 13% to 23% of the administered dose after 48 hours. The available studies on 1-bromopropane metabolism show that CYP-catalyzed oxidation (primarily via CYP2E1) reactions and glutathione conjugation are the primary metabolic pathways. At least 16 urinary metabolites have been identified in rodent studies (either rats or mice), including several reactive intermediate metabolites (bromoacetone, glycidol, and α-bromohydrin).

3 Human Cancer Studies

No epidemiological studies or case reports were identified that evaluated the relationship between human cancer and exposure specifically to 1-bromopropane.

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4 Studies of Cancer in Experimental Animals

This section reviews and assesses the carcinogenicity studies in experimental animals exposed to 1-bromopropane. These studies were identified by searching databases, comprehensive reviews, and citations from studies retrieved from the literature searches as described in Appendix A. Identified citations were reviewed using exclusion and inclusion criteria that limited selection of the studies to those examining neoplastic lesions, non-neoplastic or preneoplastic lesions relevant to carcinogenicity, or subchronic studies that provide information on dose selection. Chronic (2-year) inhalation studies conducted by NTP and the associated subchronic (90-day) studies in mice and rats were the only studies identified that examined tissues for neoplastic or preneoplastic endpoints.

The characteristics, methodology, and relevant non-neoplastic findings from the chronic studies by NTP and the associated subchronic studies are reported in Section 4.1. An assessment of the evidence for carcinogenicity is discussed in Section 4.2 and the recommendation for the level of evidence is provided in Section 4.3.

4.1 Studies in experimental animals: characteristics, methodology, and relevant non-neoplastic findings

Both the subchronic and chronic studies in rats and mice were conducted in the same facility using 1-bromopropane with purity greater than 99% and the same animal husbandry and testing procedures as in the chronic study under FDA Good Laboratory Practice regulations (NTP 2011a). The subchronic studies in rats and mice were used to determine the exposure groups in the chronic study. $B6C3F_1$ mice or F344/N rats were administered 1-bromopropane (99% pure) by whole-body exposure in inhalation chambers for 6 hours and 10 minutes per day, 5 days a week, for either 14 weeks (subchronic studies, 10 males and 10 females per exposure group) or 105 weeks (chronic studies, 50 males and 50 females per exposure group), with controls exposed to filtered air only. (Note: The additional 10 minutes of exposure were based on experimental data for the time required to achieve 90% of the target concentration [T_{90}] after the beginning of vapor generation.) Complete necropsies and histopathology were performed on all animals. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were processed and stained for histopathologic examination.

4.1.1 *Rats*

Subchronic study

The subchronic study did not identify any neoplastic lesions at the exposure levels tested (0, 62.5, 125, 250, 500, or 1,000 ppm). Male rats exposed to 1,000 ppm had reduced body weight compared with controls; rats had evidence of hepatotoxicity at this dose. Sorbitol dehydrogenase activity was increased at 500 ppm (males only) and 1,000 ppm (males and females). Liver weight and cytoplasmic vacuolization were increased at 250 ppm or greater exposures in males. In females, liver weight increased at 125 ppm or greater, liver vacuolization at 500 ppm or greater, and hepatocyte degeneration was observed at 1,000 ppm. During selection of the maximum level of exposure for the chronic study, liver vacuolization was considered a tolerable toxicity and not life threatening, while hepatocyte degeneration was considered intolerable.

Chronic study

Fischer 344/N rats were exposed to 0, 125, 250, and 500 ppm of 1-bromopropane based on decreased body weights and increased incidences of liver lesions at 1000 ppm reported in the subchronic study. During the chronic study, survival in males was significantly decreased in the group exposed to 500 ppm, and survival decreased with increasing level of exposure (statistically significant negative trend). Survival in females was not significantly decreased in a pair-wise analysis for any exposure level, but there was a statistically significant negative trend with the level of exposure. Body weights of exposed males and females were similar to those of controls.

No neoplastic lesions were found in the respiratory tract, but several non-neoplastic lesions, including inflammation, hyperplasia, and metaplasia were found in the upper respiratory tract of both sexes of rats. Hyperplasia of the respiratory epithelium was found at significantly increased incidences in the nasal cavity of females at 125 and 500 ppm and in the trachea of females at 500 ppm. Hyperplasia of glands in the nasal cavity, mostly in level II, was at a significantly increased incidence in both sexes in all exposed groups of rats. Significant increases in the incidences of metaplasia in females were found in the nasal cavity as olfactory epithelium with morphology of respiratory epithelium at 500 ppm and in the larynx as squamous metaplasia at 500 ppm. Chronic suppurative inflammation of the nasal cavity had a significantly increased incidence in males and females at 500 ppm. Despite the high incidence of chronic active inflammation seen in untreated controls, the incidences of this non-neoplastic lesion were significantly increased in the nasal cavity of females at all exposure levels, in the larynx of males at 250 ppm and of females at 250 and 500 ppm, as well as in the trachea of females at 500 ppm. Abscesses on the tail, Harderian gland, head, and salivary gland of five exposed rats were tested for bacterial growth under anaerobic and aerobic conditions. *Pseudomonas aeruginosa* was the primary isolate (4 out of 5 sites) in all aerobic cultures and Splendore-Hoeppli bodies were later observed microscopically in these lesions (see discussion in Appendix E, “Immunotoxicity”). Although inflammation and infections were associated with immunosuppression in rats, it was not noted in the Technical Report (NTP 2011a) whether the abscesses were directly associated with tumors. No evidence of suppurative inflammation was reported in the mouse study, although mice were also immunosuppressed after subchronic 1-bromopropane exposure.

4.1.2 *Mice*

Subchronic study

The NTP subchronic study did not identify any neoplastic lesions at the exposure levels tested (0, 62.5, 125, 250, 500 ppm). Survival (number surviving/number at study start) was decreased in the high-dose female (5/10) and male (6/10) groups and one death at 250 ppm in males (9/10). There was an increase in kidney, liver, and lung weights in the 500-ppm female group, and the kidney weights of the 500-ppm male group were decreased.

Chronic study

Based on mortality at the highest exposure concentration, changes in organ weights, and the incidences of various non-neoplastic lesions in the subchronic study, 1-bromopropane

exposure concentrations selected for the chronic inhalation study in mice were 62.5, 125, and 250 ppm. During the chronic study, survival and body weights of both sexes in exposed groups were similar to those in control groups.

4.2 Assessment of neoplastic findings

The chronic inhalation studies in B6C3F$_1$ mice and Fischer 344/N rats conducted by NTP were of sufficient duration to adequately assess the carcinogenic potential of 1-bromopropane. Factors considered in study design were the number of animals per exposure group, exposure period, dose selection, monitoring of animal health, and complete necropsies of all animals and histopathologic examination of all major tissues. This study is considered a high quality study and provides strong evidence to support the cancer assessment. Details of study quality criteria and assessment are found in Appendix C. Important factors taken into account in data assessment are the significance of the effect as compared with the concurrent control (pairwise comparison), whether there is a change in the effect with dose (trend analysis), and the rarity of the event (historical control range). In the NTP assessments of experimental animal data in this report, a Poly-3 trend analysis is employed, which is similar to the Cochran-Armitage trend test but is survival adjusted.

In rats, there was a significantly increased incidence with a positive trend for benign tumors (adenoma) of the large intestine (colon or rectum) in females, but the incidence did not reach significance for male rats (Table 4-1). However, these are rare tumors and the tumor incidence exceeded the historical control range for male and female rats for inhalation studies and studies by all exposure routes and are considered to be of biological significance. (An adenomatous polyp was listed for a male rat exposed to 125-ppm 1-bromopropane [see Appendix Table A1 of the NTP Technical Report 564, NTP 2011a] but was not included in the data analysis conducted by the authors. Addition of this tumor increases the total number of benign tumors of the large intestine in all 1-bromopropane–exposed male rats from 3 to 4 tumors, which provides additional support for an exposure-related effect.) The time to first incidence of tumors of the colon or rectum was lower with increasing dose in male rats (729 days at 250 ppm and 682 days at 500 ppm); but no clear trend was seen with increasing dose for female rats (730 days at 125 ppm, 607 days at 250 ppm, and 719 days at 500 ppm). Spontaneous adenoma of the large intestine is rare in male and female rats, occurring at a rate of less than 0.2%. Increased incidences of adenocarcinoma of the large intestine were observed in both male and female rats after oral treatment with brominated methanes (bromodichloromethane or tribromomethane (NTP 1987, 1989) and in male rats after treatment with glycidol (NTP 1990), a metabolite of 1-bromopropane. Therefore, the findings of intestinal tumors after 1-bromopropane exposure are considered to be exposure related. Although no carcinomas of the large intestine were observed in male or female rats in the current study, adenoma of the large intestine can progress to carcinoma (NTP 2011a).

Table 4-1. Large intestine tumors observed in Fischer 344/N rats exposed to 1-bromopropane by inhalation for 2 years

Sex	Conc. (ppm)	Number of rats surviving to study termination	Large intestine tumor (adenoma) (% incidence)		
			Colon	Rectum	Colon or rectum combined
Male	0	23	0/50 (0)	0/50 (0)	0/50 (0.0)[a,b]
	125	26	0/50 (0)	0/50 (0)[c]	0/50 (0.0)
	250	18	0/50 (0)	2/50 (4)	2/50 (5.3)
	500	13*	1/50 (2)	0/50 (0)	1/50 (2.8)
	trend[+]	$P = 0.009$[d]	NR	NR	$P = 0.197$
Female	0	34	0/50 (0)	0/50 (0)	0/50 (0.0)[a,b]
	125	33	1/50 (2)	0/50 (0)	1/50 (2.3)
	250	30	1/50 (2)	1/50 (2)	2/50 (4.7)
	500	24	1/50 (2)	4/50 (8)	5/50 (13.3)*
	trend[+]	$P = 0.028$[d]	NR	NR	$P = 0.004$

Source: NTP 2011a.
NR = not reported.
*$P \leq 0.05$ (compared with concurrent controls by Poly-3 test for tumor incidence or life-table pairwise comparisons for survival).
[+]Determined by Poly-3 trend test.
[a]Number of animals with tumors; (Poly-3 estimated tumor incidence percent after adjustment for intercurrent mortality).
[b]Historical control range: 0% for inhalation studies and 0%–2% for studies by all routes.
[c]Appendix Table A1 of the NTP Technical Report (TR 564) indicated that an adenomatous polyp was observed at this treatment dose, but the polyp was not included in the data analysis (see TR 569 [NTP 2011a], Table 9).
[d]Survival analysis performed by life-table trend test.

Male rats had a significant increase in the incidence of malignant or benign skin tumors (keratoacanthoma; keratoacanthoma or squamous-cell carcinoma combined; and keratoacanthoma, squamous-cell carcinoma, basal-cell adenoma, or basal-cell carcinoma combined) as well as significant positive trends for these three groups of skin tumors (Table 4-2). These effects are also considered to be exposure related. Female rats had a significant positive trend for keratoacanthoma, squamous-cell papilloma, basal-cell adenoma, or basal-cell carcinoma combined, with the high-dose group (500 ppm) outside of the historical control range for inhalation studies and studies by all exposure routes, so these combined skin tumors may be exposure related. Keratoacanthomas also occurred in females, but the incidences were not increased compared with the concurrent or historical controls. Keratoacanthomas can progress to squamous-cell carcinoma, a malignant tumor; however, no squamous cell-carcinomas were identified in female rats.

Table 4-2. Skin tumors observed in Fischer 344/N rats exposed to 1-bromopropane by inhalation for 2 years

Sex	Conc. (ppm)	Number of rats surviving to study termination	Skin tumors (% incidence)[a]			
			KA	KA or SCC combined	KA, SCC, BCA or BCC combined	KA, SCP, BCA, or BCC combined
Male	0	23	0/50 (0.0)[b]	1/50 (2.4)[b]	1/50 (2.4)[c]	NR
	125	26	3/50 (7.4)	4/50 (9.8)	7/50 (17.0)*	
	250	18	6/50 (15.4)*	6/50 (15.4)*	9/50 (22.6)**	
	500	13*	6/50 (16.2)**	8/50 (21.4)**	10/50 (26.7)**	
	trend[+]	P = 0.009[d]	P = 0.008	P =0.006	P = 0.003	
Female	0	34	1/50 (2)[e,g]	1/50 (2)[g]	1/50 (2)[f,g]	1/50 (2.2)[f]
	125	33	0/50 (0)	0/50 (0)	1/50 (2)	1/50 (2.3)
	250	30	1/50 (2)	1/50 (2)	1/50 (2)	1/50 (2.4)
	500	24	1/50 (2)	1/50 (2)	3/50 (6)	4/50 (10.6)
	trend[+]	P = 0.028[d]	NR	NR	NR	P = 0.05

Source: NTP 2011a.
BCA = basal-cell adenoma, BCC = basal-cell carcinoma, KA = keratoacanthoma, NR = not reported, NS = not significant, SCA = squamous-cell papilloma, SCC = squamous-cell carcinoma.
*$P \leq 0.05$, **$P \leq 0.01$ (compared with concurrent controls by Poly-3 test).
[+]Determined by Poly-3 trend test.
[a]Number of animals with tumors (Poly-3 estimated tumor incidence percent after adjustment for intercurrent mortality).
[b]Historical control range: 0%–8% for inhalation studies and 0%–16% for studies by all routes.
[c]Historical control range: 0%–10% for inhalation studies and 0%–20% for studies by all routes.
[d]Survival analysis performed by life table trend test.
[e]Historical control range: 0%–2% for inhalation studies and 0%–4% for studies by all routes.
[f]Historical control range: 0%–2% for inhalation studies and 0%–6% for studies by all routes.
[g]Percent incidence is overall rate (non-Poly-3 adjusted).

Male rats had a significant positive trend of malignant mesothelioma (*tunica vaginalis* of the epididymis) with a significant increase in tumor incidence at the high dose that was slightly greater (10.8%) than the historical control range (0% to 6%) for inhalation studies and studies by all exposure routes (Table 4-3). Therefore, these results may be exposure related. A significant increase was also observed in the incidence of malignant or benign pancreatic islet-cell tumors (adenoma and adenoma or carcinoma combined) for all exposure groups for adenoma and for 125 ppm and 250 ppm for adenoma and carcinoma combined in male rats; the incidence of adenoma and carcinoma was increased (but not statistically significant) at the highest exposure level (500 ppm). Although the tumor incidences were within the historical control range for inhalation studies and studies by all exposure routes, there was a significant positive trend for benign pancreatic islet-cell tumors (adenoma) suggesting that the tumors may have been caused by 1-bromopropane exposure. No exposure-related response of pancreatic islet-cell tumors was observed in female rats.

Table 4-3. Malignant mesotheliomas and pancreatic islet-cell tumors observed in Fischer 344/N rats exposed to 1-bromopropane by inhalation for 2 years

Sex	Conc. (ppm)	Number of rats surviving to study termination	Malignant mesothelioma (% incidence)[a,b]	Pancreatic islet cell tumor (% incidence)[b]		
				Adenoma	Carcinoma	Adenoma or carcinoma combined
Male	0	23	0/50 (0.0)[c]	0/50 (0.0)[d]	3/50 (7.2)[e]	3/50 (7.2)[f]
	125	26	2/50 (4.9)	5/50 (12.2)*	7/50 (17.0)	10/50 (24.2)*
	250	18	2/50 (5.2)	4/50 (10.4)*	5/50 (13.0)	9/50 (23.1)*
	500	13*	4/50 (10.8)*	5/50 (13.9)*	3/50 (8.3)	8/50 (22.2)
	trend[+]	$P = 0.009$[g]	$P = 0.031$	$P = 0.043$	$P = 0.0516$N	$P = 0.093$
Female	0	34	NR	0/50 (0)[h,i]	1/50 (2)[g,h]	1/50 (2.2)[f]
	125	33		2/50 (4)	1/50 (2)	3/50 (6.9)
	250	30		1/50 (2)	1/50 (2)	2/50 (4.7)
	500	24		0/50 (0)	0/50 (0)	0/50 (0.0)
	trend[+]	$P = 0.028$[g]		NR	NR	$P = 0.537$N

Source: NTP 2011a.
N = negative trend, NR = not reported.
*$P \leq 0.05$ (compared with concurrent controls by Poly-3 test).
[+]Determined by Poly-3 trend test.
[a]Epididymis in all affected animals with other tissues variably affected.
[b]Percentage reported as the adjusted rate, which takes into account the survival rate and is calculated during the Poly-3 test analysis.
[c]Historical control ranges for inhalation studies and studies by all routes are 0%–6%.
[d]Historical control range: 0%–12% for inhalation studies and 0%–14% for studies by all routes.
[e]Historical control range: 2%–10% for inhalation studies and 0%–10% for studies by all routes.
[f]Historical control range: 6%–18% for inhalation studies and 0%–18% for studies by all routes.
[g]Survival analysis performed by life table trend test.
[h]Historical control range: not reported for inhalation studies and studies by all routes.
[i]Percentage reported as the overall incidence rate (non-Poly-3 adjusted).

In female mice, there were significantly increased incidences of benign and malignant lung tumors (alveolar/bronchiolar adenoma, alveolar/bronchiolar carcinoma, and combined) with positive dose-response trends for benign lung tumors (alveolar/bronchiolar adenoma) and combined groups. Some females in the 250-ppm group had multiple adenomas and some females in all of the exposed groups had multiple carcinomas. Based on positive pairwise comparisons, positive trend data for adenoma and highly significant trend data for combined, and tumor incidences outside of historical control ranges, these results are considered to be exposure related. There was no evidence of neoplastic lesions in male mice (Table 4-4).

Table 4-4. Lung tumors observed in B6C3F$_1$ mice exposed to 1-bromopropane by inhalation for 2 years

Sex	Conc. (ppm)	Number of mice surviving to study termination	Lung tumors (% incidence)[a]		
			Alveolar/ bronchiolar adenoma	Alveolar/ bronchiolar carcinoma	Combined
Male	0	37	6/50 (13.3)[c]	8/50 (17.8)[c]	13/50 (28.3)[c]
	62.5	33	5/50 (11.5)	7/50 (15.9)[b]	12/50 (27.3)
	125	32	4/49 (9.0)	10/49 (22.0)[b]	14/49 (30.8)
	250	36	5/49 (11.9)[b]	10/49 (24.3)[b]	15/49 (35.7)
	trend[+]	P = 0.934[d]	P = 0.476N	P = 0.209	P = 0.225
Female	0	36	1/50 (2.2)[e]	0/50 (0)[f]	1/50 (2.2)[g]
	62.5	40	6/50 (12.8)	7/50 (14.9)**	9/50 (19.2)**
	125	37	4/50 (8.9)	5/50 (11.1)*	8/50 (17.8)*
	250	42	10/50 (20.8)**	4/50 (8.5)	14/50 (29.2)***
	trend[+]	P = 0.363N[d]	P = 0.007	P = 0.277	P < 0.001

Source: NTP 2011a.
N = negative trend.
*$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$ (compared with concurrent controls by Poly-3 test).
[+]Trend of tumor incidence compared with the overall change in exposure levels by Poly-3 trend test.
[a]Number of animals with tumors (includes multiple) (Poly-3 estimated neoplasm incidence percentage after adjustment for intercurrent mortality).
[b]Incidence of mice with multiple lung tumors - adenoma: 0/50, 0/50, 0/50, 2/49 and carcinoma: 0/50, 2/50, 1/50, 1/50.
[c]Historical control range: not reported for inhalation studies and studies by all routes.
[d]Survival analysis performed by life table trend test.
[e]Historical control range: 2%–12% for inhalation studies and 0%–12% for studies by all routes.
[f]Historical control range: 0%–6% for inhalation studies and 0%–12% for studies by all routes.
[g]Historical control range: 2%–12% for inhalation studies and 2%–18% for studies by all routes.

As mentioned in Section 4.1.1, an inflammatory response was observed in rats, which could potentially be related to tumor development; however, the inflammatory response did not correlate with tumorigenicity. Chronic active and chronic suppurative inflammation were observed in the respiratory tract of both sexes of rats; however, incidences of lung and nasal tumors were not increased. In contrast, 1-bromopropane did cause lung tumors in male mice, but no chronic suppurative or chronic active inflammation of the respiratory tract was reported for either male or female mice.

4.3 NTP level of evidence conclusion

These data meet the Report on Carcinogens criteria for sufficient evidence of carcinogenicity in experimental animals based on an increased incidence of tumors in rats and mice, at multiple tissue sites, and the occurrence of rare tumors. This conclusion is based on exposure-related neoplastic lesions in the skin of male rats, large intestines of male and female rats, and lung of female mice.

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5 Mechanistic Data and Other Relevant Effects

The purpose of this section is to review data that are relevant for identifying and evaluating the potential mechanisms of action for the carcinogenic effects discussed in Section 4. Data reviewed in this section include the following: (1) genetic and related effects (Section 5.1 with data tables in Appendix D), (2) relevant toxicological effects (Section 5.2 and Appendix E), (3) mechanistic considerations (Section 5.3), and (4) carcinogenic effects of metabolites and analogues (Section 5.4).

5.1 Genetic and related effects

1-Bromopropane has been tested in several short-term assays to evaluate potential induction of mutagenic or other genotoxic effects. The database of genotoxicity studies includes DNA and protein adducts (Section 5.1.1) *in vitro* studies in bacteria (Section 5.1.2) and in mammalian cells (Section 5.1.3), and *in vivo* studies in rodents (Section 5.1.4) and in 1-bromopropane–exposed workers (Section 5.1.5). Genotoxicity studies are also available on some metabolites of 1-bromopropane (Section 5.1.6). An overall assessment of the genotoxicity of 1-bromopropane is presented in the final section (Section 5.1.7). Data tables for genotoxicity studies discussed in Section 5.1 are provided in Appendix D.

5.1.1 *DNA and protein adducts*

No published data were identified for 1-bromopropane DNA adducts. However, DNA adducts are formed by some 1-bromopropane metabolites (see Section 5.1.5), and the N^7-guanine DNA adduct was formed when 2-bromopropane was incubated with 2'-deoxyguanosine (Zhao *et al.* 2002) (see Section 5.4.2).

Although no *in vivo* studies of 1-bromopropane DNA adducts were identified, 1-bromopropane can form covalent adducts with protein *in vivo* (binding to sulfhydryl groups). One study measured *S*-propylcysteine (PrCys) adducts with globin and neurofilaments in rats after inhalation exposure (Valentine *et al.* 2007). Rats exposed to 1-bromopropane for two weeks at 0 to 800 ppm had a statistically significant linear dose response for PrCys globin and neurofilament adducts; exposure to 50 ppm for 8 hours/day, 5 days/week for 4 weeks produced a linear accumulation of PrCys globin adducts. Although there are very few data, DNA and protein adducts could be involved in 1-bromopropane–induced toxicity and carcinogenicity (see Section 5.3).

Valentine *et al.* (2007) measured *S*-propylcysteine globin adducts in 26 female factory workers in China who were exposed to 1-bromopropane by inhalation and possibly by skin contact. Controls were age-matched workers from a Chinese beer factory. Exposure to 1-bromopropane was assessed via individual “passive” (diffusion) samplers, and exposure levels ranged from 0.34 to 49.2 ppm for the workers who gave blood samples and 0 to 170.54 ppm for the workers who gave urine samples. There was a significant increase in the *S*-propylcysteine adducts measured in the globin of exposed workers (1.52 pmol/mg globin) over controls (0.11 pmol/mg globin). The level of urinary *N*-acetyl-*S*-(*n*-propyl)-L-cysteine (AcPrCys) increased with increasing exposure concentrations.

5.1.2 In vitro *studies in bacteria*

1-Bromopropane has been tested *in vitro* to evaluate mutagenic effects in bacterial strains of *Salmonella typhimurium* and *Escherichia coli*. Results of the mutagenicity studies of 1-bromopropane in bacteria are summarized in Appendix D, Table D-1.

1-Bromopropane was reported to be mutagenic in a dose-dependent manner in two tester strains: TA100 and TA1535, when the *S. typhimurium* assay was modified by using a closed chamber specifically designed for testing volatile substances (Barber *et al.* 1981). In this study, the authors compared the mutagenic potency of 10 volatile halogenated alkane solvents in the standard assay versus a closed-chamber assay. They reported that while only 2 of the solvents were positive in the standard assay (1-bromopropane was negative), 7 of the 10 substances, including 1-bromopropane, were positive in the closed system. In the closed-system assay, results were similar both in the absence and presence of metabolic activation (S9), indicating that 1-bromopropane is a direct-acting mutagen.

In standard test assays, in two independent laboratories, 1-bromopropane was reported to be non-mutagenic at doses tested up to 3,333 µg/plate; higher doses (to 10,000 µg/plate) were tested but were too toxic to evaluate (NTP 2011a). In addition, there were no mutagenic effects with S9 (prepared from Aroclor 1254-induced livers of rat or hamster) metabolic activation added to the culture at 10% or 30%. These studies were conducted in an open system, so the volatility of 1-bromopropane could have lowered the amount that the bacteria were exposed to. The observation of toxicity at high treatment doses indicated that exposure to 1-bromopropane did, in fact, occur, but it is unclear what the actual exposure levels were to the bacteria. The Barber study reported mutagenicity at lower doses using a modified closed system protocol; the treatment concentration was determined by using gas chromatography to measure 1-bromopropane in water placed in the chamber rather than by the amount of chemical added to the culture plate. This study also reported mutagenic effects for several other volatile substances that were previously reported as non-mutagenic when tested in the standard protocol bacterial assay. 1-Bromopropane was not mutagenic in *S. typhimurium* in several strains, both with and without S9, in two unpublished studies reviewed in NTP 2003 (Elf Atochem 1994, Kim *et al.* 1998). The NTP description of the Elf Atochem study noted that the cultures were incubated in closed stainless steel chambers but other important details, such as protocol modifications for sample preparation and treatment with a volatile substance, were not specified. In addition, other specific details were not provided in the NTP review of these studies (e.g., numbers of revertant colonies in either study, as well as cytotoxicity observations, solvent specification, and incubation conditions in the Kim *et al.* study), which makes it difficult to evaluate the discrepancy between these and the Barber *et al.* study results.

In summary, the data indicate that 1-bromopropane is a direct-acting mutagen in *S. typhimurium*, because similar findings were observed both with and without the addition of metabolic activation, in the only reported study that used appropriate methodology (treatment and incubation in a closed chamber) for testing a volatile substance.

5.1.3 In vitro *studies in mammalian cells*

Available *in vitro* studies suggest that 1-bromopropane induces mutations and DNA damage in mammalian cells. Two studies were identified that utilized mammalian cells *in vitro* to assess DNA damage of 1-bromopropane in human leukocytes and mutagenicity in mouse lymphoma cells (see Appendix D, Table D-2). The comet assay showed that *in vitro* exposure to the highest dose of 1-bromopropane in human leukocytes induced an increase in DNA damage as measured by comet tail moment but no increase was observed for lower doses (Toraason *et al.* 2006). In the same study, the temporal response to high-dose 1-bromopropane treatment was assessed using the comet assay, and DNA damage was significantly increased after both 4- and 8-hour exposures; DNA damage was higher after 8 hours compared with 4 hours. Toraason *et al.* also reported a dose-dependent increase in the percentage of apoptotic cells in 1-bromopropane–treated human leukocytes. 1-Bromopropane induced mutations at the thymidine kinase locus in the L5178Y mouse lymphoma cell assay, both with and without the addition of S9 metabolic activation (Elf Atochem 1996 as cited in NTP 2003a).

5.1.4 In vivo *studies in rodents*

The micronucleus assay was used to evaluate the potential effects of a three-month exposure of up to 500-ppm 1-bromopropane in male and female $B6C3F_1$ mice by inhalation (NTP 2011a). No increases in the frequencies of micronucleated normochromatic erythrocytes were reported for either sex of mice. In addition, two unpublished studies, reviewed by NTP (2003a), also reported that micronuclei were not increased in mice treated by i.p. injection or in rats exposed by inhalation to 1-bromopropane (Kim *et al.* 1998 and Elf Atochem 1995, both cited in NTP 2003a). (See Appendix D, Table D-3 for findings from *in vivo* studies in rodents.)

Dominant lethal mutation assays were negative in ICR mice (Yu *et al.* 2008) and in Sprague-Dawley rats (Saito-Suzuki *et al.* 1982) as shown in Appendix D, Table D-3. Male ICR mice were administered 1-bromopropane by i.p. injection while male Sprague-Dawley rats were given five consecutive daily doses in olive oil by oral gavage prior to mating with untreated females. The dominant lethal mutation assay identifies germ-cell mutagens by measuring a chemical's ability to penetrate gonadal tissue and produce embryonic death via chromosomal breakage in parent germ cells. Limitations for evaluating genotoxicity using this assay are that it does not detect somatic mutations and, because the spontaneous mutation frequency is high, the assay may have limited sensitivity for detection of small increases in induced mutation frequency (Singer *et al.* 2006). The study in rats also tested four other structurally related halogenated 3-carbon compounds that have a similar structure to a known mutagen, 1,2-dibromo-3-chloropropane (DBCP). Only 1,2,3-tribromopropane and DBCP induced dominant lethal mutations; the authors suggested that in order for propanes to induce dominant lethal mutations, they should have bromine or chlorine on each carbon atom and 2 of the 3 halogen atoms should be bromine.

5.1.5 *Studies in exposed workers*

The comet assay was used to assess DNA damage (strand breaks) in peripheral blood leukocytes from 64 workers (18 males and 46 females) exposed occupationally to

1-bromopropane (Toraason *et al.* 2006) at two facilities (designated as A and B) that utilized spray adhesives containing 1-bromopropane. There was no unexposed population so the workers were divided into higher-exposure (sprayer) and lower-exposure groups (non-sprayers) (see Appendix D, Table D-4).

In analysis by facility (A and B) and job type (sprayer and non-sprayer), no clear exposure-response patterns were observed. DNA damage (as measured by tail moment) in leukocytes from sprayers were numerically higher for both start- and end-of-workweek samples than non-sprayers but none of the increases were statistically significant and sprayers at Facility B (lower-exposure facility) had higher measures of DNA damage than sprayers at Facility A (higher-exposure facility) at the start, but not at the end, of the work week. No exposure-response patterns were observed for DNA damage as assessed by tail moment dispersion coefficient.

Multivariate analyses were also performed that evaluated the association between DNA damage (start-of-workweek and end-of-workweek comet tail moment and dispersion coefficients) and three 1-bromopropane exposure indices – 1-bromopropane TWA levels, and serum and urinary bromide concentrations – in models that controlled for gender, age, smoking status, facility, and two DNA polymorphisms (GSTM1 and GSTT1). For each of the three exposure indices, both linear regression models using log-transformed exposure indices and exposure quartiles analyses were performed. Both start-of-workweek and end-of-workweek comet tail moments in leukocytes were significantly associated with serum bromide quartiles; end-of-workweek values were also significantly associated with 1-bromopropane TWA quartiles. Although not statistically significant, all of the other associations between 1-bromopropane exposure indices and DNA damage were positive, with the exception of the end-of-workweek urinary bromide. The strengths of this study are that the assessment of exposure to workers was at the individual level and that these workers were exposed to a wide range of levels of 1-bromopropane, which allowed for the evaluation of exposure-response relationships. Multivariate analyses were considered to be more informative than the analysis by job and facility. Limitations to this study include small numbers of exposed workers, no unexposed controls, and multiple comparisons.

These results provided limited evidence that 1-bromopropane causes DNA damage *in vivo*.

5.1.6 *Genotoxic effects of 1-bromopropane metabolites*

The genotoxic effects of several known or postulated metabolites of 1-bromopropane have been evaluated in numerous *in vitro* and *in vivo* studies. Two reviews by the International Agency for Research on Cancer (IARC) provided most of the information for glycidol (IARC 2000) and propylene oxide (IARC 1994) and primary studies were used to update or supplement this information (see Appendix D, Table D-5).

Both glycidol (known metabolite in rats) and propylene oxide (postulated metabolite) are mutagenic in bacteria, yeast, *Drosophila*, and mammalian cells; they are direct-acting mutagens, as the addition of metabolic activation did not change the response. Both metabolites have been shown to form DNA adducts, and both induce DNA damage and

chromosomal damage *in vitro* in rodent and human cells. Available *in vivo* test results for glycidol indicate that it induces micronucleus formation but not chromosomal aberrations (CA) in the mouse. Studies of propylene oxide for chromosomal damage reported positive responses in mouse bone marrow for micronucleus induction and chromosomal aberration tests, as well as DNA damage in the sister chromatid exchange (SCE) assay, but results with monkey lymphocytes for both CA and SCE were negative. In occupationally exposed propylene oxide workers, DNA damage was induced in the SCE assay, and both DNA and hemoglobin (protein) adducts were formed. Propylene oxide has also been shown to bind to DNA in rodents and to hemoglobin in rodents, dogs, and monkeys. Other 1-bromopropane metabolites have been shown to be direct-acting mutagens and to induce DNA damage in bacteria. 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*.

5.1.7 *Synthesis of results*

Studies *in vivo* show that 1-bromopropane can covalently bind to protein in exposed rats and occupationally exposed workers. The available data provide some support that 1-bromopropane is genotoxic as it induced mutations in bacterial and mammalian cells and DNA damage in human cells. There is limited evidence that DNA damage was induced in leukocytes from 1-bromopropane–exposed workers. 1-Bromopropane did not induce chromosomal damage in exposed rodents (micronucleus induction assay) or gene-cell mutations (dominant lethal mutation assay).

Table 5-1. Summary of 1-bromopropane genotoxicity information

Effect	*In vitro*	*In vivo*	
		Rodents	Humans
Mutation			
Bacteria	±[a]		
Mammalian cells	+	NT	NT
DNA damage	+	NT	+
Micronuclei induction	NT	–	NT
Dominant lethal mutation	NT	–	NT

+ = positive, ± = both positive and negative, – = negative.
NT = not tested.
[a]Positive in the only study whose design was appropriate for testing volatile chemicals.

Several known or postulated metabolites of 1-bromopropane have been identified as mutagens and two, glycidol and propylene oxide (proposed), were shown to cause chromosomal and DNA damage in cultured mammalian cells. Both metabolites caused chromosomal damage in cells from rodents exposed *in vivo*, and propylene oxide induced DNA damage in cells from exposed workers (Table 5-2). Three other 1-bromopropane metabolites (α-bromohydrin, 3-bromo-1-propanol, and 1-bromo-2-propanol) were mutagenic or caused DNA damage in bacteria (Table 5-2).

Table 5-2. Summary of genotoxicity data for 1-bromopropane metabolites[a]

Effect Metabolite	*In vitro* (cell type[b])	*In vivo* (mammals)	Humans (Epidemiology studies)
DNA adducts			
Glycidol	+ (mammal)	NT	NT
Propylene oxide	+ (bacteria, mammal)	+ (rodents, dogs)	+
Mutation			
Glycidol	+[c]	NT	NT
Propylene oxide	+[c]	– (germ cell)	NT
α-Bromohydrin	+ (bacteria)	NT	NT
3-Bromo-1-propanol	+ (bacteria)	NT	NT
1-Bromo-2-propanol	NT	NT	NT
DNA damage			
Glycidol	+[d]	NT	NT
Propylene oxide	+[d]	NT	+
α-Bromohydrin	NT	NT	NT
3-Bromo-1-propanol	+ (bacteria)	NT	NT
1-Bromo-2-propanol	+ (bacteria)	NT	NT
Chromosomal damage			
Glycidol	+ (mammal, human)	± (rodents)	NT
Propylene oxide	+ (mammal, human)	+ (rodents); – (monkeys)	Inc

NT = not tested; Inc = inconclusive, + = positive, – = negative, ± = positive and negative results.
[a]Does not include findings from insect studies or gene conversion studies in yeast.
[b]Positive in bacteria, yeast, mammalian cells, and human cells.
[c]Positive in bacteria, yeast, and mammalian cells.
[d]Positive in bacteria, mammalian cells, and human cells.

5.2 Relevant toxicological effects

1-Bromopropane has caused neurological, developmental, reproductive, immunological, and hepatotoxic effects in rodents and neurological effects in humans (Lee *et al.* 2007a, Lee *et al.* 2010a, Lee *et al.* 2010b, NTP 2003a, 2011a). Studies on toxic effects were reviewed (see Appendix E) to determine whether they could inform potential mechanisms of carcinogenicity. Several studies indicate that metabolic activation and glutathione depletion are important factors for many of the toxic effects observed in rodents. Appendix E provides a brief review of the toxic effects that have been linked to metabolic activation and/or glutathione depletion and oxidative stress and other alterations, and provides background information for Section 5.3, which discusses these mechanisms as they relate to carcinogenicity.

5.3 Mechanistic considerations

The biological events associated with chemically induced cancer are not completely understood even for chemicals that have been extensively studied and are known to cause cancer in humans (e.g., benzene and arsenic) (Guyton *et al.* 2009). It is important to recognize that chemicals can act through multiple toxicity pathways and mechanisms to induce cancer or other health effects, and the relative importance of the various pathways may vary with life stage, genetic background, and dose. Thus, it is unlikely that for any

chemical a single mechanism or mode of action will fully explain the multiple biological alterations and toxicity pathways that can cause normal cells to transform and ultimately form a tumor.

Although no studies were identified that were specifically designed to investigate possible modes of action for 1-bromopropane–induced carcinogenesis, the available data indicate that metabolic activation, genetic damage, and oxidative stress from glutathione depletion are important factors. As discussed in the previous section, these factors were linked to several of the primary non-neoplastic toxic effects of 1-bromopropane, including immunosuppression, neurotoxicity, reproductive toxicity, and hepatotoxicity. Other factors that have been associated with carcinogenesis and may be relevant for 1-bromopropane are discussed and include immune-response modulation, altered cell signaling and gene expression, inflammation, and cytotoxicity and compensatory cell proliferation.

5.3.1 *Metabolic activation and genotoxicity*

As mentioned above, there is some evidence that 1-bromopropane and its metabolites are mutagenic and genotoxic (see Section 5.1). Metabolism of many halogenated hydrocarbons results in the formation of highly reactive oxidative intermediates that can alkylate proteins and nucleic acids (Morgan *et al.* 2011). Reactive metabolites of 1-bromopropane include bromoacetone (1-bromo-2-propanone), glycidol, propylene oxide (proposed), and α-bromohydrin (see Section 5.1.6). Bromoacetone and other α-bromoketones have been shown to disrupt enzymatic processes by alkylating trypsin at histidine residues or glutathione-*S*-transferases at cysteine residues (Beeley and Neurath 1968, Mitchell *et al.* 1998). Garner *et al.* (2006) reported that rats pretreated with ABT, a potent inhibitor of CYP, had a 10-fold reduction in hepatic radiochemical content (4.1 to 0.46 μg equivalents per gram of tissue) suggesting that oxidative metabolism leads to more reactive species.

5.3.2 *Oxidative stress*

Oxidative stress due to cellular glutathione depletion could contribute to the carcinogenicity of 1-bromopropane (Morgan *et al.* 2011). Although no studies were identified that directly investigated the possible role of glutathione levels and oxidative stress in 1-bromopropane–induced carcinogenicity, several studies have shown evidence that exposure to 1-bromopropane causes toxic effects in the liver and in the reproductive and nervous systems of mice and rats that are associated with glutathione depletion and oxidative stress (Huang *et al*. 2011, Lee *et al.* 2007a, Lee *et al*. 2005a, Lee *et al.* 2005b, Lee *et al.* 2010a, Lee *et al.* 2007b, Lee *et al.* 2010b, Liu *et al.* 2009, Liu *et al.* 2010, Subramanian *et al*. 2012). A dose-dependent depletion of glutathione by 1-bromopropane was reported in mice (Lee *et al.* 2007a, b), and a role for Cyp2e1 metabolism in this effect was indicated by a greater depletion of glutathione in wild-type mice than in Cyp2e1 knockout mice (Garner *et al.* 2007). Oxidative stress in rodents exposed to 1-bromopropane is consistent with dose-dependent increases in oxidative stress markers (ROS, RNS) in rat cerebellum (Subramanian *et al.* 2012), increased lipid peroxidation in male mice (Liu *et al.* 2010), and altered expression of oxidative stress genes (NQO1 and HO-1) in mice (Liu *et al.* 2009, Liu *et al.* 2010) (for more information, see Appendix E).

Glutathione conjugation is generally regarded as a detoxification mechanism (Morgan *et al.* 2011). Most of the urinary metabolites of 1-bromopropane are derived from glutathione conjugates, thus, chronic exposure could produce levels of metabolites that exceed the amount of glutathione available for conjugation. Glutathione levels also may be depleted by oxidative metabolites that inhibit enzymes required for glutathione synthesis. Liu *et al.* (2009) also reported lower hepatocellular glutathione-*S*-transferase (GST) activity in susceptible mouse strains exposed to 1-bromopropane. Lower GST activity could reduce glutathione conjugation and increase toxicity. Huang *et al.* (2011) reported differential expression of several proteins in the hippocampus of rats exposed to 1-bromopropane that support the hypothesis that oxidative stress plays a role in 1-bromopropane–induced damage. These proteins included HSP60, GRP78, DJ-1, GSTA3, and GSTP1. The proteins HSP60, GRP78, GSTA3, and GSTP1 were up-regulated after 1-bromopropane exposure. HSP60 is a mitochondrial matrix protein induced by various kinds of stresses and GRP78 is an endoplasmic reticulum-resident molecular chaperone that suppresses oxidative stress. GSTA3 and GSTP1 belong to a family of detoxification enzymes that also protect against oxidative stress. DJ-1 has been shown to prevent oxidative stress in age-related neurodegeneration and was down-regulated after 1 week of exposure. Thus down-regulation of DJ-1 could result in increased oxidative stress.

5.3.3 *Immunosuppression and other factors*

Immune-response modulation, cell signaling, altered gene expression, inflammation, and cytotoxicity and compensatory cell proliferation are other key events that have been associated with carcinogenesis. Recent studies have shown that 1-bromopropane causes immunosuppression in rodents (Anderson *et al.* 2010, Lee *et al.* 2007a, Lee *et al.* 2007b). In particular, deleterious effects on T-cell numbers and subpopulations were reported. Since T-cells play an important role in detecting and eliminating tumor cells, a compromised immune system could facilitate tumor progression (Töpfer *et al.* 2011). Anderson and Rice (1987) demonstrated that athymic nude mice that do not have T-cells were more sensitive to skin tumorigenesis that euthymic mice. In addition, data from genetic, disease, and drug-induced immunosuppression in humans have consistently shown that immunosuppression is associated with an increased risk of skin tumors and certain other cancers (DePry *et al.* 2011, Kuschal *et al.* 2012, Weaver 2012). However, a possible role of immunosuppression in 1-bromopropane–induced skin cancer in rodents has not been described.

Chronic inflammation was one of the key events associated with various carcinogenic modes of action (Guyton *et al.* 2009). In a series of studies, Han *et al.* (2008, 2012) investigated the effect of 1-bromopropane on nitric oxide and proinflammatory cytokine production and the role of NF-κB in 1-bromopropane–mediated inducible nitric oxide synthases (iNOS) and proinflammatory cytokine expression in mouse macrophages. iNOS catalyzes the formation of nitric oxide and may be an important mediator of carcinogenesis in some circumstances. Overexpression of iNOS has been described in human cancer, and tumor-associated production of nitric oxide by iNOS may elevate tumor progression. 1-Bromopropane caused proinflammatory changes in mouse macrophages including upregulation of iNOS and cytokines (IL-1β, IL-6, and TNF-α),

enhanced the production of prostaglandin E_2 (PGE_2), and dose-dependently increased cyclooxygenase-2 (COX-2) protein and mRNA levels. Increased PGE_2 production may contribute to the tumorigenic process through effects on cell proliferation, apoptosis, and vascular growth. Thus, 1-bromopropane exposure induced a variety of effects, including increased levels of proinflammatory cytokines, increased macrophage activation, and over expression of COX-2, that collectively support the assertion that 1-bromopropane induces inflammation.

Exposure-related increased incidences of chronic respiratory tract inflammation (nasal cavity, larynx, and trachea) occurred in rats, and increased incidences of cytoplasmic vacuolization in the nasal cavity, larynx, trachea, and bronchiolar epithelium occurred in mice (NTP 2011a). Bronchiole regeneration also was significantly increased in exposed male and female mice. These lesions are indicative of local irritant effects, but there was no apparent association with carcinogenic effects because lung tumors occurred only in female mice, and upper respiratory tract tumors were not increased in mice or rats.

There is also some evidence from neurotoxicity studies in rodents that 1-bromopropane causes hyperexcitability of the hippocampus due to dysfunction of γ-aminobutyric acid (GABA) feedback inhibition (Fueta *et al.* 2004, Fueta *et al.* 2002a, Mohideen *et al.* 2009) (see Appendix E). Although a primary role of GABA is as an inhibitory neurotransmitter in the adult mammalian nervous system, there is substantial evidence that it is involved in the proliferation, differentiation, and migration of several cell types, including cancer cells (Watanabe *et al.* 2006). Young and Bordey (2009) reported that GABAergic signaling and its control over proliferation is widespread through peripheral organs containing adult stem cells (e.g., liver, pancreas, kidney, intestine, prostate, testis, and ovary). GABA is a strong inhibitor of cell proliferation; however, it is possible that altered GABAergic signaling in tumors cells leads to abnormal proliferation. Tatsuta *et al.* (1990) demonstrated that GABA or a $GABA_B$ receptor agonist inhibited *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine-induced gastric carcinogenesis in Wistar rats. Maemura *et al.* (2003) examined the expression of GABA in human intramucosal colonic tumors. Tissue samples included 56 protruded-type colonic tumors that were classified as adenocarcinoma, adenoma with severe atypia, or adenoma with mild to moderate atypia. The level of GABA expression was proportional to the degree of atypia in colonic neoplasms and was proposed as a possible tumor marker. Schuller *et al.* (2008) reported that GABA may have tumor suppressor function in small airway epithelia and that downregulation of GABA by nicotine-derived carcinogens may contribute to lung cancer in smokers.

5.3.4 *Sex differences in chemical carcinogenesis*

Sex differences were observed for 1-bromopropane–induced tumors in both rats and mice in the NTP experimental animal studies, as described in detail in Section 4. While both sexes of rats developed large intestinal tumors, the incidence was higher in females; skin tumors were induced in male rats, but the findings were only equivocal in females. In mice, lung tumors were observed in females but not in males.

In a recent survey of 278 chemicals identified as carcinogenic in rats in the NTP 2-year bioassay, 201 exhibited statistically significant sex differences ($P < 0.05$) in at least one

non-reproductive organ (Kadekar *et al.* 2012) with males showing a dominance: tumors were induced in non-reproductive organs in male rats for 130 chemicals and in females for 59. Induction of both skin tumors and tumors of the large intestine were significantly greater in male rats ($P < 0.05$), which is consistent for the skin tumors but not the large intestinal tumor findings for 1-bromopropane. However, this general pattern of increased incidence in males is based on a review of a large database of multiple chemicals, which may induce tumors via more than one mechanism. Greater male susceptibility to cancer has also been noted in surveys of human cancers (Cook *et al.* 2009, Edgren *et al.* 2012); however, no clear explanation for the male dominance in rats or humans was apparent.

As discussed in Section 2.2.4 and Appendix E, CYP2E1 and glutathione *S*-transferase (GST) are important in 1-bromopropane metabolism and toxicity and thus probably play a role in carcinogenicity. There is some evidence that there are sex differences in enzymatic activity in 1-bromopropane–exposed rats. *p*-Nitrophenol hydroxylase (*p*NPH), associated with CYP2E1 expression, and NADPH b_5 reductase levels increased in a dose-dependent fashion and were consistently higher in male than female rats for the control treatment and all doses tested. GST and lipid peroxide (LPO) levels also increased with increasing dose; in general, GST levels were higher in males, however LPO levels were higher in females (Kim *et al.* 1999b). It is unclear how these sex differences in enzymatic activity translate to sex differences in tumor incidence in 1-bromopropane–exposed rats; some of the differences would suggest a potential increase in reactive oxygen species or oxidative damage (CYP2E1 in males), while others suggest a decrease (e.g., LPO*). It is also not known if sex differences occur similarly at other tissue sites.

In mice, an evaluation of the NTP 2-year bioassay historical control database indicates that there is a sex difference in the spontaneous incidence of lung tumors: 32% of males had tumors, compared with 8% of females (see NTP database http://ntp.niehs.nih.gov/go/datasearch). No studies looking at gender differences specific for 1-bromopropane exposure in mice were identified; however, normal CYP2E1 expression measured in mice was found to vary by tissue type as well as by sex (Chanas *et al.* 2003). Expression was significantly greater in the kidneys of males and slightly higher (non-significant) in lungs of females, but no sex difference was observed in the liver.

Overall, 1-bromopropane caused tumors at different sites in male and female rats and mice, and some data from the NTP database for chemical carcinogenesis were consistent with the observed pattern; however, there is limited information on sex differences in 1-bromopropane metabolism or other mechanistic data.

5.4 Carcinogenicity of 1-bromopropane metabolites and analogues

While 1-bromopropane and other halogenated hydrocarbons are generally stable compounds, they can undergo metabolism or bioactivation that results in toxic effects, usually subsequent to dehalogenation, i.e., their toxicity is generally associated with the reactive, electrophilic metabolites formed from the carbon skeleton rather than with the halide ion released from the molecule (Anders 1983).

5.4.1 *Metabolites*

Glycidol is the only urinary metabolite of 1-bromopropane that has been tested for carcinogenicity; it is currently listed as *reasonably anticipated to be a human carcinogen* by the NTP (2011b). Propylene oxide, a proposed intermediate metabolite of 1-bromopropane, also is currently listed as *reasonably anticipated to be a human carcinogen* by the NTP (2011c). α-Bromohydrin is another reactive metabolite of 1-bromopropane, but it has not been tested for carcinogenicity.

Oral administration of glycidol caused benign and malignant tumors at multiple tissue sites in rats and mice (NTP 1990). Organs and tissues affected in rats included the oral mucosa, forestomach, glandular stomach, intestines, mammary glands, skin, *tunica vaginalis*, clitoral gland, thyroid gland, brain, and Zymbal gland. Tissues affected in mice included the mammary glands, forestomach, Harderian gland, lung, liver, skin, uterus, and urinary bladder. The tumor profile for glycidol was more varied than that for 1-bromopropane but there were some similarities. In particular, glycidol and 1-bromopropane induced mesothelioma in the *tunica vaginalis* covering the epididymis and testes, benign but rare intestinal tumors, and skin tumors in rats. Glycidol also induced lung tumors in male mice, while 1-bromopropane induced lung tumors in female mice. Glycidol also has induced immunosuppressive effects in mice (Guo *et al.* 2000).

Propylene oxide caused benign and malignant tumors in rats and mice at several tissue sites when administered by inhalation, stomach tube, or s.c. injection (IARC 1994). Rats developed nasal cavity, adrenal gland, forestomach, abdominal cavity, and mammary tumors. Mice developed nasal-cavity and injection-site tumors.

5.4.2 *Analogues*

1-Bromopropane is one member of the large class of halogenated alkanes, and chemical characteristics shared by these related molecules could be informative for the carcinogenicity of 1-bromopropane. In general, the presence of a halogen substituent on a carbon atom has an electron-withdrawing effect making the carbon atom more electrophilic, which increases the reactivity of the carbon atom (van Hylckama Vlieg and Janssen 2001). Among the halogens, bromine is recognized as a better leaving group than the smaller, more electronegative chlorine and fluorine atoms. Thus, halogenated, and particularly brominated, alkanes would be expected to more readily form activated intermediates that could covalently modify biological molecules. Activated intermediates may result from bioactivation by CYP. These bioactive (electrophilic) compounds can also be conjugated by the nucleophile, glutathione, a reaction catalyzed by glutathione-*S*-transferases (GSTs) (Anders 1982, 2001). Exposure of mice to 1-bromopropane causes hepatotoxicity and may be related to glutathione depletion associated with conjugate formation and subsequent formation of reactive oxygen species (see Section 5.2.3). Since glutathione is an important cellular defense mechanism against reactive oxygen species, reduced levels of glutathione can lead to oxidative stress, enhanced toxicity, and possibly carcinogenicity.

The nearest structural analogue for 1-bromopropane is 2-bromopropane, an isomer that has not been tested for carcinogenicity. However, 2-bromopropane has been studied in a number of genotoxicity assays. Similar to 1-bromopropane, 2-bromopropane caused

base-pair mutations in *Salmonella* strains TA100 and TA1535 (NTP 2003b) and DNA damage in cultures of rat Leydig cells (Wu *et al.* 2002), but did not induce chromosomal aberrations in Chinese hamster lung cells. In rodents, it induced micronucleus formation in embryos from pregnant mice exposed to 2-bromopropane by i.p. injection but did not cause micronuclei in bone marrow of adult rats exposed by i.p. injection. 2-Bromopropane also formed N^7-isopropyl guanine adducts (Zhao *et al.* 2002) and caused massive depurination (Sherchan *et al.* 2009a, Sherchan *et al.* 2009b). Unrepaired apurinic sites lead to lethality or base substitution errors. Although 2-bromopropane causes similar types of toxicities (neurological [Yu *et al.* 2001], hematological [Kim *et al.* 1999a], immunological [Anderson *et al.* 2010], and reproductive [NTP 2003b]), the primary metabolic products are different from those of 1-bromopropane.

Other analogues for 1-bromopropane are monobrominated, short-chain alkanes, such as bromomethane, bromoethane, 1-bromobutane, and 2-bromobutane. Bromomethane (methyl bromide) is classified by NIOSH as a potential occupational carcinogen (CDC 2010) and by IARC as Group 3, not classifiable as to its carcinogenicity in humans, but neither it nor the bromobutane isomers have been tested in 2-year bioassays by the NTP or reviewed for the Report on Carcinogens. Bromoethane has been tested in a 2-year bioassay by the NTP, and it is listed by IARC as Group 3; it has not been reviewed by NTP for the Report on Carcinogens. Bromoethane is classified by the American Conference of Governmental Industrial Hygienists as A3, confirmed animal carcinogen with unknown relevance to humans.

While the examination of the potential carcinogenicity of all members of the large class of halogenated alkanes is beyond the scope of this document, several halogenated alkanes (bromodichloromethane, carbon tetrachloride, chloroform, 1,2-dibromo-3-chloropropane, 1,2-dibromoethane (ethylene dibromide), 1,2-dichloroethane, dichloromethane, hexachloroethane, and 1,2,3-trichloropropane) are listed in the NTP Report on Carcinogens as *reasonably anticipated to be a human carcinogen* and classified by IARC as possible or probable carcinogens. In addition to the analogues described above, more than a dozen other halogenated alkanes have been reviewed by IARC and listed as Group 3. No mechanistic data were identified to suggest that these molecules would act by a common mechanism with 1-bromopropane and they are not discussed further here.

A search of the IARC website (www.iarc.fr) identified 12 additional halogenated alkanes that had been reviewed by IARC and placed in Group 3, i.e., not classifiable as to their carcinogenicity in humans. The majority of these molecules (bromoform [tribromomethane], chlorodibromomethane, chloroethane, chlorofluoromethane, 2-chloro-1,1,1,-trifluoroethane, 1,2-dichloropropane, methyl iodide, pentachloroethane, and 1,1,2-trichloroethane) were reported to have no epidemiological data relevant to their carcinogenicity and limited data in experimental animals. One other molecule (chlorodifluoromethane) also had limited data in experimental animals and data in humans were considered inadequate; the last two molecules (methyl chloride and 1,1,1-trichloroethane) had inadequate data in both humans and experimental animals. Two halogenated alkanes (1,1,1,2-tetrachloroethane and 1,1,2,2-tetrachloroethane) have been recently listed by IARC as Group 2B, possibly carcinogenic to humans, and are pending publication in Volume 106.

6 Overall Cancer Evaluation – Synthesis of Animal, Human, and Mechanistic Data

This section synthesizes the information from the animal and mechanistic studies and applies the RoC listing criteria to that body of knowledge to reach a preliminary listing recommendation. No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 1-bromopropane. As stated in Section 4, cancer studies in experimental animals identified 1-bromopropane–induced tumors in the intestine, skin, and lungs that met the RoC criteria for sufficient evidence of carcinogenicity in experimental animals. That assessment did not consider data on mechanisms of carcinogenesis. This section (1) briefly summarizes the assessment of the cancer studies in experimental animals (as reported in Section 4) and (2) discusses the data on mechanisms of carcinogenesis and metabolism of 1-bromopropane reported in Sections 2 and 5, including a synthesis of the information available from studies in humans. The RoC listing recommendation for 1-bromopropane follows the discussion.

6.1 Cancer studies in experimental animals

Inhalation exposure to 1-bromopropane increased the incidences of skin tumors (keratoacanthoma; keratoacanthoma and squamous-cell carcinoma combined; and keratoacanthoma, squamous-cell carcinoma, basal-cell adenoma, and basal-cell carcinoma combined) in male rats, large-intestine tumors (adenoma of the colon and rectum) in rats of both sexes, and lung tumors (alveolar/bronchiolar adenoma and carcinoma) in female mice. Increased incidences of skin tumors in male rats, intestinal tumors in female rats, and lung tumors in female mice were statistically significant and dose-related. The increased incidence of intestinal tumors in male rats, although not statistically significant, was considered to be of biological significance because of the rarity of this type of tumor (incidence of less than 0.2% in historical controls). The incidence of adenocarcinoma of the large intestine was increased in rats of both sexes after oral exposure to brominated methanes (bromodichloromethane or tribromomethane) and in male rats after exposure to glycidol, a metabolite of 1-bromopropane. Additional tumors that may have been related to 1-bromopropane exposure included malignant mesothelioma of the abdominal cavity and pancreatic islet tumors (adenoma) in male rats and skin tumors (keratoacanthoma, basal-cell adenoma, and basal-cell carcinoma combined) in female rats.

6.2 Mechanistic and other relevant data

No studies were found that evaluated mechanisms of carcinogenicity of 1-bromopropane at the tumor sites found in experimental animals (skin, large intestine, and lung). However, 1-bromopropane, either directly or via reactive metabolites, causes molecular alterations related to carcinogenicity, including genotoxicity, oxidative stress, glutathione depletion, immunosuppression, and inflammation (see Section 5.3 for details). These alterations, observed mainly *in vitro* and in toxicity studies in rodents, are relevant to possible mechanisms of carcinogenicity in humans and support the relevance of the cancer studies in experimental animals to cancer in humans.

The available studies suggest that both direct effects and metabolic activation are important in 1-bromopropane–induced carcinogenesis. There is some evidence that 1-bromopropane is directly genotoxic. It has been shown to bind to macromolecules, forming *S*-propylcysteine globin adducts in exposed animals and humans. It also caused mutations in bacteria (in the only reported study whose design was appropriate for testing a highly volatile chemical) and cultured mammalian cells with or without exogenous mammalian metabolic activation and DNA damage in cultured human cells without exogenous metabolic activation. In rodents exposed to 1-bromopropane *in vivo*, negative results were reported for the only two end points measured, micronucleus formation (in bone marrow or peripheral blood erythrocytes) and dominant lethal mutation. However, the dominant lethal mutation assay detects only germ-cell mutations and is generally regarded as relatively insensitive for the detection of mutagenic agents.

There is evidence suggesting that metabolic activation plays a role in the genotoxicity and toxicity of 1-bromopropane. Several potential reactive metabolites or proposed reactive intermediates have been identified in rodents, including glycidol and α-bromohydrin, and propylene oxide has been proposed as a metabolite (see Section 2.2). These compounds cause genotoxic effects *in vitro* (including DNA adduct formation, mutations, and DNA or chromosome damage). Glycidol and propylene oxide cause chromosome damage *in vivo* and are carcinogenic in experimental animals. Both chemicals are listed in the Report on Carcinogens as *reasonably anticipated to be human carcinogens*. These reactive and genotoxic metabolites may be responsible for at least some of the carcinogenic effects of 1-bromopropane. As with 1-bromopropane, oral exposure to glycidol caused rare tumors of the large intestine in rats, as did oral exposure to two halogenated alkane analogues of 1-bromopropane, tribromomethane and bromodichloromethane.

Chronic exposure to 1-bromopropane may produce levels of oxidative metabolites that exceed the capacity for glutathione conjugation or may inhibit enzymes required for glutathione synthesis. The resulting reduction in glutathione levels can lead to oxidative stress, increased toxicity, and carcinogenesis. Numerous studies on mechanisms of toxicity in rodents have shown that 1-bromopropane causes oxidative stress and glutathione depletion. Moreover, studies with Cyp2e1$^{-/-}$ knockout mice, cytochrome P450 inhibitors, or a glutathione synthesis inhibitor showed that this pathway (metabolic activation leading to oxidative stress from glutathione depletion) is involved in 1-bromopropane-induced toxicity (see Appendix E for details). Although no studies have evaluated the role of oxidative stress in 1-bromopropane-induced carcinogenicity, oxidative stress is a relevant mechanism for carcinogenicity in humans.

Other effects associated with 1-bromopropane that could be relevant to carcinogenesis include immunosuppression and inflammation. Recent studies in rodents have shown that 1-bromopropane causes immunosuppression, increased levels of proinflammatory cytokines, increased macrophage activation, and overproduction of cyclooxygenase 2. In addition, there is some evidence from neurotoxicity studies in rodents that 1-bromopropane causes reduced GABAergic feedback inhibition. Although GABA's primary role is as an inhibitory neurotransmitter in the adult mammalian nervous system,

there is substantial evidence that it is involved in the proliferation, differentiation, and migration of several cell types, including cancer cells.

Although the available data on 1-bromopropane metabolism, genotoxicity, and mechanisms of action in humans are limited, they provide some support for the relevance of the findings in experimental animals to humans. Data on human metabolism of 1-bromopropane suggest that metabolic pathways are similar in humans and experimental animals. Urinary mercapturic conjugates identified from workers exposed to 1-bromopropane were also reported as urinary metabolites in rodents, and CYP2E1, the major cytochrome P450 enzyme involved in 1-bromopropane metabolism, is produced in human lung and other tissues. Although it is likely that humans metabolize 1-bromopropane to reactive metabolites, no studies in humans have explored potential pathways leading to additional metabolites or likely intermediates identified from rodent or *in vitro* studies, such as propylene oxide, glycidol, and α-bromohydrin. Studies of 1-bromopropane-exposed workers have found *S*-propylcysteine adducts in globin and limited evidence of DNA damage in leukocytes. Case reports and epidemiological studies suggest that 1-bromopropane causes neurological effects, and studies in experimental animals have shown that glutathione depletion and oxidative stress play a role in this toxicity.

6.3 NTP listing recommendation

1-Bromopropane is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals. These studies found that exposure to 1-bromoproane caused tumors at several tissue sites in rats and mice. 1-Bromopropane, either directly or via reactive metabolites, causes molecular alterations that typically are associated with carcinogenesis, including genotoxicity, oxidative stress, and glutathione depletion. These alterations, observed mainly *in vitro* and in toxicity studies in rodents, are relevant to possible mechanisms of human carcinogenicity and support the relevance of the cancer studies in experimental animals to cancer in humans.

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Abbreviations

1-BP:	1-bromopropane
3-BPA:	3-bromopropionic acid
ABT:	1-aminobenzotriazole
ACGIH:	American Conference of Governmental Industrial Hygienists
AcPrCys:	*N*-acetyl-*S*-(*n*-propyl)-L-cysteine
ADD:	average daily dose
ALT:	serum alanine aminotransferase, alanine aminotransferase
ANOVA:	analysis of variance
AST:	serum aspartate aminotransferase, aspartate aminotransferase
atm:	atmosphere
BSO:	DL-buthionine (S,R)-sulfoximine
CDC:	Centers for Disease Control and Prevention
CERHR:	Center for the Evaluation of Risks to Human Reproduction
cm^2:	square centimeter
COX-2:	cyclooxygenase-2
DBCP:	1,2-dibromo-3-chloropropane
DLMI:	dominant lethal mutation index
DLMR:	dominant lethal mutation rate
EQ:	exposure quartiles model
FDA:	Food and Drug Administration
FR:	*Federal Register*
ft:	feet
GC/MS:	gas chromatography/mass spectrometry

GSH:	glutathione
GSSH:	oxidized glutathione
GST:	glutathione-*S*-transferase
HHE:	Health Hazard Evaluation
HHS:	Department of Health and Human Services
HIC:	highest ineffective concentration
HID:	highest ineffective dose
HO-1:	heme oxygenase-1
hr:	hour
in:	inch
i.s.:	internal standard
iNOS:	inducible nitric oxide synthases
L:	liter
LEC:	lowest effective concentration
LED:	lowest effective dose
m^3:	cubic meter
mg:	milligram
MMWR:	Morbidity and Mortality Weekly Report
MN:	micronuclei
mol:	mole
NCE:	normochromatic erythrocyte
NCTR:	National Center for Toxicological Research
ND:	not done
NIC:	Notices of Intended Changes
NIEHS:	National Institute of Environmental Health Sciences

NIH:	National Institutes of Health
NIOSH:	National Institute for Occupational Safety and Health
nPB:	*normal* propyl bromide
NQO1:	NAD(P)H:quinone oxidoreductase
NR:	not reported
NS:	non-sprayer
NTP:	National Toxicology Program
OHAT:	Office of Health Assessment and Translation
OSHA:	Occupational Safety and Health Administration
PBZ:	personal breathing zone
PCE:	polychromatic erythrocyte
PEL:	permissible exposure limit
PERC:	tetrachloroethylene (perchloroethylene)
PGE_2:	prostaglandin E_2
ppm:	parts per million
PrCys:	*S*-propylcysteine
r:	correlation coefficient
RoC:	Report on Carcinogens
RTG:	relative total growth
s.c.:	subcutaneous
SD:	standard deviation
SNAP:	Significant New Alternatives Policy
Solv.:	aerosol solvents use
SP:	sprayer
TBARS:	thiobarbituric acid-reactive substance

TLV:	threshold limit value
TM:	tail moment
TMD:	tail moment dispersion coefficient
TWA:	time weighted average
VOC:	volatile organic compound
µg:	microgram

Glossary

Aerosol solvent: A cleaning agent stored in a metal container (i.e., a hand-held can) under pressure and then released through a push-button valve or nozzle as a suspension of particles in air.

Apoptosis: Cell deletion by fragmentation into membrane-bound particles, which are phagocytosed by other cells.

Aroclor 1254-induced liver: Liver tissue treated with the polychlorinated biphenyl mixture Aroclor 1254 used as a source of S9 fraction for mutagenic and genotoxic effects testing.

Assembly worker: A foam seat cushion manufacturing facility employee who sprays adhesive on foam pieces and presses them together by hand to form the cushion. Assembly department workers are either sprayers or assemblers.

Ataxia: Loss of the ability to coordinate muscular movement.

Axial exhaust fan: An air-moving device in which the air flow is parallel (or axial) to the shaft on which the propeller is mounted; also called a propeller fan.

Boiling point: The boiling point of the anhydrous substance at atmospheric pressure (101.3 kPa) unless a different pressure is stated. If the substance decomposes below or at the boiling point, this is noted (dec). The temperature is rounded off to the nearest °C.

Cauda epididymis: The tail of the epididymis; part of the reservoir for spermatozoa.

$CD8^+$ T-cell blast: An immature, undifferentiated lymphocyte that expresses the CD8 transmembrane glycoprotein.

Chemical Data Reporting Rule: Chemical Data Reporting (CDR) is the new name for Inventory Update Reporting (IUR). The purpose of Chemical Data Reporting is to collect quality screening-level, exposure-related information on chemical substances and to make that information available for use by the U.S. Environmental Protection Agency (EPA) and, to the extent possible, to the public. The IUR/CDR data are used to support risk screening, assessment, priority setting and management activities and constitute the most comprehensive source of basic screening-level, exposure-related information on chemicals available to EPA. The required frequency of reporting currently is once every four years.

Comet assay: A genotoxicological technique for measuring DNA damage in an individual cell using single-cell gel electrophoresis. Cell DNA fragments assume a "comet with tail" formation on electrophoresis and are detected with an image analysis system. Alkaline assay conditions facilitate sensitive detection of single-strand damage.

Conversion factor: A numerical factor used to multiply or divide a quantity when converting from one system of units to another.

Cooking: In dry cleaning, boiling the solvent cleaner to remove impurities.

Cover worker: A foam seat cushion manufacturing facility employee who places covers around the assembled cushions and seals the cover around the cushion with adhesive. All workers in the Covers department are sprayers.

Dehydrodehalogenation: An elimination reaction in which a halogen is removed from one carbon and a hydrogen is removed from an adjacent carbon.

Disposition: The description of absorption, distribution, metabolism, and excretion of a chemical in the body.

Distal latency: The interval between the stimulation of a compound muscle and the observed response. Normal nerve conduction velocity is above 40 m/sec in the lower extremities and above 50 m/sec in the upper extremities, but age, muscle disease, temperature, and other factors can influence the velocity.

Dominant lethal mutation assay: The dominant lethal assay identifies germ cell mutagens by measuring the ability of a chemical to penetrate gonadal tissue and produce embryonic death due to chromosomal breakage in parent germ cells.

ELISA assay: Enzyme-linked immunosorbent assay; a sensitive immunoassay that uses an enzyme linked to an antibody or antigen as a marker for the detection of a specific protein, especially an antigen or antibody.

EPA SNAP program: The U.S. Environmental Protection Agency Significant New Alternatives Policy program reviews alternatives to ozone depleting substances and approves the use of alternatives that do not present substantially greater risk to the public health and environment than the substance they replace or other substitutes available.

F_0 generation: F_0 generation is the initial parent generation in a multi-generation reproduction study.

F_1 and F_2 offspring: F_1 offspring is the first filial generation, which comprises offspring resulting from a cross between strains of distinct genotypes. The F_1 generation is the generation resulting immediately from a cross of the first set of parents (parental generation, i.e., F_0 generation). F_2 offspring is the second filial generation, which comprises offspring resulting from a cross of the members of F_1 generation. The F_2 generation is the result of a cross between two F_1 individuals (from F_1 generation).

FDA Good Laboratory Practice Regulations: A quality system codified by the U.S. Food and Drug Administration that prescribes operating procedures for conducting nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by the Food and Drug Administration.

Heat-separated human epidermal membrane: A skin sample used for dermal absorption testing. The method of preparation of epidermal membranes varies across

species due to the inherent differences in skin morphology and follicle depth. Commonly, heat separation (60°C for one to two minutes) is used for human and pig skin; the epidermal membrane is peeled from the dermis using forceps.

Helminthes: Eukaryotic animals with worm-like appearance (i.e., small animals with long, slender bodies and without appendages) and mostly parasitic.

Henry's Law constant at 25°C: The ratio of the aqueous-phase concentration of a chemical to its equilibrium partial pressure in the gas phase. The larger the Henry's law constant the less soluble it is (greater tendency for vapor phase).

Immersion cleaning: A process in which a tank containing cleaning solvent at a temperature below its boiling point is used for metal parts cleaning. To use the vapor degreaser, the operator places the parts to be cleaned in a metal wire basket, removes the cover, and lowers the basket of parts by hand into the cleaning solvent. After a brief period of time, the operator raises the basket and allows the parts to drip-dry inside the degreaser.

Karmen unit: A formerly used enzyme unit for aminotransferase activity; a change of 0.001 in the absorbance of reduced nicotinamide adenine dinucleotide (NADH) per minute.

Lymphokine-activated killer cell: Killer cell lymphocytes activated in the presence of interleukin-2 (IL-2). Lymphokine-activated killer cells (LAKs) are cytotoxic effector cells with an exceptionally wide target cell spectrum including normal and malignant cells of different origins. LAKs exhibit a profound heterogeneity with regard to phenotype surface marker expression; it remains to be determined if they represent a unique cell lineage.

Melting point: The melting point of the substance at atmospheric pressure (101.3 kPa). When there is a significant difference between the melting point and the freezing point, a range is given. In case of hydrated substances (i.e., those with crystal water), the apparent melting point is given. If the substance decomposes at or below its melting point, this is noted (dec). The temperature is rounded off to the nearest °C.

Molecular chaperone: Any of a diverse group of proteins that oversee the correct intracellular folding and assembly of polypeptides without being components of the final structure.

Molecular weight: The molecular weight of a substance is the weight in atomic mass units of all the atoms in a given formula. The value is rounded to the nearest tenth.

Natural killer cells: A type of white blood cell that contains granules with enzymes that can kill tumor cells or microbial cells. Also called large granular lymphocytes.

Octanol/water partition coefficient (log K_{ow}): A measure of the equilibrium concentration of a compound between octanol and water.

Ozone-depleting substance: A family of man-made compounds that includes, but are not limited to, chlorofluorocarbons (CFCs), bromofluorocarbons (halons), methyl chloroform, carbon tetrachloride, methyl bromide, and hydrochlorofluorocarbons (HCFCs). These compounds have been shown to deplete stratospheric ozone.

Personal breathing zone: A sampling area as close as practical to an employee's nose and mouth, (i.e., in a hemisphere forward of the shoulders within a radius of approximately nine inches) so that it does not interfere with work performance or safety of the employee.

Phase I metabolism: metabolism of drugs or other xenobiotic molecules, usually by oxidation or hydrolysis and involving a cytochrome P450 monooxygenase.

Phase II metabolism: a conjugation reaction that forms a covalent linkage between a functional group on a xenobiotic molecule and glucuronic acid, sulfate, glutathione, amino acid, or acetate.

Plaque assay: An assay for antibody production by single lymphocytes using cells isolated from the spleen or lymph nodes of animals injected with sheep red blood cells as an antigen. Incubation of the antibody-forming cells together with sheep red cells in an agar layer with exposure to guinea pig serum as complement results in formation of microscopic plaques (i.e., circular areas of hemolytic clearance around a lymphoid cell) due to release of hemolysin.

Plate incorporation: A commonly used procedure for performing a bacterial reverse mutation test. Suspensions of bacterial cells are exposed to the test substance in the presence and in the absence of an exogenous metabolic activation system. In the plate-incorporation method, these suspensions are mixed with an overlay agar and plated immediately onto minimal medium. After two or three days of incubation, revertant colonies are counted and compared with the number of spontaneous revertant colonies on solvent control plates.

Poly-3 test: A survival-adjusted statistical test that takes survival differences into account by modifying the denominator in the numerical (quantal) estimate of lesion incidence to reflect more closely the total number of animal years at risk.

Pyknotic shrinkage: A thickening, especially the degeneration of a cell in which the nucleus shrinks in size and the chromatin condenses to a solid, structureless mass or masses.

S9 metabolic activation: Addition of the supernatant fraction obtained from an organ (usually liver) homogenate by centrifuging at 9000 g-force for 20 minutes in a suitable medium to a biological assay (e.g., genetic toxicology) to provide metabolic enzymes.

Saw worker: A foam seat cushion manufacturing facility employee who cuts bulk foam with various saws.

SKF-525A: An inhibitor of drug metabolism and cytochrome P-450 activity.

Solubility: The ability of a substance to dissolve in another substance and form a solution.

Specific gravity: The ratio of the density of a material to the density of a standard material, such as water at a specific temperature; when two temperatures are specified, the first is the temperature of the material and the second is the temperature of water.

Sperm motility: Movement characteristics of spermatozoa in a fresh specimen. It is measured as the percentage of sperms that are moving, and as the percentage of sperms with productive flagellar motion such as rapid, linear, and forward progression.

Spinnerette: A small, thimble-shaped, metal nozzle having fine holes through which a spinning solution is forced to form a filament.

Splendore-Hoeppli reaction material: Homogeneous, eosinophilic material that coats the grains that are characteristic of the exudate in lesions of botryomycosis.

Sprayer: Any cushion manufacturing facility employee who works directly with adhesive formulations via spray application using a compressed air spray gun.

Static diffusion cell: A diffusion cell consists of a donor chamber and a receptor chamber between which the skin is positioned. The cell should provide a good seal around the skin, enable easy sampling and good mixing of the receptor solution in contact with the underside of the skin, and provide good temperature control of the cell and its contents. In a static diffusion cell, the receptor fluid is sampled at intervals and replaced with equal volumes of fresh receptor fluid.

Temperate marine macroalgae: Algae growing in the ocean in large seaweed form, generally visible to the naked eye (e.g., kelp), in regions where the climate undergoes seasonal change in temperature and moisture. Temperate regions of the earth lie primarily between 30 and 60 degrees latitude in both hemispheres.

Time-weighted average: The average exposure concentration of a chemical measured over a period of time (not an instantaneous concentration).

Toxicokinetics: The mathematical description (toxicokinetic models) of the time course of disposition of a chemical in the body.

Vapor degreasing: A type of cleaning procedure using a refrigerated cooling coil around the top of the interior of a vapor chamber to condense solvent vapor into liquid droplets on the surface of parts to remove surface impurities. Excess solvent drips back into the solvent sump and is recycled as the parts ascend from the vapor to condensing zones.

Vapor density, relative: A value that indicates how many times a gas (or vapor) is heavier than air at the same temperature. If the substance is a liquid or solid, the value applies only to the vapor formed from the boiling liquid.

Vapor pressure: The pressure of the vapor over a liquid (and some solids) at equilibrium, usually expressed as mm Hg at a specific temperature (°C).

Appendix A: Literature Search Strategy

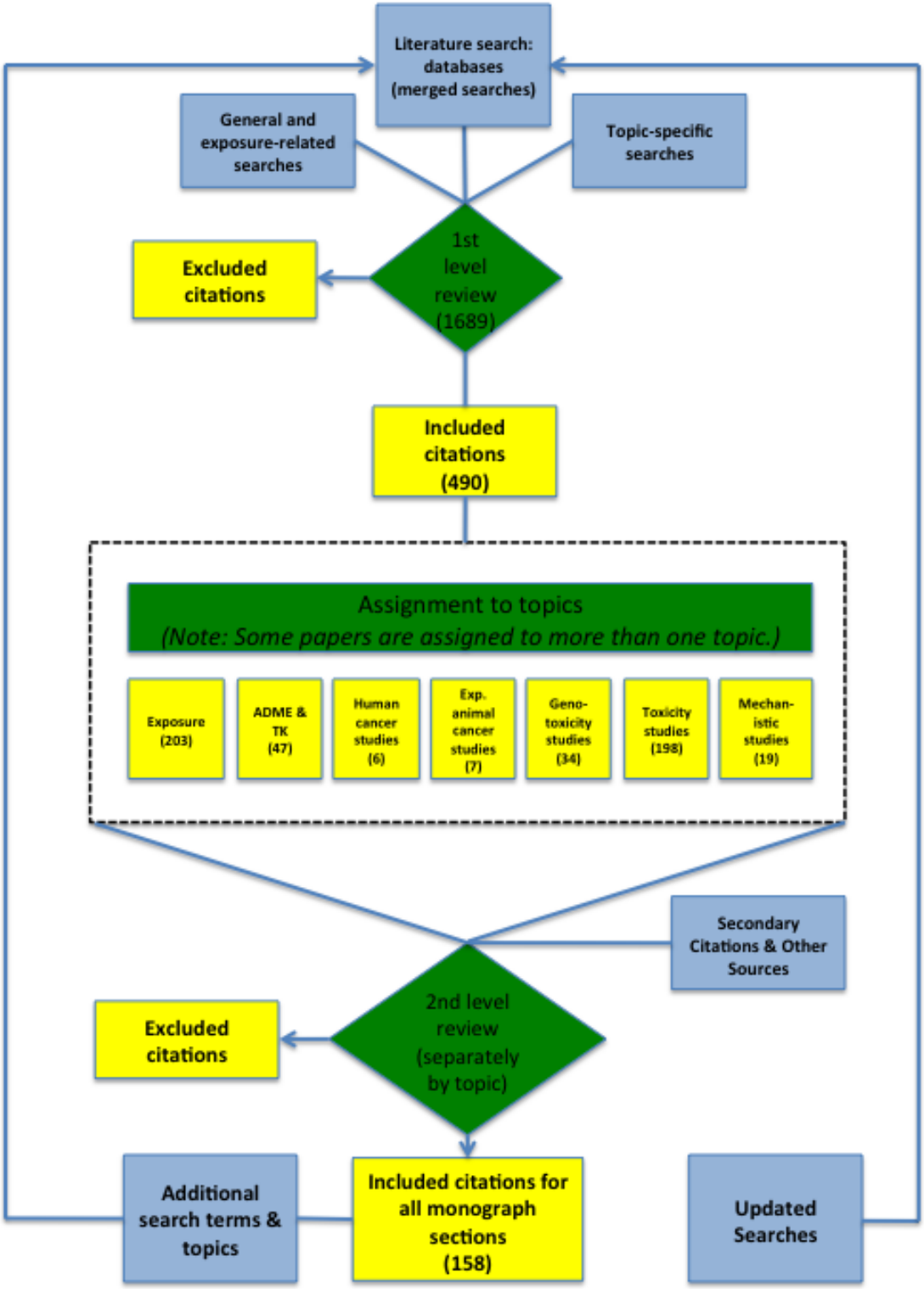
This document identifies the data sources, search terms, and search strategies that were used to identify literature for the monograph on 1-bromopropane *(*CASRN 106-94-5). The literature search strategy used for 1-bromopropane involved several approaches designed to identify potentially useful information for the broad range of topics covered by a Report on Carcinogens (RoC) monograph, as listed below.

- Properties and Human Exposure (focusing on the U.S. population)
- Disposition (ADME) and Toxicokinetics
- Human Cancer Studies (if available)
- Cancer Studies in Experimental Animals
- Mechanisms and Other Relevant Effects
  - Genotoxicity
  - Toxicity as It Relates to Mechanisms
  - Mechanisms of Carcinogenicity

The methods for identifying the relevant literature for the 1-bromopropane monograph including (1) the search strategy, (2) updating the literature search, and (3) review of citations using web-based systematic review software are illustrated in Figure A-1 and discussed below.

Click here to return to text citing Appendix A.

Figure A-1. Literature search strategy and review



Search strategies

Relevant literature is identified using search terms, data sources, and strategies as discussed below.

1. **General data search:** This search covers a broad range of general data sources (see Table A-1) for information relevant to many or all of the wide range of monograph topics pertaining to 1-bromopropane.

2. **Exposure-related data search:** This search covers a broad range of potential sources (see Table A-2) for exposure-related information and physical-chemical properties.

3. **Database searches in PubMed, Scopus, and Web of Science:** The majority of the primary literature used to draft the 1-bromopropane monograph was identified from searches of these three extensive databases available through the NIEHS Library. Synonyms, metabolites (both Phase I and Phase II), and the chemical class for 1-bromopropane were identified from the sources listed in Table A-3 and the search terms are listed in Table A-4. Information on metabolites and structurally related chemicals may be important for evaluating potential mechanisms of carcinogenicity. Initial literature searches were conducted to obtain all literature (not restricted to topic) on 1-bromopropane, its metabolites and chemical class. The searches for the four debrominated Phase I metabolites of 1-bromopropane and the relevant chemical class brought up several thousand references and thus subsequent topic-specific searches were conducted to focus the search on identifying mechanistic information for these chemicals. See Table A-4 for details on this approach and Table A-5 for topic-specific search terms.

   Searches for human cancer studies are somewhat unique because they involve the identification of search terms for exposure scenarios that might result in exposure of people to 1-bromopropane. The major uses of 1-bromopropane are as a cleaner/degreaser, as an adhesive for manufacture of foam cushions, and as a solvent in dry cleaning. The use of 1-bromopropane in dry cleaning is more recent, since 2006. Because the expansion in the use of 1-bromopropane has been fairly recent, epidemiologic studies of workers may not be able to evaluate potential risks for cancer, which is associated with long latency periods. Formal searches were not conducted for epidemiologic studies of dry cleaners because these workers would most likely have been exposed to other solvents such as tetrachloroethylene. Literature searches conducted using search terms for spray adhesive and degreaser industries were combined with search terms for cancer epidemiologic studies (see Tables A-4 and A-5).

4. **QUOSA library of occupational case-control studies:** A search of the QUOSA-based library of approximately 6,000 occupational case-control studies, approximately 60% of which are currently available as searchable full-text PDFs, was conducted using the synonyms “1-bromopropane,” “propyl bromide,” and the CASRN number (106-94-5).

5. **Special topic-focused search:** One of the key questions in the concept document on 1-bromopropane was whether the reported alterations in immune surveillance in rodents lead to an increased incidence of tumors. An additional literature search of the three databases was conducted to identify information on immunosuppression and chemically induced cancer using the following search terms: (cancer OR tumor OR neoplasm) AND (immune suppression OR immunosuppression) AND (skin OR dermal) AND (chemically induced). The review of these citations was limited to review articles.

6. **Secondary sources:** Citations identified from authoritative reviews or from primary references located by literature search, together with publications citing key papers identified using the Web of Science "Cited Reference Search," were also added.

Updating the literature search

The literature search was updated prior to submitting the draft monograph for peer review and was updated prior to finalizing the monograph. Monthly search alerts for 1-bromopropane synonyms, metabolites, chemical class, exposure scenarios (human cancer), and topic-focused searches were created in PubMed, Scopus, and Web of Science, and the results of these searches from the closing date of the initial search were downloaded for review.

Review of citations using web-based systematic review software

Citations retrieved from literature searches were uploaded to web-based systematic review software and screened using inclusion and exclusion criteria. Multi-level reviews of the literature were conducted, with initial reviews (Level 1) based on titles and abstracts only to identify citations that could be excluded and to assign the included literature to one or more monograph topics; subsequent reviews (Level 2) for literature assigned to the various monograph topics were based on full-text (i.e., PDFs) of the papers and were carried out by the writer and scientific reviewer for each monograph section. Two reviewers, at least one of whom is a member of the ORoC at NIEHS, participated at each level of review.

Inclusion/exclusion questions for literature

Level 1:

1. Should we obtain a PDF of this article?
   - ❍ Yes
   - ❍ No

1. If yes, for which sections of the monograph does this article contain useful information? Check all that apply.
   - ☐ Properties and Human Exposure
   - ☐ Toxicokinetics (also includes ADME, i.e., absorption, distribution, metabolism, and excretion)
   - ☐ Human Cancer Studies
   - ☐ Studies of Cancer in Experimental Animals
   - ☐ Mechanisms- Genetic Toxicology

☐ Mechanisms- Toxicity
☐ Mechanisms of Carcinogenicity

2. If no, check the reason that applies below or enter a reason in the textbox for "Other."
   ❍ It does not contain relevant information on 1-bromopropane or any related substance (metabolite or structural analogues).
   ❍ It is related to 1-bromopropane but does not contain information relevant to any topic covered by the monograph.
   ❍ Other

Note: In the context of the systematic review of literature used for 1-bromopropane, "useful" or "relevant" information as it applies to primary screening can include any of the following:

- The article specifically mentions 1-bromopropane, a metabolite, or structural analogue and reports information on one of the topics included in a cancer evaluation (see Question #1 above for a list of topics)
- The article does not specifically mention 1-bromopropane, or any related substance, but it does one of the following:
  - It reports information on one of the topics included in a cancer evaluation with potential for exposure to 1-bromopropane and should be included until full-text review, which would provide more information if the study is specific for exposure to 1-bromopropane or a related substance.
  - It reports information on an exposure scenario that could include exposure to the 1-bromopropane.
  - It reports information on methodology that is potentially informative for evaluating cancer or mechanistic studies on exposure to 1-bromopropane.
  - It reports information on a potential mode of action that may be informative for 1-bromopropane.

Level 2- Exposure:

1. Does this paper contain information that could be useful in answering the key questions about exposure?
   ❍ Yes
   ❍ No

2. If the answer to Question #1 is "No" select the reason below for excluding it from review.
   ❍ It does not contain relevant information on the candidate substance (or one of its metabolites or analogues).
   ❍ It is related to the candidate substance (or one of its metabolites or analogues), but the paper does not contain information that will help answer the key questions about exposure.
   ❍ Other

Note: In the context of the systematic review of literature used for 1-bromopropane, "useful" or "relevant" information as it applies to screening for the exposure section can include information, from either primary research papers, review articles, databases, or other published sources, on any of the following topics: occupational exposure, environmental occurrence, occurrence in consumer products, food, cigarette smoke, or other sources, biological indices of exposure, and Federal regulations or guidelines to reduce exposure.

Toxicokinetics:

1. Does this paper contain information that could be useful in answering the key questions about toxicokinetics?
   - ❍ Yes
   - ❍ No

2. If the answer to Question #1 is "No" select the reason below for excluding it from review.
   - ❍ It does not contain relevant information on the candidate substance (or one of its metabolites or analogues).
   - ❍ It is related to the candidate substance (or one of its metabolites or analogues), but the paper does not contain information that will help answer the key questions about toxicokinetics.
   - ❍ Other

Note: In the context of the systematic review of literature used for 1-bromopropane, "useful" or "relevant" information as it applies to screening for the toxicokinetics (and ADME) section can include (but is not limited to) information from primary research papers or review articles on any of the following topics: absorption, distribution, metabolism, excretion (ADME), toxicokinetics, and physiologically based pharmacokinetic models (PBPK).

Human Cancer:

1. Does this paper contain information that could be useful in answering the key questions about human cancer?
   - ❍ Yes
   - ❍ No

2. If the answer to Question #1 is "No" select the reason below for excluding it from review.

- ❍ It does not contain relevant information on the candidate substance (or one of its metabolites or analogues).
- ❍ It is related to the candidate substance (or one of its metabolites or analogues), but the paper does not contain information that will help answer the key questions about human cancer.
- ❍ Other

Note: In the context of the systematic review of literature used for 1-bromopropane, "useful" or "relevant" information as it applies to screening for the human cancer section can include, but is not limited to, epidemiologic studies, descriptive studies, pooled analyses, meta-analyses, case reports, reviews, letters to editors, exposure-assessment studies (for use in epidemiologic studies) and information on co-exposures or potential confounders and other special topics of relevance to the evaluation.

Animal Tumors:

1. Does this paper contain information that could be useful in answering the key questions about animal tumors?
   - ❍ Yes
   - ❍ No

2. If the answer to Question #1 is "No" select the reason below for excluding it from review.
   - ❍ It does not contain relevant information on the candidate substance (or one of its metabolites or analogues).
   - ❍ It is related to the candidate substance (or one of its metabolites or analogues), but the paper does not contain information that will help answer the key questions about animal tumors.
   - ❍ Other

Note: In the context of the systematic review of literature used for 1-bromopropane, "useful information" as it applies to screening for the animal tumors section can include, but is not limited to, information from primary research papers or review articles on (1) chronic studies (ideally for lifetime of the animal) in experimental animals that are assessing neoplastic endpoints, non-cancer data important for cancer assessment, such as preneoplastic lesions that are considered part of a morphologic continuum to neoplasia, or (2) subchronic studies in experimental animals that provide information on preneoplastic lesions, neoplastic lesions, or on dose setting for chronic studies.

Level 2- Genetic Toxicology:

1. Does this paper contain information that could be useful in answering the key questions about genetic toxicology?
   - ❍ Yes
   - ❍ No

2. If the answer to Question #1 is "No" select the reason below for excluding if from review.
   - ❍ It does not contain relevant information on the candidate substance (or one of its metabolites or analogues).
   - ❍ It is related to the candidate substance (or one of its metabolites or analogues), but the paper does not contain information that will help answer the key questions about genetic toxicology.
   - ❍ Other

Note: In the context of the systematic review of literature used for 1-bromopropane, "useful" or "relevant" information as it applies to screening for the genetic toxicology section can include, information from primary research papers or review articles on studies in experimental systems (both *in vitro* and *in vivo*) and in exposed humans assessing the following endpoints: both direct and indirect DNA or chromosomal damage, events associated with mutagenesis, cellular transformation or other related effects.

Level 2- Toxicity:

1. Does this paper contain information that could be useful in answering the key questions about toxicity?
   - ❍ Yes
   - ❍ No

2. If the answer to Question #1 is "No" select the reason below for excluding if from review.
   - ❍ It does not contain relevant information on the candidate substance (or one of its metabolites or analogues).
   - ❍ It is related to the candidate substance (or one of its metabolites or analogues), but the paper does not contain information that will help answer the key questions about toxicity.
   - ❍ Other

Note: In the context of the systematic review of literature used for 1-bromopropane, "useful" or "relevant" information as it applies to screening for the toxicity section can include any of the following: information from primary research papers or review articles

on toxicity of 1-bromopropane to organs or tissues that were identified as tumor sites from studies in experimental animals.

Level 2- Mechanisms of Action:

1. Does this paper contain information that could be useful in answering the key questions about mechanisms of action?
   - ❍ Yes
   - ❍ No

2. If the answer to Question #1 is "No" select the reason below for excluding if from review.
   - ❍ It does not contain relevant information on the candidate substance (or one of its metabolites or analogues).
   - ❍ It is related to the candidate substance (or one of its metabolites or analogues), but the paper does not contain information that will help answer the key questions about mechanisms of action.
   - ❍ Other

Note: In the context of the systematic review of literature used for 1-bromopropane, "useful" or "relevant" information as it applies to screening for the mechanism data section can include information from primary research papers or review articles on data related to molecular alterations associated with carcinogenicity or potential modes of action, such as genotoxicity, epigenetics, gene expression, immune-response modulation, inflammation, cytotoxicity and compensatory cell proliferation, mitogenicity, chronic metabolic or physiologic overload, nutrient deficiency, and interference with intercellular communication, for 1-bromopropane, its metabolites and analogues.

Table A-1. General sources checklist for: 1-Bromopropane

Source	Name of document
A) Comprehensive sources or reviews	
1) NTP technical reports	NTP2011
2) NTP nomination for toxicological evaluation documents	NTP1999
3) OHAT (formerly CERHR) Public comments to CERHR- 10 listed on NTP website	NTP2003a (1BP) NTP 2003b (2BP) Albemarle2001a Albemarle2001b Atofina2001 BSC2000 BSC2001a BSC2001b Envirotech2001 IRTA2001 EPA2002 Envirotech2002
4) IARC monographs	--
5) ATSDR Toxicological Profiles	--
6) EPA IRIS	--
7) NAS Reports and Publications	NAS2007 (Climate Change) NAS2008 (Review of NIOSH HHE Program)
8) WHO (IPCS) INCHEM-related documents (a-k below)	--
a) CICADS	--
b) EHC	--
c) HSGs	--
d) ICSCs	IPCS2004
e) JECFA	--
f) JMPR	--
g) KemI-Riskline	--
h) PDs	--
i) PIMS	--
j) SIDS	--
k) UKPID	--
9) California EPA Prop 65 hazard identification documents	CAEP 2004 CAEPA2008
10) Health Canada	HealthCanada2009a HealthCanada, 2009b
11) New York State Department of Health- Health Topics A to Z	--
B) General information sources	
1) U.S. National Library of Medicine (NLM)- TOXNET	--
a) HSDB	HSDB2006
b) CCRIS	CCRIS2008
c) GENETOX	--
d) ITER	--
e) LactMed	--
f) CPD	--
g) CTD	CTD2012
2) PubChem	PubChem2012
3) Kirk-Othmer Encyclopedia	Wypych2006

Source	Name of document
	Pocius&Campbell2009 Suh2000
4) USGS (Minerals)	--
C) European Union– sources to search	
1) International Uniform Chemical Information Database (IUCLID)	--
2) European Chemicals Agency	--
3) The International Portal on Food Safety, Animal and Plant Health (IPFSAPH)	--
4) The European Food Safety Authority	--
5) European Centre for Disease Prevention and Control (ECDC)	--
6) European Monitoring Centre for Drugs and Drug Addiction	--
7) International Labour Organization (ILO)	ILO2005
8) United Nations Environment Programme (UNEP)	--

Table A-2. Exposure-related sources checklist for: 1-Bromopropane

Source	Name of document
Exposure- and properties-specific sources	
1) U.S. National Library of Medicine (NLM)- TOXNET	--
a) ChemIDplus	ChemIDplus2012
b) Haz-Map	Haz-Map2012
c) HPD	--
d) TOXMAP	--
2) Akron database	Akron2012
3) SRI Directory of Chemical Producers	SRI2012
4) Chem Sources Suppliers	ChemSources2012
5) National Health and Nutrition Examination Survey (NHANES) data studies	--
6) National Occupational Exposure Survey (NOES) (1981-1983)	--
7) National Institute for Occupational Safety and Health (NIOSH) - Health Hazard Evaluations	5 HHE: Eisenberg2010 Harney2002 Harney2003 Reh2001 Reh2002
8) National Response Center (NRC) Database	NRC2012a NRC2012b
9) U.S. International Trade Commission (USITC)- Import/Export data	USITC2012
10) EPA Toxics Release Inventory (TRI)	--
11) Environmental Protection Agency (EPA) AP-42, Compilation of Air Pollutant Emission Factors	--
12) EPA EJView Database	--
13) EPA High Production Volume Chemicals (HPV Challenge Program Chemical List)	--
14) EPA Inventory Update Rule (IUR)	EPA2012
15) EPA Locating and Estimating (L&E) documents	--
16) EPA/Office of Pesticide Programs (OPP) Chemical Ingredients Database	--
17) Food and Drug Administration (FDA) Pesticide Monitoring Database	--
18) FDA Orange Book	--
19) FDA Total Diet Study	--
20) Medline Plus	MedlinePlus2012
21) United States Patent Office	USPTO2011 USPTO2012a USPTO2012b
22) Trademark Electronic Search System (TESS)	--
23) Material Safety Data Sheets (MSDS)	Multiple found Sigma-Aldrich2011
24) Dow Chemical Product Safety Assessments	--

Table A-3. Data sources for 1-bromopropane searches

Information type	Data sources
Synonyms	National Library of Medicine databases (e.g., ChemIDplus, Hazardous Substances Data Base)
Metabolites	Cheever *et al.* 2009, Garner *et al.* 2006, Ghanayem and Hoffler 2007, Ishidao *et al.* 2002, Jones and Walsh 1979.

Table A-4. Literature search approach for 1-bromopropane

Substance	Search terms	Topics (combined with)[a]
1-Bromopropane synonyms	bromopropane, propyl bromide, and 106-94-5	None
Chemical class and synonyms	bromoalkanes, alkyl bromides, haloalkanes, alkyl halides	Animal tumors Genotoxicity Toxicity Mechanism
1-Bromopropane brominated Phase I metabolites and their synonyms	3-bromopropanol, 3-bromopropionic acid, 1-bromo-2-propanol, bromoacetone, 2-oxo-1-bromopropane, and alpha-bromohydrin	None
1-Bromopropane debrominated Phase I metabolites and their synonyms	propylene oxide, *n*-propanol, glycidol, and 3-hydroxypropionate	Animals tumors Genotoxicity Toxicity Mechanism
1-Bromopropane Phase II metabolites	1-bromo-2-hydroxypropane-*O*-glucuronide, *N*-acetyl-S-propylcysteine, *N*-acetyl-*S*-(2-hydroxypropyl)cysteine, *N*-acetyl-*S*-(3-hydroxypropyl)cysteine, *N*-acetyl-*S*-(2-carboxyethyl)cysteine, *N*-acetyl-*S*-(2-oxopropyl)cysteine, 2,3-dihydroxypropylmercapturic acid, *N*-acetyl-3-(propylsulfinyl)alanine, *N*-acetyl-3-[(2-hydroxypropyl)sulfinyl]alanine, *N*-acetyl-3-[(2-oxopropyl)sulfinyl]alanine, *N*-acetyl-3-[(2-propenol)sulfinyl]alanine	None
Exposure scenario	(Spray* AND Adhes*) or Degreas*	Human cancer studies

[a]Search terms for each of these topics were developed in consultation with an informational specialist and are listed in Table A-5.

Table A-5. Search terms for monograph topics for 1-bromopropane

Monograph Topic	Search terms used in PubMed, Scopus, and Web of Science	MeSH terms used in Pubmed
Human cancer studies	*Cancer search terms* - cancer* OR neoplas* OR carcinogen* OR malignan* OR oncogene* OR tumor* OR tumour* OR adenoma* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR precancer* OR preneoplast* OR lesion* OR cyst* OR lymphoma* OR leukemia* OR metastas* OR cell transform* OR cell proliferat* *Combine with* AND *Epidemiologic study search terms* - person* OR people OR individual* OR subject* OR participant* OR worker* OR employee* OR staff OR human OR woman OR women OR man OR men OR epidemiolog* OR case report* OR case control OR cohort OR case-referent OR registry OR prevalen* OR inciden*	*Cancer search terms* - "neoplasms"[Mesh] OR "carcinogens"[Mesh] *Combine with* AND *Epidemiologic study search terms* - "epidemiology"[Subheading] OR "epidemiologic studies"[Mesh] OR "case reports"[publication type] OR "epidemiologic factors"[mh] OR "epidemiologic methods"[mh] OR "persons"[mh] OR "occupational diseases"[mh] OR "occupational exposure"[mh] OR "vital statistics"[mh]
Animal Tumors	*Cancer search terms*- cancer OR neoplasm* OR carcinogen* OR malignan* OR oncogene* OR tumor* OR tumour* *Combine with* AND *Animal study search terms*- animal* OR mouse OR mice OR rat OR hamster OR "guinea pig" OR rabbit OR monkey OR dog	*Cancer search terms*- "neoplasms"[Mesh]) OR "carcinogens"[Mesh]
Genotoxicity	*General search terms* - "genetic toxicology" OR genotoxic*[a] *Endpoint-specific search terms* - clastogen* OR "DNA strand break*" OR "unscheduled DNA synthesis" OR "UDS" OR aneuploid OR aneuploid* OR polyploid OR polyploid* OR "neoplastic cell transformation" OR "chromosom* aberration*" OR cytogenetic OR cytogenetic* OR "DNA adduct*" OR "DNA damage" OR "DNA repair" OR crosslink* OR "germ-line mutation" OR micronucle* OR mutagen OR mutagen* OR mutation OR mutation* OR oncogen* OR "sister chromatid exchange" OR "SCE" OR "SOS response*" OR "Ames test" OR "gene expression" OR "cell proliferation" OR cytotoxic OR cytotoxic* OR "comet assay"	"DNA Damage"[Mesh] OR "DNA Repair"[Mesh] OR "Mutagens"[Mesh] OR "Mutation"[Mesh] OR "Cytogenetic Analysis"[Mesh] OR "Oncogenes"[Mesh] OR "Mutagenicity Tests"[Mesh][a]
Toxicity	toxic* OR toxin*OR cytotoxic* OR (nephrotoxic* OR hepatotoxic* OR pneumotoxic* OR thyrotoxic*	"Toxic Actions"[Mesh]) OR "Toxicity Tests"[Mesh]) OR "adverse effects" [Subheading]

Monograph Topic	Search terms used in PubMed, Scopus, and Web of Science	MeSH terms used in Pubmed
Mode of action	(mode* AND "of action") OR (mechanism* AND "of action") OR genetic OR epigenetic OR inhibit* OR promot* OR interact* OR activate* OR detoxific* OR "oxidative damage" OR cytotoxicity	

[a]Only the MeSH terms (or their equivalents (i.e., "genetic toxicology" OR genotoxic* OR "DNA Damage" OR "DNA Repair" OR mutagens OR mutation OR "cytogenetic analysis" OR oncogenes OR "mutagenicity tests") were used in the searches for debrominated metabolites.

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Appendix B: Human Exposure Tables and Regulations and Guidelines

Human exposure tables

The eight tables on the following pages contain data discussed in the "Properties and Human Exposure" section (Section 1) for the potential for occupational exposure (Section 1.4).

Data for 1-bromopropane exposure are reported for personal (Table B-1) and area samples (Table B-2) during adhesives applications, personal (Table B-3) and area samples (Table B-4) during bromopropane manufacturing, personal (Table B-5) and area samples (Table B-6) during dry-cleaning applications, and personal (Table B-7) and area samples (Table B-8) during vapor degreasing applications. The symbol "–" shown before a range of concentration values in the tables denotes "data for mean not reported."

Click here to return to text citing Appendix B.

Table B-1. Adhesives applications – personal samples of 1-bromopropane in air, urinary biomarkers (AcPrCys and Br), and 1-bromopropane in blood and exhaled air

Location (source)	Type of job	Number of workers	1-Bromopropane in air		Urinary biomarkers		1-BP in blood, mean conc. (range), mg/L	1-BP in exhaled air, mean conc. (range), ppm
			TWA (range), ppm	Short-term conc. (range), ppm	AcPrCys, mean conc. (range), mg/(g – Cr)	Bromide, mean conc. (range), mg/(g – Cr)		
Polyurethane seat cushion mfr. – NC Hanley *et al.* 2005, Hanley *et al.* 2006a, Hanley *et al.* 2009[c]	Sprayers	13[a]	92[b] (45–200)	–	41.1[b] (14.3–127)[d]	195[b] (119–250)[e]	–	10.4 (3.2–20.6)[f]
	Non-sprayers	17[a]	11[b] (0.6–60)	–	10.2[b] (0.373–1.5)[d]	42.9[b] (5.5–149)[e]	–	5.8 (0.13–12.9)[f]
Furniture factory – UT Majersik *et al.* 2007	Cushion gluer	6	108[g] (92–127[g])	–	–	–	[– (440–1,700)] (values reported in mg/dL)	–

Location (source)	Type of job	Number of workers	1-Bromopropane in air		Urinary biomarkers		1-BP in blood, mean conc. (range), mg/L	1-BP in exhaled air, mean conc. (range), ppm
			TWA (range), ppm	Short-term conc. (range), ppm	AcPrCys, mean conc. (range), mg/(g – Cr)	Bromide, mean conc. (range), mg/(g – Cr)		
Furniture foam cushion mfr. – NC Harney *et al.* 2003, Toraason *et al.* 2006[h]	Exposed workers (1999 HHE)	16	81.2[b] (18.1–253.9)	–	–	–	–	–
	All workers (2001 HHE)	40	3.7[b] (0.1–280.5)	–	–	[465 mg/L[i] (150–5,950)]	[48[i] (17–435)]	–
	Unexposed workers (2001 HHE)	27	1.1[b] (0.1–4.9)	–	–	[285 mg/L[i] (150–1,510)]	[27[i] (17–110)]	–
	Exposed workers (2001 HHE)	13[i]	45.7[b] (7.2–280.5)	–	–	[1,518 mg/L[i] (270–5,950)]	[149[i] (30–435)]	–
	All sprayers (1999 HHE)	12	107.6[b] (57.7–253.9)	–	–	–	–	–
	All sprayers (2001 HHE)	8	101.4[b] (38.0–280.5)	–	–	–	–	–
Commercial aircraft industry seat cushion mfr. – NC Reh *et al.* 2002	All workers (1998 HHE)	69	168.9 (60.0–381.2)	–	–	–	–	–
	All workers (2000 HHE)	30	19.0 (1.2–58.0)	–	–	–	–	–
	Assembly workers[k] (1998 HHE)	36	169.8 (60–250.7)	–	–	–	–	–
	Assembly workers (2000 HHE)	11	18.8 (6.1–32.0)	–	–	–	–	–
	Sprayers	15	193 (115.3–	–	–	–	–	–

Location (source)	Type of job	Number of workers	1-Bromopropane in air		Urinary biomarkers		1-BP in blood, mean conc. (range), mg/L	1-BP in exhaled air, mean conc. (range), ppm
			TWA (range), ppm	Short-term conc. (range), ppm	AcPrCys, mean conc. (range), mg/(g – Cr)	Bromide, mean conc. (range), mg/(g – Cr)		
	(1998 HHE)		250.7)					
	Sprayers (2000 HHE)	12	–	– (12.3–95.8)	–	–	–	–
	Assemblers (1998 HHE)	20	154.7 (60.0–234.9)	–	–	–	–	–
	Cover workers (1998 HHE)	21	197.0 (117.3–381.2)	–	–	–	–	–
	Cover workers (2000 HHE)	12	29.2 (2.8–58.0)	–	–	–	–	–
	Saw workers (1998 HHE)	12	117.1 (85.1–59.2)	–	–	–	–	–
	Saw workers (2000 HHE)	6	1.8 (1.6–2.0)	–	–	–	–	–
	Sew worker (2000 HHE)	1	1.2 (–)	–	–	–	–	–
Furniture company sofa cushion mfr. – NC Harney *et al.* 2002, Toraason *et al.* 2006[m]	Sprayers (2000 HHE)	12 (TWA), 9 (Short-term)	65.9 (41.3–143.0)	– (33.7–173.9)	–	–	–	–
	Sprayers[l] (2001 HHE)	12 (TWA), 10 (Short-term)	16.6 (8.8–31.9)	– (0.2–56)	–	–	–	–

Location (source)	Type of job	Number of workers	1-Bromopropane in air		Urinary biomarkers		1-BP in blood, mean conc. (range), mg/L	1-BP in exhaled air, mean conc. (range), ppm
			TWA (range), ppm	Short-term conc. (range), ppm	AcPrCys, mean conc. (range), mg/(g – Cr)	Bromide, mean conc. (range), mg/(g – Cr)		
	Non-sprayers (2001 HHE)	10	– (1.1–5.8)	–	–	–	–	–
	Floaters (2000 HHE)	2	– (6.3–14.1)	–	–	–	–	–
	Exposed workers (2001 HHE)	7	–	–	–	7.7[n] (2.5–38.0)	–	–
	Sprayers (2000 HHE)	11 (TWA), 1 (Short-term ceiling)	–	– (39.5–151.9)				
	Sprayers (2001 HHE)	10	–	– (< 0.14–8)				
Furniture company sofa cushion mfr. – NC Ichihara *et al.* 2002	Sprayers	11	133 (60–261)	–	–	–	–	–
Furniture foam cushion mfr. – NC Raymond and Ford 2007	Gluers	4	–	–	–	–	[– (240–1,000)][o]	–
Unidentified foam cushion fabricators Raymond and Ford 2007	Gluers	5	– (52–137)	–	–	–	–	–
Adhesives mfr. –	Exposed	3[a,p]	3.79[b] (0.264–	–	0.485[b] (0.111–	4.51[b] (1.87–	–	0.10[q] (ND–

Location (source)	Type of job	Number of workers	1-Bromopropane in air		Urinary biomarkers		1-BP in blood, mean conc. (range), mg/L	1-BP in exhaled air, mean conc. (range), ppm
			TWA (range), ppm	Short-term conc. (range), ppm	AcPrCys, mean conc. (range), mg/(g – Cr)	Bromide, mean conc. (range), mg/(g – Cr)		
OH Hanley *et al.* 2007, Hanley *et al.* 2010	workers		18.9)		1.22)	12.4)		0.18)
	Unexposed workers	8[a,p]	0.325[b] (0.072–1.59)	–	0.128[b] (ND–1.33)	2.01[b] (0.90–3.55)	–	–

[a]Workers in this study were sampled on two consecutive days so the total number of samples is twice; e.g., for sprayers in Hanley *et al.* 2009, N = 13 x 2 = 26.
[b]Geometric mean.
[c]Raw data from Hanley *et al.* 2005 field study were used for analysis in Hanley *et al.* 2006a and Hanley *et al.* 2009.
[d]As cited in Hanley *et al.* 2009. Forty-eight hour composite urinary AcPrCys concentrations, adjusted for creatinine.
[e]As cited in Hanley *et al.* 2006a. Forty-eight hour composite urinary bromide concentrations, adjusted for creatinine.
[f]Combined mean, calculated from raw data reported for Day 1 post-shift sampling for 2 plants in Hanley *et al.* 2005 field study. Day 2 sampling data were mostly similar to Day 1 data.
[g]Seven hour time-weighted average and range; mean ambient air concentration = 130 ppm (range = 91 – 176 ppm).
[h]Toraason *et al.* 2006 study conducted on a sub-population of 42 workers from Marx Industries NIOSH HHE who consented to participate in the study.
[i]End-of-week concentration in mg/L; geometric mean. Values reported in mg/dL.
[j]Exposed workers included 8 sprayers and 5 other workers who were not actively spraying.
[k]As noted per Reh *et al.* 2002, data from 1 supervisor omitted.
[l]Day 2 sampling results: 11 samples, mean = 16.8 ppm, range = 7.7–29 ppm. Day 3 sampling results: 11 samples, mean = 23.3 ppm, range = 14.3–34.9 ppm. Day 1 sampling results are shown in the table.
[m]Toraason *et al.* 2006 study conducted on a sub-population of 22 workers from STN Cushion Company NIOSH HHE who consented to participate in the study.
[n]End-of-week concentration in mg/L; geometric mean.
[o]Values reported as 3 – 12.5 mEq/L. Conversion factor: 8 mg/dL = 1 mEq/L, Golomb 1999.
[p]As cited in Hanley *et al.* 2010.
[q]As cited in Hanley *et al.* 2007 for Day 1 post-shift sampling for 11 total workers. Day 2 sampling data were mostly similar to Day 1 data.
Click here to return to text citing Table B-1.

Table B-2. Adhesives applications – area samples

Location (source)	Type of job/area	Number of samples	Mean conc. (range), ppm
Polyurethane seat cushion manufacturer, Plant A – NC Hanley *et al.* 2005[a]	Cloth cutting	2	0.9[b]
	Sewing, south	2	14.1[b]
	Sewing, north	2	20.4[b]
	Spray table 1, farthest north	2	68[b]
	Pillow fill	2	16.7[b]
Polyurethane seat cushion manufacturer, Plant B – NC Hanley *et al.* 2005[a]	Main glue, south of glue lines	1	36.9
	Main glue, between glue lines	1	59.4
	Cutting machine cage	1	1.0
	Cutting table, near auxiliary glue line	1	10.5
	Sewing table, near auxiliary glue line	1	2.7
Furniture foam cushion manufacturer – NC Harney *et al.* 2003	Focus saw area near springs line (1999 HHE[b])	1	8.7
	Cutting area adjacent to glue line (1999 HHE)	1	5.3
Commercial aircraft industry seat cushion manufacturer – NC Reh *et al.* 2002	Sew department, randomly selected stations (1998 HHE)	11	128.1 (107.3–160.9)
	Sew department, randomly selected stations (2000 HHE)	5	– (1.1–1.9)
Furniture company sofa cushion manufacturer – NC Harney *et al.* 2002	Middle of the saw room (2000 HHE)	1	7.7
	Middle of the fabrication room (2000 HHE)	1	7.2
	Middle of the poly cut room (2000 HHE)	1	1.7
	Non-sprayers (2001 HHE)	7	– (0.01–6.1)
Furniture factory – UT Majersik *et al.* 2007	Cushion gluing	6	130 (91–176)

[a]Sampling conducted on two days; data shown for Day 1 sampling. Day 2 sampling data were mostly similar to Day 1 data.
[b]Time-weighted average; two samples were collected at each location for approximately four hours each. For cloth cutting, the morning (AM) sample was 0.8 ppm and the afternoon (PM) sample was 1.0 ppm. For sewing, south, AM sample = 6.4 ppm, PM sample = 22.1 ppm; for sewing, north, AM sample = 12.3 ppm, PM sample = 28.8 ppm; for spray table 1, farthest north, AM sample = 43.2 ppm, PM sample = 94.0 ppm; for pillow fill, AM sample = 9.6 ppm, PM sample = 23.9 ppm.
[c]HHE = Health Hazard Evaluation. NIOSH conducted health hazard evaluation surveys at three facilities in the adhesives use sector (Reh *et al.* 2002, Harney *et al.* 2002).
Click here to return to text citing Table B-2.

Table B-3. 1-Bromopropane manufacturing – personal samples

Location (Source)	Type of Job	Number of samples	Air	
			TWA (Range), ppm	Short-term Conc. (Range), ppm
Mfg. plant, China Ichihara *et al.* 2004a	Operators (Female workers)	24	– (0.9–170.5)	–
	Various (Male workers)	13	– (ND[a]–43.3)	–
Mfg. plant, China Ichihara *et al.* 2004b	Material/Product handlers (Female workers)	23	2.92[b] (0.34–49.2)	–
Mfg. plants, China Li *et al.* 2010b	Material/Product handlers (Female workers)	60	6.6[c] (0.07–106.4)	–
	Material/Product handlers (Male workers)	26	4.6[c] (0.06–114.8)	–
Mfg. plant, unspecified location Ichihara *et al.* 2006	Not reported	40	15.3 (0.65–73.7)	–

[a]Not detectable; detection limit = 0.13 ppm.
[b]Geometric mean.
[c]Median.
Click here to return to text citing Table B-3.

Table B-4. 1-Bromopropane manufacturing – area samples

Location (source)	Type of job/area	Number of samples	Mean conc. (range), ppm
Mfg. plant, China Ichihara *et al.* 2004a	Various; in front of reaction pot, in front of stock vessel, above bottle when pouring solution into bottles, product analysis room, site outside plant for washing vessel	Not reported	– (1.1–90.2)
Mfg. plants, China Li *et al.* 2010b	Various; reaction pot, distillation pot, raw product collection	30	– (2.2–22)
	Various; reaction pot, distillation pot, recording spot	9	– (ND–16.5)
	Various; reaction pot, distillation pot, raw product collection	64	– (ND–88)
	Various; reaction pot, operation desk, aisle	72	– (ND–22)

ND = Not detected.
Click here to return to text citing Table B-4.

Table B-5. Dry-cleaning applications – personal samples of 1-bromopropane

Location (source)	Type of job	Number of samples	Air	
			TWA (range), ppm	Partial shift conc., ppm (minutes)
Dry-cleaning facility 1 Eisenberg and Ramsey 2010	Operator	2	40 (23–56)	–
	Cashier	2	17 (10–24)	–
Dry-cleaning shops Blando *et al.* 2010[a]	Operator, shop A	NR	– (12.7–54.55)	–
	Operator, shop B	NR	41.64	–
	Operator, shop C	NR	– (< 0.004–0.35)	–
	Clerk, shop A	NR	– (8.31–21.85)	–
	Clerk, shop B	NR	0.65	–
	Seamstress, shop C	NR	< 0.004	–
Dry-cleaning facility 2 Eisenberg and Ramsey 2010	Operator	1	–	7.2 (209 min)
	Cashier	1	–	1.5 (212 min)
Dry-cleaning facility 3 Eisenberg and Ramsey 2010	Operator	1	–	11 (163 min)
Dry-cleaning facility 4 Eisenberg and Ramsey 2010	Operator	1	–	160 (241 min)
	Cashier	1	–	2.4 (246 min)

NR = Not reported.
[a]Ranges are reported because data points were collected over a 4-day period depending on the shop owner's willingness to participate in the study (i.e., Shop A has sampling data for all 4 days, Shop B for only 1 day, and Shop C for 3 days).
Click here to return to text citing Table B-5.

Table B-6. Dry-cleaning applications – area samples of 1-bromopropane in air

Location (source)	Type of job/area	Air concentration, ppm[a]
Dry-cleaning facility 1 Eisenberg and Ramsey 2010	Behind dry-cleaning machine, morning	103
	Behind dry-cleaning machine, afternoon	48
	In front of dry-cleaning machine, morning	66
	In front of dry-cleaning machine, afternoon	36
Dry-cleaning facility 2 Eisenberg and Ramsey 2010	Behind dry-cleaning machine	1.5
	In front of dry-cleaning machine	6.4
Dry-cleaning facility 3 Eisenberg and Ramsey 2010	Front counter	8.6

Location (source)	Type of job/area	Air concentration, ppm[a]
Dry-cleaning facility 4 Eisenberg and Ramsey 2010	Behind dry-cleaning machine	170
	In front of dry-cleaning machine	33
Dry-cleaning shops Blando *et al.* 2010	Rear left of shop by machine, shop A	17.66
	Front right of shop by customer counter, shop B	3.8
	Front left of shop by customer counter, shop B	2.67
	Rear right of shop, shop B	3.17
	Rear left of shop by machine, shop B	5.4
	Rear right of shop, shop C	< 0.004
	Rear left of shop by machine, shop C	< 0.004
	Rear left of shop by machine, shop D	20.47
Unidentified New Jersey dry-cleaning facility MMWR 2008	During handling of clothes	75–250 times background levels

[a]One measurement per location was reported.

Click here to return to text citing Table B-6.

Table B-7. Vapor degreasing applications – personal samples of 1-bromopropane in air, of urinary biomarkers (AcPrCys and Br^-), and of 1-bromopropane in exhaled air

Location (source)	Type of job	Number of TWA samples	1-BP in air	Urine		1-BP in exhaled air, mean conc. (range), ppm
			Mean TWA (range), ppm	AcPrCys, mean conc. (range), mg/L	Bromide, mean conc. (range), mg/L	
Helicopter transmission factory Hanley and Dunn 2006[b]	Plating (Day 1)	5[a]	1.55 (0.077–3.23)	[2.134 (0.028–7.551)][c]	8.5 (4.7–12.5)	0.17 (0.12–0.22)
Aerospace components mfr., Plant A, Plant B, Hanley *et al.* 2006b[b]	Cell/corrosion treatment, non-destructive testing, paint and wire dept. (Plant A) (Day 1)	7[a]	0.69 (0.19–1.1)	[0.25 (0.0156–0.883)][c]	4.1 (1.9–8.1)	0.23 (0.12–0.38)
	Assembly prep, repair-overhaul, paint and wire dept. (Plant B) (Day 1)	4[a]	1.5 (0.82–2.1)	[1.35 (0.607–2.390)][c]	14 (7.6–21)	0.23 (0.11–0.33)
Hydraulic power control component mfr. Hanley and Johnson 2007b[b]	Assembly dept. (Day 1)	4[a]	0.85 (0.22–1.4)	[1.01 (0.15–3.21)][c]	3.9 (1.1–7.9)	– (ND–0.20[d])
Optical prism and assemblies mfr. Hanley and Dunn 2007[b]	Milling and maintenance workers (Day 1)	7[a]	5.1 (0.52–9.8)	[2.52 (0.289–5.92)][c]	13 (3.7–23)	0.90 (0.10–2.5)
Printed electronics circuit assembly mfr.	Assembly dept. (Day 1)	5[a]	7.0 (1.3–14)	[5.54 (0.351–13.3)][c]	34 (8.6–67)	2.9 (0.30–6.1)

Location (source)	Type of job	Number of TWA samples	1-BP in air	Urine		1-BP in exhaled air, mean conc. (range), ppm
			Mean TWA (range), ppm	AcPrCys, mean conc. (range), mg/L	Bromide, mean conc. (range), mg/L	
Hanley and Johnson 2007a[b]						
Facilities in the five rows shown above, near degreasers and away from degreasers Hanley *et al.* 2010[b]	Near degreasers (Day 1)	22[a]	2.63[e] (0.078–21.4)	1.33[f] (0.0108–24.2)	8.94[f] (1.69–115)	–
	Away from degreasers (Day 1)	9[a]	0.308[e] (0.077–1.69)	0.115[f] (0.00512–0.726)	3.74[f] (1.69–15.6)	–
Below-boiling vapor degreaser Reh and Nemhauser 2001	Assembler	20	– (0.01–0.63)	–	–	–

[a]Number of workers is reported; note that each worker was sampled on two consecutive days so the total number of samples is x 2; e.g., for Hanley and Dunn 2006, N = 5 x 2 = 10.
[b]Raw data for TWA air concentrations and urinary bromide and AcPrCys concentrations from Hanley and Dunn 2006, Hanley *et al.* 2006b, Hanley and Dunn 2007, Hanley and Johnson 2007a, and 2007b field studies were used for summary analysis presented in Hanley *et al.* 2010. Data categorized by workers "near degreasers" and "away from degreasers" not presented in Hanley and Dunn 2006, Hanley *et al.* 2006b, Hanley and Dunn 2007, Hanley and Johnson 2007a, and 2007b field studies.
[c]Data reported in µg/L.
[d]ND = not detected. 1-Bromopropane was only detected in one sample for this collection period.
[e]Geometric mean.
[f]Geometric mean. Forty-eight hour composite concentration, adjusted for creatinine; units are mg/(g-Cr).
Click here to return to text citing Table B-7.

Table B-8. Vapor degreasing applications – area samples

Location (source)	Type of job/area	Air concentration, ppm[a]
Vapor degreaser Reh and Nemhauser 2001	On exhaust duct above degreaser	4.42
	On cart, 5 feet from degreaser	1.70
	Outside of cleaning room (5 samples)	0.02–0.03
	On metal rack, near degreaser room door	0.02
	Near degreaser room window	0.02
	Five feet from degreaser room window	0.02
	Office next to degreaser room	0.02

[a]One measurement per location was reported.

Click here to return to text citing Table B-8.

Regulations and guidelines

Table B-9. Existing U.S. standards and guidelines with exposure limits for 1-bromopropane (ppm)[a]

Type of Guideline	Duration of exposure
	8 hours
Threshold Limit Value – Time Weighted Average (ACGIH)	10
Permissible Exposure Limit (PEL) – Time Weighted Average (California OSHSB)	5
Acceptable Exposure Limit – Time Weighted Average (EPA)[b]	25

[a]As cited in CDC 2008, FR 2003.
[b]The EPA acceptable exposure limit is a non-binding, recommended, voluntary workplace exposure limit. Because there is currently no OSHA PEL for 1-bromopropane, EPA – under the Significant New Alternatives Policy (SNAP) program – determined a safe workplace exposure to evaluate whether the use of 1-bromopropane would pose significantly greater risk than the use of other substitutes available in the same end uses, EPA 2007.

Note: The EPA SNAP program reviews alternatives to ozone-depleting substances and approves the use of alternatives that do not present substantially greater risk to the public health and environment than the substance they replace or other available substitutes. Table B-10 lists EPA SNAP program determinations regarding different end uses of 1-bromopropane (EPA 2007, FR 2007 - information is current as of 1/18/13).

Table B-10. EPA SNAP program determinations regarding different end uses of 1-bromopropane

1-bromopropane end use	Substitute	EPA SNAP program determination
Solvent in industrial equipment for metals cleaning, electronics cleaning, or precision cleaning	1-bromopropane as a substitute for CFC–113 and methyl chloroform	Acceptable[a]
Coatings	1-bromopropane as a substitute for CFC–113, HCFC–141b, and methyl chloroform	Acceptable subject to the use condition that use is limited to coatings facilities that have provided EPA data which demonstrates their ability to maintain acceptable workplace exposures[b]
Aerosol solvents	1-bromopropane as a substitute for CFC–113, HCFC–141b, and methyl chloroform	Unacceptable[b]
Adhesives	1-bromopropane as a substitute for CFC–113, HCFC–141b, and methyl chloroform	Unacceptable[b]

[a]EPA final rule, EPA 2007.
[b]EPA proposed rule, FR 2007.

Note: The American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV) of an 8-hr time-weighted average of 10 ppm is being considered for a change to 0.1 ppm in the Notices of Intended Changes (NIC) for the 2013 TLVs (ESIS 2012). Exposure limits proposed by vendors of 1-bromopropane–based products range from 5 to 100 ppm (EPA 2007).
Click here to return to text citing Table B-10.

Appendix C: Assessment of the Quality of the Individual Animal Cancer Studies

Only two studies were identified that met the inclusion criteria and these studies was evaluated for study quality. Because similar protocols were used for the NTP 2-year bioassays in rats and mice and results of assessments were similar, the studies are considered together in the table below. Each primary study was systematically evaluated to determine if it is informative for a cancer assessment. Studies that were given the most weight in the evaluation are those that were of sufficiently long duration to identify a cancer endpoint (ideally an exposure approaching the lifetime of the animal), and provided a detailed account of the study design and data collection. Ideally, studies should use an exposure route comparable to human exposure and appropriate statistical methods in reporting of results. Comparison with historical control values is sometimes helpful in assessing the significance of a finding, especially in the case of rare tumors, lower powered studies, or assessment of background tumor incidences. The number of animals used in a study, the incidence of tumors in control vs. treated group, and the rarity of a tumor influence the statistical power of a study to detect an effect and are parameters that need to be taken into account in study design and results assessment. *Post hoc* power calculations can be performed. However, rare tumors will be considered in the assessment even if their incidence does not reach significance. Study performance elements for evaluating the different components of study quality are described below.

Click here to return to text citing Appendix C in the foreward.

Click here to return to text citing Appendix C in Section 4.

NTP TR 564 Inhalation Toxicology and Carcinogenesis Studies of 1-Bromopropane (CAS No. 106-94-5) in Rats and Mice

Substance characterization	**Independent experiments were conducted in rats and mice at Battelle Toxicology Northwest (Richland, WA)**
Is the chemistry of the substance well characterized? Are the purity, solubility and stability adequate for attributing any adverse effects to the substance?	Yes. Overall purity of the chemical was determined by gas chromatography and three impurities were identified as 1-propanol (0.03%), 2-bromopropane (0.02%), and di-n-propylether (0.02%); stability of bulk chemical, and vapor concentration throughout the experiment monitored against a standard by gas chromatography.
Animal husbandry	
Are the source, species, and strain of the animals adequately described?	Yes. Rats (F344/N) and mice (B6C3F$_1$) were from Taconic Laboratory Animals and Services (Germantown, NY).
Are the care, diet, housing and maintenance of the animals adequate for attributing any adverse effects to the substance?	Yes. The studies were conducted in and Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) inspected and approved facility; testing was also done on bedding, water and diet for possible chemical contamination; sentinel animals were used and

	sera tested for subclinical disease.
Were control animals housed in the same room, and tested at the same time under the same conditions as the dosed groups?	Yes. Each animal was housed individually. Animal care and maintenance were described.
Study design	
Animal model: Are the species and sex appropriate for determination of any exposure-related effect? Were the dose groups randomized?	Yes. Rats and mice of both sexes were tested; there is an adequate historical control database on these species and strains for inhalation studies from this laboratory.
Dosing and observation conditions: Are the study period, dosing period, route of exposure, and doses used adequate for determination of any adverse effect?	Yes. The animals were exposed throughout most of their lifespan (2 yr) by inhalation at a route relevant to human exposure.
Statistical Power: Does the study have adequate number of animals per group to detect an adverse effect, if present?	These studies follow NCI/NTP guidelines with respect to number of animals (Haseman JK. 1984. Environ Health Perspect, 58: 385-392). Whether the adverse effect is statistically significant will depend on 1) what the tumor endpoint is and 2) the incidence of spontaneous tumors for that endpoint. Based on available historical NTP control data, skin tumors and intestinal adenomas in rats and the lung tumors in mice were were detected at approximately 70% power; mesotheliomas and pancreatic islet-cell tumors in rats were below 50% power.
Clinical observations, necropsy and pathology	
Were clinical observations performed?	Yes. A timetable of clinical observations was reported.
Was a full necropsy done on these animals and was histopathology done on tissues from at least all major organs?	Yes. Complete necropsies were done on all animals. All organs and tissues were examined for gross lesions and complete histopathology was performed on all major organs.
Are pathology procedures well described and adequate for determination for any exposure-related effect?	Yes, tissue fixation method, microscopic evaluations and quality assessment of the data are presented.
Data reporting and statistical methods	
Is data reporting well characterized?	Yes. Data are presented in a tabular format; individual animal data are provided in appendices.
Have tumors (benign/malignant) from the same organ been appropriately combined? If so, do they originate from the same cell type? e.g., fibrosarcoma would not be combined with adenoma.	Yes (Rats) Yes (Mice)
Were statistical analyses performed on the data and adequately described?	Yes (Rats) Yes (Mice)

Are appropriate historical control data available?	Historical control values for studies by inhalation and by all routes are reported.
Are these studies informative for cancer assessment?	Yes (Rats) Yes (Mice) No major limitations on cancer study quality were found.

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Appendix D: Genotoxicity Studies

The five tables on the following pages contain data discussed in the "Mechanisms and Other Relevant Effects" section (Section 5) for genetic and related effects (Section 5.1).

Data are reported for *in vitro* studies of 1-bromopropane mutagenicity in bacteria (Table D-1), *in vitro* genotoxicity studies of 1-bromopropane in mammalian cells (Table D-2), *in vivo* studies of cytogenetic effects of 1-bromopropane in rodents (Table D-3), *in vivo* studies of cytogenetic effects of 1-bromopropane in humans (Table D-4), and a summary of *in vitro* and *in vivo* studies of genotoxicity of 1-bromopropane metabolites (Table D-5).

Click here to return to text citing Appendix D.

Table D-1. *In vitro* studies of 1-bromopropane mutagenicity in bacteria

Reference	Strain	Method	LED/HID		Results		Cytotoxicity		Evaluation: limitations and conclusions[a]
			– S9	+ S9	– S9	+ S9	– S9	+ S9	
Barber *et al.* 1981	*S. typhimurium* TA98, TA100 TA1535	Plate incorporation; closed-system incubation	TA98 (HID) 2,497 µg/plate[b]	TA98 (HID) 2,497 µg/plate[b]	–	–	NR	NR	No toxicity was observed up to and including the highest dose tested (2,497 µg/plate[b]) for each strain.
			TA100 (LED) 1107 µg/plate[b]	TA100 (LED) 1107 µg/plate[b]	+	+	NR	NR	For strains showing mutagenicity, positive effects were observed at the same doses for with or without S9.
			TA1535 (LED) 603 µg/plate[b]	TA1535 (LED) 603 µg/plate[b]	+	+	NR	NR	Test results with other strains, TA1537 and TA1538, reported as negative (data not provided by study authors).

Reference	Strain	Method	LED/HID		Results		Cytotoxicity		Evaluation: limitations and conclusions[a]
			– S9	+ S9	– S9	+ S9	– S9	+ S9	
Elf Atochem 1994, as cited in NTP 2003a	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	Protocol (plate incorporation or preincubation) not specified; closed-system incubation	10,000 µg/plate	10,000 µg/plate	–	–	10,000 µg/plate	10,000 µg/plate	A brief description of this study was presented in the NTP 2003 review, but protocol not specified, and number of replicate plates and resultant data (i.e., numbers of revertants/ plate for each dose of the tested strains) were not provided. Insufficient information to evaluate because protocol not specified.
Kim *et al.* 1998, as cited in NTP 2003a	*S. typhimurium* TA98, TA100 TA1535, TA1537 and	Protocol not specified and no indication if closed-system was used	5,000 µg/plate	5,000 µg/plate	–	–	NR	NR	A brief description of this study was presented in the NTP 2003 review, but the protocol was not specified and details on methods (e.g., solvent) and observations regarding cytotoxicity were not given. Also, the number of replicate plates and resultant data (i.e., numbers of revertants/ plate for each dose of the tested strains) were not provided. Insufficient information to evaluate because protocol not specified.
	E. coli WP2uvrA		5,000 µg/plate	5,000 µg/plate	–	–	NR	NR	

Reference	Strain	Method	LED/HID		Results		Cytotoxicity		Evaluation: limitations and conclusions[a]
			– S9	+ S9	– S9	+ S9	– S9	+ S9	
NTP 2011a (two studies, independent contract labs)	Study 1								
	S. typhimurium TA97, TA98, TA100, TA1535	Preincubation	All strains: 10,000 µg/plate, but ≥ 3,333 µg/plate was too toxic to evaluate	All strains: 10,000 µg/plate, but ≥ 3,333 µg/plate was too toxic to evaluate	–	–	≥ 3,333 µg/plate	≥ 3,333 µg/plate	All strains were tested to 10,000 µg/plate; unable to adequately evaluate mutagenicity at doses ≥ 3,333 µg/plate due to high toxicity. Not mutagenic at non-toxic doses. +S9: 10% and 30% rat or hamster. Study 2 used same chemical lot as 2-year NTP bioassay. Not mutagenic.
	Study 2								
	S. typhimurium TA98, TA100	Preincubation	Both strains: 5,000 µg/plate	Both strains: 10,000 µg/plate	–	–	≥ 3,500 µg/plate	TA98: 10,000 µg/plate	+S9: 10% rat. TA100: not toxic at highest dose (10,000 µg/plate) tested. Not mutagenic.
	E. coli WP2uvrA/ pKM101	Standard protocol	5,000 µg/plate	10,000 µg/plate	–	–	≥ 5,000 µg/plate		+S9: Not toxic at highest dose (10,000 µg/plate) tested. Not mutagenic.

LED/HID = lowest effective dose/highest ineffective dose, NR = not reported, + = positive, – = negative.
[a]Evaluations of some studies (as indicated) presented in this table are limited by the information provided in the cited review paper.
[b]Reported dose levels of 1-bromopropane were determined by using gas liquid chromatography to analyze samples of distilled water that were in the test chambers during treatment. To facilitate comparison with other studies, data reported by these authors as µmoles per plate were converted to µg/plate.
Click here to return to text citing Table D-1.

Table D-2. *In vitro* studies of 1-bromopropane in mammalian cells

Reference	Effect	Test system	Concentration (LEC or HIC)	Cytotoxicity	Results		Evaluation: limitations and conclusions[a]
					-S9	+S9	
Elf Atochem 1994, cited in NTP 2003a	Mutation	L5178Y mouse lymphoma cells (2 experiments)	-S9: 1,000mg/L +S9: 1,500 mg/L	≥ 2,000 mg/L (10%–60% RTG)	+	+	Adequate information provided in NTP review on methodology; reproducible two-fold increase in mutation frequency and evidence of dose response, but actual numbers of revertant colonies not available. Evidence of mutagenicity.
Toraason *et al.* 2006	DNA damage (dose response)	Comet assay, using human leukocytes from venous blood from unexposed adult males.	LEC = 1 mM 8-hr exposure		Dose (mM) / Comet tail moment[a] 0 / 1000 0.01 / 1000 0.1 / 1250 1.0 / 3500*	ND	Did not perform assays in presence of S9, since Barber *et al.* 1981 had previously shown 1-bromopropane to be mutagenic with or without added metabolic activation in the *S. typhimurium* assay. Evidence of DNA damage.
	DNA damage (temporal response)	Comet assay, using human leukocytes from venous blood from unexposed adult males.	LEC = 1 mM 4-hr exposure		Exp (hr) / Comet tail moment[a] 1 / 750 2 / 750 4 / 1250* 8 / 3250*	ND	
	Apoptosis	DNA diffusion assay using human leukocytes	LEC = 0.1 mM		Dose (mM) / Apoptotic cells (%)[a] 0 / 2.75 0.01 / 2.50 0.1 / 3.25* 1.0 / 4.75*	ND	

Exp = Exposure, LEC/HIC = lowest effective concentration/highest ineffective concentration, ND = not done, RTG = relative total growth.
*$P < 0.05$ (ANOVA).
[a]Data estimated from graph.
Click here to return to text citing Table D-2.

Table D-3. *In vivo* studies of cytogenetic effects of 1-bromopropane in rodents

Reference	Endpoint	Species/sex/#	Exposure	Results	Comments and evaluation[a]
Kim *et al*. 1998, cited in NTP 2003a	Micronuclei	Rat (Sprague-Dawley) bone marrow males and females 10 animals/ sex/group	Inhalation 0, 50, 300, 1,800 ppm 6 hr/day for 5 days/week for 8 weeks	No increases in bone marrow micronucleated polychromatic erythrocytes	Information limited to that provided in summary of study in review; values for micronuclei were not provided. NTP 2003a stated that animals exposed to 1,800 ppm had decreased bodyweight and ataxia. Treatment doses differed by a factor of 6; intermediate doses might have been informative. Negative.
Elf Atochem 1994, cited in NTP 2003a	Micronuclei	Mouse (Swiss mice) bone marrow males and females 5 animals/ sex/group	Intraperitoneal injection M: 0, 100, 400, 600, 800 mg/kg F: 0, 100, 400, 800 mg/kg Two injections; animals sacrificed 24 hr after last injection.	Bone marrow micronucleated erythrocytes M: 600 mg/kg - no increases F: 800 mg/kg - no increases	Information limited to that provided in summary of study in review; values for micronuclei were not provided. Only 800 mg/kg for females and 600 mg/kg for males were evaluated for micronuclei because the PCE/NCE ratio in controls from other doses (100, 400) were outside the historical control range Negative.

Reference	Endpoint	Species/sex/#	Exposure	Results	Comments and evaluation[a]
NTP 2011a	Micronuclei	Mouse ($B6C3F_1$) peripheral blood erythrocytes males and females 5 animals/ sex/group	Inhalation: 3 mo 0 ppm 62.5 125 250 500	NCE[b] Males / Females 2.00 ± 0.61 / 1.80 ± 0.25 3.10 ± 0.81 / 1.70 ± 0.25 2.70 ± 0.64 / 1.60 ± 0.19 1.30 ± 0.41 / 1.40 ± 0.33 2.30 ± 0.46 / 1.80 ± 0.20	Percent of polychromatic erythrocytes (reticulocytes) was unaltered indicating a lack of bone marrow toxicity. Negative.
Saito-Suzuki *et al.* 1982	Dominant lethal mutation assay	Rat (Sprague-Dawley) 15 exposed males mated with females (1 female/ week/male) for 8 weeks, examined vital status of fetuses 13-14 days after mating	Gavage 400 mg/kg 5 days	Week / DLMI[c] 1 / -2.1 2 / 1.8 3 / 0.4 4 / 1.3 5 / 3.3 6 / 8.0 7 / 0.9 8 / 9.3	An increase in the number of dead implants in fetuses from rats mated 8 weeks after 1-bromopropane exposure compared with controls was observed but the mutational index was not increased. Negative.
Yu *et al.* 2008	Dominant lethal mutation assay	Mouse (ICR) 20 males/exposure group, mated with 40 unexposed females (2 females/week/ male) for 6 weeks; examined vital status of fetuses at 15 to 17 days gestation	Gavage Males exposed to 300 or 600 mg/kg/day 10 days	Week / DLMR[d] 300 / 600 1 / 0.17 / -0.26 2 / 2.17 / 0.88 3 / 0.3 / -2.71 4 / 3.14 / -2.03 5 / 2.98 / -4.66 6 / 3.68 / 0.27	Negative.

DLMI = Dominant Lethal Mutation Index, DLMR = Dominant Lethal Mutation Rate, NCE = normochromatic erythrocytes.
[a]Evaluations of some studies (as indicated) presented here are limited by the information provided in the cited review paper.
[b]Micronucleated NCEs/1000.
[c](1-live embryos per test female/live embryos per control female) x 100.
[d](1-[{mean of live fetuses in treated group/mean of implants in treated group} x {mean of implants in controls/mean of live fetuses in controls}]) x 100.
Click here to return to text citing Table D-3.

Table D-4. *In vivo* studies of 1-bromopropane in humans

Reference	Effect	Population and analyses	Exposure	Results	Evaluation: limitations and conclusions
Toraason *et al.* 2006	DNA damage Comet assay: Tail moment and dispersion coefficients[a;] 100 leukocytes per sample	*Population* 64 workers (18 males and 46 females) at two spray adhesive facilities (A and B) Facility A (42) 29 non-sprayers 13 sprayers Facility B (22) 16 non-sprayers 6 sprayers *Analyses* Exposure to 1-bromopropane and DNA damage were evaluated by analyses involving (1) facility and job type, and (2) exposure indices (workplace air, urine and serum) in multivariate models controlling for age, gender, facility, cigarette smoking and GSTM1 and GSTT1 polymorphisms.	Exposure assessed by TWA (ppm) and bromide serum (mg/dL) and urine levels (mg/dL). Facility/ worker — TWA — Urine[b] — Serum[b] A/NS — 2 ± 2 — 28 ± 9 — 2.6 ± 0.7 A/SP — 83 ± 85 — 238 ± 17 — 19.5 ± 11.4 B/NS — 5 ± 1 — 2 ± 2 — 0.3 ± 0.1 B/SP — 21 ± 5 — 10 ± 14 — 0.9 ± 0.3 TWA significantly correlated with both start-of-week and end-of-week urine and serum bromide concentrations	*Analysis by work type and facility* Facility A NS — SP TM/Start — 2517 — 2867 TM/End — 3080* — 3178 TMD/Start — 562 — 496 TMD/End — 678 — 752* Facility B NS — SP TM/Start — 2856 — 3430 TM/End — 2770 — 2974 TMD/Start — 580 — 596 TMD/End — 653 — 616 *Analysis by exposure indices* *Tail moment - P values* Start — End TWA (log) — 0.654 — 0.148[d] Urine (log) — 0.075[c] — 0.108[d] Serum (log) — 0.191 — 0.171[d] TWA (EQ) — 0.567 — 0.016[d] Urine (EQ) — 0.106[c] — 0.141 Serum (EQ) — 0.007[c] — 0.049[d] Dispersion coefficient – no statistically significant	End-of-the-workweek DNA damage (TMD) was higher, albeit not statistically significant, among workers (sprayers and non-sprayers) at both facilities with GSTM1-positive genotypes. In multivariate analysis, GSTM1 had a significant effect in models of end-of-workweek DNA damage (TMD) and 1-bromopropane TWA log-transformed levels. The exposure quartile analyses might have had greater statistical power than the models using log-transformed values since participants with missing data for one exposure indices could be included in the analyses based on their ranking for another exposure indices. *Strengths*: Wide range of exposures allowed for evaluation of exposure response. Assessment of 1-bromopropane exposure was at the individual level. Multivariate analyses was considered to be more informative than the analysis by job and facility *Limitations*: Small numbers of

Reference	Effect	Population and analyses	Exposure	Results	Evaluation: limitations and conclusions
				associations observed between DNA damage and exposure to 1-bromopropane in any of the models.	subjects, no unexposed controls, multiple comparisons. *Conclusion*: Limited evidence that exposure to 1-bromopropane causes DNA damage in leukocytes from workers.

EQ = exposure quartiles model, ppm = parts per million, NS = non-sprayer, SP = sprayer, TWA = time weighted average, TM = tail moment, TMD = tail moment dispersion coefficient.
*End-of-the-workweek measures significantly higher than start-of-the-workweek measures for the same individual (paired *t*-test, $P < 0.05$).
[a]Dispersion coefficient = variance divided by mean of tail moment from 100 leukocytes.
[b]End of week measure.
[c]Significant association of facility in model.
[d]Significant association of gender in model.

Click here to return to text citing Table D-4.

Table D-5. Summary of *in vitro* and *in vivo* studies of 1-bromopropane metabolites

Test System	Effect	Glycidol		Propylene oxide		α-Bromohydrin		3-Bromo-1-propanol		1-Bromo-2-propanol	
		-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9
In vitro											
Bacteria	Mutation[#]	+[a]	+[a]	+[b]	+[b]	+[c, d]	+[c, d]	+[*, d]	+[*, d]		
	DNA damage	+[a]		+[*b]	+[*, b]			+[*, e]		+[*, e]	
	DNA adducts			+[f, g]							
Yeast	Mutation	+[a]	+[*, a]	+[b]	+[*, b]						
	Gene conversion			+[*, b]							
Insects	Mutation	+[*, a]		+[b, h, i]							
	Heritable translocation	+[*, a]									
	DNA adducts			+[*, h]							
Mammalian cells (other than human)	Mutation	+[a]	+[*, a]	+[b]							
	Chromosomal damage	+[a]	+[a]	+[b]	+[*, b]						
	DNA damage	+[a, j]	+[*, a]	+[b]	+[*, b]						
	DNA adducts	+[*, a]		+[*, k]							
Human cells	Chromosomal damage	+[*, a]		+[b]							
	DNA damage	+/–[a]	+[*, a]	+[b, l, m, n]							
In vivo											
Mammals (rodents, dogs, monkeys)	Mutation (germ cell)			–[b]							
	Chromosomal damage	+/–[a]		+/–[b]							
	DNA adducts			+[b, k, o, p, q]							
	Binding to protein			+[b, p, r]							
Human: exposed workers	Chromosomal damage			?[b]							
	DNA damage			+[*, s]							
	DNA adducts			+[b, s]							
	Binding to protein			+[b, s]							

Sources: [a]IARC 2000, [b]IARC 1994, [c]Stolzenberg and Hine 1979, [d]Stolzenberg and Hine 1980, [e]Hyman *et al.* 1980, [f]Mazon *et al.* 2009, [g]Snow *et al.* 1994, [h]Nivard *et al.* 2003, [i]Vogel and Nivard 1997, [j]El Ramy *et al.* 2007, [k]Plna *et al.* 1999, [l]Chovanec *et al.* 2001, [m]Kolman *et al.* 1997, [n]Fabiani *et al.* 2012, [o]Segerbäck *et al.* 1998, [p]Ríos-Blanco *et al.* 2000, [q]Ríos-Blanco *et al.* 2003, [r]Couch *et al.* 1996, [s]Czene *et al.* 2002.

+ = Positive in all or most of available studies; – = negative in all or most of available studies; +/– = available studies are mixed positive and negative, ? = inconclusive (variable response in adequate study).

[#]Mutation test results were positive for multiple bacterial strains, except for α-bromohydrin, which was positive for *S. typhimurium* TA100 but not TA98, and for 3-bromo-1-propanol, which was only tested in TA100.

[*]Result is based on one study.

Click here to return to text citing Table D-5.

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Appendix E: Relevant Toxicological Effects

Studies on neurological, developmental, reproductive, immunological, and hepatotoxic effects were identified to determine whether they could inform potential mechanisms of carcinogenicity. Several studies indicate that metabolic activation and glutathione depletion are important factors for many of the toxic effects observed in rodents. Appendix E provides a brief review of the toxic effects that have been linked to metabolic activation and/or glutathione depletion and oxidative stress and other alterations and provides background information for Section 5.3, which discusses these mechanisms as they related to carcinogenicity.

Click here to return to text citing Appendix E in Section 4.

Click here to return to text citing Appendix E in Section 5.

Click here to return to text citing Appendix E in Section 6.

Reproductive toxicity

NTP (2003a) evaluated the reproductive toxicity of 1-bromopropane. There was convincing evidence that 1-bromopropane caused reproductive effects in experimental animals but the evidence in humans was limited to a health hazard survey conducted by NIOSH at a plant that used a spray adhesive that contained 1-bromopropane. Three of 42 workers reported fertility problems (2 males and 1 female). Ichihara *et al.* (2002) presented case reports for three female workers who used a spray gun with 1-bromopropane as a solvent. Most of the symptoms and signs were neurological in nature but two of the women reported irregular periods and decreased sexual desire.

NTP (2003a) also reviewed a two-generation reproductive toxicity study that reported significant effects in males, females, and offspring. Reproductive capabilities were examined in the F_0 and F_1 generations, and neonatal survival, growth, and development were evaluated in the F_1 and F_2 offspring. Whole-body inhalation exposures (6 hours/day, 7 days/week at nominal concentrations of 100, 250, 500, or 750 ppm) began at 7 weeks of age for the F_0 parents and at weaning for the F_1 generation. Exposures began at least 70 days prior to mating. Prior to weaning on postnatal day 22, the F_1 offspring were indirectly exposed to the test chemical *in utero* and through nursing. Effects in F_0 parents included reduced sperm motility and prostate weight, abnormal sperm, increased estrous cycle length and ovarian follicular cysts, decreased numbers of implantation sites and litter size, and complete infertility in the high-dose group (750 ppm). Reproductive effects in F_1 offspring were similar. The only significant effect reported in the F_2 rats was reduced postnatal weight gain. Other studies reported that Wistar rats exposed to 1-bromopropane for 12 weeks had decreased sperm count and sperm motility, irregular estrous cycles, and a decrease in the number of normal growing follicles (NTP 2003a, 2011a).

Some of the reproductive effects have been linked to metabolic activation. Garner *et al.* (2007) investigated the relationship between 1-bromopropane oxidative metabolism and

sperm toxicity in mice. Wild-type and Cyp2e1$^{-/-}$ (knockout) mice (4 per group) were exposed to [1,2,3-^{13}C]-1-bromopropane at 800 ppm for 6 hours in an inhalation chamber. In addition, *ex vivo* experiments were conducted using caudal sperm (collected from the cauda epididymis) from unexposed wild-type and knockout mice incubated with either 1-bromopropane or its metabolite 1-bromo-2-hydroxypropane (1-bromo-2-propanol) in a sealed test tube. Exposed wild-type mice had a 37% reduction in the percentage of motile sperm compared with unexposed controls (Table E-1a). In contrast, the percentage of motile sperm in exposed knockout mice was not significantly different from unexposed controls. In addition, liver glutathione levels were reduced by 76% in exposed wild-type mice compared with 47% in exposed knockout mice (Table E-1a). Epididymal sperm were isolated from unexposed wild-type and knockout mice and were incubated with 0.05 mM 1-bromopropane or 1-bromo-2-hydroxypropane for 2 hours (Table E-1b). Sperm isolated from wild-type mice had significantly reduced motility when incubated with either test compound. In contrast, sperm from knockout mice did not show a significant change in motility when incubated with 1-bromopropane but motility was significantly reduced when incubated with 1-bromo-2-hydroxypropane. The authors did not address the apparent differences in sperm motility between wild-type and knockout mice in the control groups for the *ex vivo* experiment. Although the sample sizes used in these experiments were small, these data suggest that products of CYP2E1-mediated oxidation of 1-bromopropane (specifically 1-bromo-2-hydroxypropane) contribute to male reproductive toxicity.

Table E-1a. 1-Bromopropane effects on sperm motility and glutathione levels in wild-type or Cyp2e1$^{-/-}$ mice

Genotype	Dose (ppm)	% Motile sperm (N = 8)	GSH (mM ± SE) (N = 3 to 4)
Wild-type	0	63	10.6 ± 1.7
	800	40*	2.6 ± 2.5**
	% change	–37	–76
Cyp2e1$^{-/-}$	0	57	13.8 ± 1.4
	800	48	7.36 ± 1.0*
	% change	–16	–47

Source: (Garner *et al.* 2007).
* $P < 0.05$ (compared with unexposed controls).
** $P < 0.01$ (compared with unexposed controls).

Table E-1b. Sperm motility following 2-hour incubations with 1-bromopropane or 1-bromo-2-hydroxypropane

Genotype	% Motile sperm (N = 3)		
	Control	1-Bromopropane	1-Bromo-2-hydroxypropane
Wild-type	73	39*	26*
Cyp2e1$^{-/-}$	57	43	23*

Source: (Garner *et al.* 2007).
* $P < 0.05$ (compared with unexposed controls, 3 animals/group).

These authors believed that reduction of sperm motility might be mediated by disruption of energetic pathways by metabolites (bromoacetone and α-bromohydrin) derived from CYP-mediated oxidation of 1-bromo-2-hydroxypropane (see Figure 2-3). Studies with α-bromohydrin and its chlorinated analogue have shown that these compounds are converted *in situ* by spermatozoa into halolacetates. Halolacetates are metabolic inhibitors that can cause reduced sperm motility. Bromoacetone also may be further metabolized either to 1-hydroxy-1-bromoacetone, ultimately forming pyruvate and CO_2, or 3-bromo-1-hydroxypropanone. 3-Bromo-1-hydroxypropanone can inhibit sperm motility by conversion to bromolactaldehyde and bromopyruvaldehyde, and ultimately yielding the metabolic poison bromopyruvate.

Neurotoxicity

Neurotoxic effects of 1-bromopropane were first described in rats and were later used to identify and analyze the initial human cases (Ichihara *et al.* 2011, Li *et al.* 2010b, Meyer-Baron *et al.* 2012). Although the molecular mechanisms of neurotoxicity are not completely understood, recent studies show that the hippocampus is especially susceptible to 1-bromopropane–induced effects and involves oxidative stress, loss of ATP production, altered GABA metabolism and reduced GABAergic feedback inhibition, inhibition of the ubiquitination-proteosome system, changes in neurotransmitter receptor expression, and modifications of intracellular signaling cascades (Fueta *et al.* 2004, Fueta *et al.* 2002b, Huang *et al.* 2011, Mohideen *et al.* 2009). Other studies indicate that the neurotoxic effects of 1-bromopropane involve glutathione depletion, protein adducts, and degeneration of noradrenergic axons (Mohideen *et al.* 2011, Valentine *et al.* 2007, Wang *et al.* 2002, Wang *et al.* 2003).

Studies in humans include more than a dozen case reports from the United States and an epidemiologic study of 1-bromopropane production factory workers in China (Ichihara *et al.* 2011, Li *et al.* 2010b). Signs and symptoms from the case reports were similar and included numbness, diminished vibration sense in the lower extremities, distal latency, and ataxia suggesting that sensory nerves were affected. Other effects included hyperreflexia, suggesting damage to the central nervous system, and neurobehavioral effects (memory disturbances and depressive or unstable mood). Li *et al.* (2010b) evaluated neurologic abnormalities in 60 women factory workers compared with age-, sex-, and region-matched controls. Significant neurological effects included dose-dependent increase in the distal latency of tibial nerves, increased threshold for vibration sense in the toes, and decreased sensory nerve conduction velocity of the sural nerve. However, the exposure assessment was based on recent exposure measurement, which may not accurately reflect past exposure.

Reported effects in rats include prolongation of motor distal latency, reduction of motor nerve conduction velocity, myelin sheath degeneration, decrease in cerebral weight, pyknotic shrinkage and degeneration of Purkinje cells in the cerebellum, ataxia, and decreased limb muscle strength (Ichihara *et al.* 2011). Wang *et al.* (2002, 2003) investigated the biochemical changes in the central nervous system of rats exposed to 1-bromopropane vapors for 7 days or 12 weeks. Groups of 9 male Wistar rats were exposed to 0, 200, 400, or 800 ppm 8 hours/day, 7 days/week. Both studies reported a

dose-dependent decrease in neurospecific γ-enolase in the cerebrum and cerebellum (suggesting functional or cellular loss of neurons) with concomitant decreases in nonprotein sulfhydryl bases, total glutathione, and creatine kinase activity. Creatine kinase also has a critical active-site sulfhydryl group and may be representative of other proteins with a functional sulfhydryl group. Therefore, the mechanisms of 1-bromopropane neurotoxicity may involve glutathione depletion and modification of functional proteins containing a sulfhydryl base. A study by Valentine *et al.* (2007) demonstrated that 1-bromopropane produces *S*-propyl cysteine adducts on globin and neurofilaments in rats and globin adducts in humans and provides further support for this mechanism proposed by Wang *et al.* (2002, 2003), which is discussed below.

Valentine *et al.* (2007) investigated the dose responses for urinary *N*-acetyl-*S*-(*n*-propyl)-L-cysteine (AcPrCys) and *S*-propylcysteine adducts on globin and neurofilaments as a function of 1-bromopropane exposure in male Wistar rats and humans. Two experiments were conducted in rats. In the first experiment, rats were divided into four groups (8 per group) and exposed to 1-bromopropane vapor at 0, 50, 200, or 800 ppm for 8 hours/day for 2 weeks. The second experiment included 2 groups of rats (12 per group) exposed to 0 or 50 ppm for 8 hours/day, 5 days/week for 4 weeks. Globin adducts were measured in both experiments, but neurofilament adducts were measured only in the first experiment. In humans, urinary AcPrCys and globin *S*-propylcysteine adducts were determined in workers at a 1-bromopropane production factory. Both globin and neurofilament adducts showed a linear dose-dependent increase, and a significant increase in globin adducts was observed in exposed workers compared with control workers. The authors concluded that the formation of *S*-propylcysteine adducts on rat spinal cord protein represents a potential mechanism to explain the observed decrease in sulfhydryl groups reported by Wang *et al.* (2002, 2003). Thus, the neurotoxic effects of 1-bromopropane may be explained in part by its ability to covalently bind to sulfhydryl groups in the nervous system either by direct addition or from reactive metabolites.

Subramanian *et al.* (2012) reported that several oxidative stress markers (e.g., thiobarbituric acid reactive substances, protein carbonyl, ROS, and reactive nitrogen species [RNS]) were increased in a dose-dependent manner in the rat cerebellum following exposure to 1-bromopropane vapor for 28 days. In addition, morphological changes in microglia were reported. Microglia activation in response to pathological stimuli in the CNS is a major source of ROS and RNS. Imbalance in the formation and removal of ROS and RNS results in disturbances of cellular homeostasis and cytotoxicity.

Huang *et al.* (2011) analyzed the differential protein expression in the hippocampus of F344 rats exposed to 1-bromopropane at 0, 400, or 1,000 ppm, 8 hours/day, for 1 to 4 weeks. 1-Bromopropane was shown to modify the hippocampal proteome in both a dose- and time-dependent manner. Twenty-six protein spots were identified with significant changes (increase or decrease) in their levels of expression compared with controls. From these 26 protein spots, 19 proteins were successfully identified. The altered proteins were classified into six groups according to their functional properties and included nucleocytoplasmic transport, immunity and defense, energy metabolism, purine metabolism, neurotransmitter metabolism, and ubiquitination-proteosome pathway.

These data suggest that 1-bromopropane–induced damage to the hippocampus involves oxidative stress, loss of ATP production, dysfunction of GABAergic feedback inhibition, and inhibition of ubiquitination-proteosome system. Several studies have reported an association between 1-bromopropane exposure and GABA inhibition (Fueta *et al.* 2004, Fueta *et al.* 2007, Ueno *et al.* 2007). Fueta *et al.* (2004, 2007) reported that excitability and convulsive behavior in rats following inhalation exposure to 700 or 1,500 ppm 1-bromopropane was related to dysfunction of GABA-mediated feedback inhibition in the hippocampus. Ueno *et al.* (2007) also reported dysfunction of the hippocampal GABAergic system in male Wistar rats following subchronic inhalation exposure to 1-bromopropane. Reduced function was related to decreased levels in the expression and function of GABA receptors. Although the relevance of GABA inhibition to the carcinogenicity of 1-bromopropane is unknown, several studies have reported that GABA is involved in the proliferation, differentiation, and migration of various cell types and that increased expression of GABA and GABA receptors have been reported in some tumor cells (Maemura *et al.* 2003, Schuller *et al.* 2008, Watanabe *et al.* 2006, Young and Bordey 2009). These data are briefly reviewed in Section 5.3.3.

Hepatotoxicity

Several studies have investigated the mechanisms underlying the hepatotoxic effects of 1-bromopropane in mice (Lee *et al.* 2007a, Lee *et al.* 2005b, Li *et al.* 2010a, Liu *et al.* 2009, Liu *et al.* 2010) and rats (Ishidao *et al.* 2002). Lee *et al.* focused on the role of metabolism following single oral doses while Liu *et al.* focused on the role of oxidative stress and biological factors that determine susceptibility in different mouse strains following inhalation exposure. The findings from these studies are summarized below.

The role of glutathione conjugation in the hepatotoxic effects of 1-bromopropane was investigated in male ICR mice (Lee *et al.* 2005a, Lee *et al.* 2005b) and female BALB/c mice (Lee *et al.* 2007a). These studies used similar protocols to investigate the dose response and the time course of effects and reported similar results. Two studies were conducted with male ICR mice. In the first study, male ICR mice (5 per group) received a single oral dose of 0, 200, 500, or 1,000 mg/kg of 1-bromopropane in corn oil and were sacrificed 12 or 24 hours later (Lee *et al.* 2005b). For the time-course study, groups of mice were administered a single oral dose of 1,000 mg/kg and sacrificed at 6, 12, or 24 hours. The second study was similar to the first but also included groups pretreated with phenobarbital or SKF-525A, a general CYP inhibitor (Lee *et al.* 2010a). Female BALB/c mice were divided into the same treatment groups as reported above but all mice were sacrificed after 12 hours in the dose-response study and at 6, 12, 24, or 48 hours in the time-course study (Lee *et al.* 2007a). Hepatotoxicity parameters measured in these three studies included serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), or malondialdehyde. Also liver homogenates were analyzed for glutathione (GSH), 1-bromopropane glutathione conjugate, or *S*-propyl GSH.

Body and liver weights were not affected by 1-bromopropane exposure in male ICR mice; however, the activities of serum ALT and AST were significantly increased at the high dose 24 hours after treatment (Table E-2) (Lee *et al.* 2005b). Hepatic GSH levels decreased and *S*-propyl GSH levels increased with dose 12 hours after treatment but returned to near normal levels after 24 hours. Levels of malondialdehyde, a marker of

lipid peroxidation, also increased with dose and were significantly elevated in groups exposed to 500 or 1,000 mg/kg.

Table E-2. 1-Bromopropane effects on serum enzymes in male ICR mice

Group (N = 5)	ALT (Karmen unit/mL ± SE)	AST (Karmen unit/mL ± SE)
Dose-response study (mg/kg)[a]		
0	46 ± 10	58 ± 6
200	33 ± 6	70 ± 9
500	34 ± 2	76 ± 7
1000	1972 ± 1648**	653 ± 478**
Time-course study (hr)[b]		
0	46 ± 10	58 ± 6
6	38 ± 3	106 ± 12
12	1031 ± 613	293 ± 120
24	1972 ± 1648**	653 ± 478**

Source: Lee *et al.* 2005b.
ALT = serum alanine aminotransferase, AST = serum aspartate aminotransferase.
** $P < 0.01$.
[a]Measured at 24 hours.
[b]1,000 mg/kg treatment dose.

Lee *et al.* (2010a) reported similar results. Serum ALT and AST were significantly increased by a single treatment of 1,000 mg/kg 1-bromopropane. Mice pretreated with phenobarbital to induce metabolic enzymes had significantly increased serum ALT and AST in groups treated with 750 mg/kg and above; however, groups of mice pretreated with the CYP inhibitor (SKF-525A) had significantly lower serum ALT and AST levels than mice treated with 1-bromopropane alone. In addition, thiobarbituric acid-reactive substance (TBARS), a byproduct of lipid peroxidation, also was significantly increased by 1,000 mg/kg 1-bromopropane. TBARS was not increased in animals pretreated with SKF-525A. Hepatotoxicity was associated with glutathione depletion by formation of GSH conjugates. Specifically, *S*-propyl and 2-hydroxypropyl GSH conjugates were identified in the liver, and hepatic GSH levels were significantly decreased 6 hours after treatment with 750 or 1,000 mg/kg. Pretreatment with phenobarbital resulted in significantly decreased hepatic GSH levels 6 hours after treatment with 500 or 1,000 mg/kg compared with mice exposed to 1-bromopropane alone. Mice pretreated with SKF-525A showed decreased GSH only at 500 mg/kg compared with 1-bromopropane alone. GSH levels were restored to control levels 24 hours after 1-bromopropane treatment in all groups except the high-dose groups pretreated with either phenobarbital or SKF-525A.

Effects of 1-bromopropane exposure in female BALB/c mice were consistent with those reported for male ICR mice (Lee *et al.* 2007a). Glutathione levels in the liver and spleen were significantly decreased in a dose-dependent manner (Table E-3). *S*-Propyl glutathione conjugate showed dose-related increases in the liver, spleen, and serum. Maximum amounts were detected at 6 to 12 hours after dosing.

Table E-3. 1-Bromopropane effects on hepatic GSH and GSH conjugate (*S*-propyl GSH) levels in female BALB/c mice

Group (N = 5)	ALT (Karmen unit/mL ± SE)	GSH (nmol/mg protein ± SE)		*S*-propyl GSH (nmol/mg protein ± SE)		
		Liver	Spleen	Liver	Spleen	Serum
Dose-response study (mg/kg)[a]						
0	28.4 ± 4.1	576.6 ± 23.8	161.5 ± 3.6	N.D.	N.D.	N.D.
200	35.2 ± 6.4	102.6 ± 34.9**	117.6 ± 8.5	3.2 ± 1.0	N.D.	0.04 ± 0.02
500	151.2 ± 100.7	102.2 ± 38.0**	126.2 ± 6.9	25.8 ± 3.2	1.4 ± 0.5	0.11 ± 0.02
1000	3367 ± 3111**	24.2 ± 4.9**	86.3 ± 8.7*	315.6 ± 162.7	10.3 ± 1.3	5.98 ± 1.54
Time-course study (hr)[b]						
0	28.4 ± 4.1	576.5 ± 23.8	161.5 ± 3.6	N.D.	N.D.	N.D.
6	18.3 ± 8.9	29.6 ± 10.8**	93.8 ± 10.0*	409.4 ± 72.2	6.3 ± 2.8	7.20 ± 1.52
12	3367 ± 3111**	24.2 ± 4.9**	86.3 ± 8.7*	315.6 ± 162.7	10.3 ± 1.3	5.98 ± 1.54
24	10,641 ± 3592**	28.8 ± 10.2**	110.6 ± 10.2	33.1 ± 9.2	1.9 ± 0.7	0.38 ± 0.15
48	2209 ± 849**	114.8 ± 28.0	135.2 ± 7.9	1.2 ± 0.6	1.3 ± 0.9	0.01 ± 0.01

Source: Lee *et al.* 2007a.
ALT = serum alanine aminotransferase, GSH = glutathione, N.D. = not detected.
* $P < 0.05$.
** $P < 0.01$.
[a]Measured at 12 hr.
[b]1,000 mg/kg treatment dose.

Hepatotoxic effects occurred in parallel with changes in glutathione and glutathione conjugate levels and were prevented by pretreatment with a general CYP inhibitor (SKF-525A) (Lee *et al.* 2007a, Lee *et al.* 2005b, Lee *et al.* 2010a). Increases in ALT levels were proportional to glutathione depletion and formation of *S*-propyl glutathione. Hepatotoxic effects included centrilobular cellular swelling and vacuolization of hepatocytes, congestion, hemorrhage, and centrilobular necrosis. In addition, lipid peroxidation was significantly increased and liver catalase activity was decreased in mice treated with 1-bromopropane. These data suggest that the hepatotoxic effects, including lipid peroxidation, could be related to two different metabolic pathways. First, hepatotoxicity may be closely related with glutathione depletion associated with GSH conjugate formation and subsequent formation of reactive oxygen species. Further, metabolism of 1-bromopropane by CYP enzymes to toxic metabolites that are not associated with GSH conjugation might be an additional factor.

Liu *et al.* (2009) compared the susceptibility of male mice in three strains (C57BL/6J, DBA/2J, and BALB/cA) to 1-bromopropane–induced hepatotoxicity. Male mice (6 per group) were exposed to 0, 50, 110, or 250 ppm for 8 hours/day for 28 days. Hepatic CYP2E1 levels, glutathione-*S*-transferase (GST) activity, total GSH, oxidized GSH (GSSH), and NAD(P)H:quinone oxidoreductase (NQO1) and heme oxygenase-1 (HO-1) mRNA levels were measured. All three strains exposed to 250 ppm developed focal necrosis and hepatocellular degeneration, and both parameters showed a significant correlation between response and dose as measured by Pearson's coefficient (Table E-4). However, BALB/cA mice were the most susceptible based on liver histopathology and

DBA/2J mice were the most resistant strain. Baseline CYP2E1 protein levels were higher while total GSH content and GST activity in the liver were lower in BALB/cA than DBA/2J mice. NQO1 and HO-1 mRNA levels were increased at 250 ppm in BALB/cA but not in DBA/2J mice. NQO1 protects cells against redox cycling chemicals and HO-1 defends against oxidant-induced injury during inflammation. Increased expression of NQO1 and HO-1 in the susceptible strain indicates increased oxidative stress compared with the resistant strain. These data indicate that CYP2E1 activity, GSH levels, and GST activity might explain the differences in susceptibility among the three mouse strains to 1-bromopropane–induced hepatotoxicity.

Table E-4. Comparison of liver histopathology among three mouse strains exposed to 1-bromopropane

Strain	N	Dose (ppm)	% Necrotic area (mean ± SD)[1]	% Lobule degeneration (mean ± SD)[a]
DBA/2J	6	0	0.00 ± 0.00	0.00 ± 0.00
	6	50	0.15 ± 0.02	15.44 ± 9.45
	6	110	0.23 ± 0.09	14.32 ± 13.18
	6	250	0.46 ± 0.27*	52.60 ± 21.88*
		Pearson's coefficient	0.780*	0.807*
C57BL/6J	6	0	0.00 ± 0.00	0.00 ± 0.00
	6	50	0.28 ± 0.11*	24.27 ± 11.12*
	6	110	0.49 ± 0.25*	35.78 ± 22.00*
	5	250	0.88 ± 0.24*	73.03 ± 21.07*
		Pearson's coefficient	0.879*	0.819*
BALB/cA	6	0	0.00 ± 0.00	0.00 ± 0.00
	6	50	0.55 ± 0.21[b]*	43.76 ± 15.16[b]*
	6	110	1.69 ± 0.53[b]*	62.30 ± 8.18[b]*
	4	250	3.80 ± 2.19[b]*	91.42 ± 9.93[c]*
		Pearson's coefficient	0.841*	0.920*

Source: Liu *et al.* 2009.
*$P < 0.05$ (compared with strain-matched controls).
[a]Percent values were converted by arcsine transformation before statistical analysis.
[b]Significantly different ($P < 0.05$) from either DBA/2J or C57BL/6J strain at same dose.
[c]Significantly different ($P < 0.05$) from DBA/2J strain at same dose.

Liu *et al.* (2010) investigated the role of oxidative stress in 1-bromopropane–induced hepatotoxicity using nuclear factor erythroid 2-related factor 2 (*Nrf2*)-null mice. *Nrf2* is a transcription factor involved in the cellular defense against oxidative stress. Male *Nrf2*-null and wild-type mice (8 per group) were exposed to 0, 100, or 300 ppm 1-bromopropane for 8 hours/day for 28 days. At the high dose, diffuse hepatocellular degeneration, focal and widespread necrosis, and focal inflammatory cell infiltration were observed in both genotypes. However, significantly larger areas of liver necrosis occurred in *Nrf2*-null mice compared with wild-type mice (Table E-5). *Nrf2*-null mice also had a higher prevalence of fatty degeneration, greater malondialdehyde levels, higher ratio of oxidized glutathione/reduced form of glutathione (GSSH/GSH), and lower total GSH content. GST activity was significantly increased in wild-type mice at 300 ppm but was

unchanged in *Nrf2*-null mice where the basal expression levels were low. Significant changes in the mRNA levels of several oxidative stress-related genes (including NQO1 and HO-1) occurred in exposed wild-type mice compared with controls. Only GST Yc2 mRNA levels were significantly increased in the high-dose *Nrf2*-null mice. Thus, these data demonstrated that *Nrf2*-null mice were more susceptible to 1-bromopropane–induced liver injury and had a reduced antioxidant response compared with wild-type mice. The compromised antioxidant response and higher level of lipid peroxidation (as indicated by higher malondialdehyde levels) in *Nrf2*-null mice suggest that liver injury is related to oxidative stress. However, since liver necrosis also may contribute to lipid peroxidation, further studies are needed to clarify the role of oxidative stress in liver injury.

Table E-5. Comparison of liver necrotic area in wild-type and *Nrf2*-null mice exposed to 1-bromopropane

Genotype	Dose (ppm)[a]		
	0	100	300
Wild-type	0.00 ± 0.00	0.43 ± 0.20*	1.08 ± 0.36*
Nrf2-null	0.00 ± 0.00	0.99 ± 0.28[b,*]	1.94 ± 0.60[b,*]

Source: Liu *et al.* 2010.
*$P < 0.05$ (compared with strain-matched controls).
[a]Percent values (± SD) were converted by arcsine transformation before statistical analysis; N = 8 except for high-dose *Nrf2*-null mice where N = 6.

In contrast with the studies in mice, Ishidao *et al.* (2002) reported that male Wistar rats exposed to 1-bromopropane vapor 6 hours/day, 5 days/week for 3 and 4 weeks at 1,500 ppm or 4 to 12 weeks at 700 ppm showed significantly decreased plasma ALT levels (Table E-6). Plasma AST levels were not significantly affected. Although the reason for the decreased ALT levels was not clear, the data indicated that plasma ALT activity was affected by 1-bromopropane. Another surprising finding was that the levels of P450 in hepatic microsomes were significantly decreased after 1-day and 1-month exposures to 700 ppm. There is some experimental evidence that exposure to ethylene oxide may decrease hepatic P450 levels by attacking the heme moiety and altering heme balance in the liver. Propylene oxide, a structural analogue of ethylene oxide, is a possible intermediate metabolite of 1-bromopropane that might affect hepatic P450 levels.

Table E-6. 1-Bromopropane effects on plasma enzymes in male Wistar rats

Treatment (ppm)	N	Duration (weeks)	AST (U/L ± SD)	ALT (U/L ± SD)
0	30	4	77.4 ± 16.3	44.8 ± 11.5
700	15		80.2 ± 11.0	23.6 ± 3.6**
0	30	12	110.0 ± 35.2	60.6 ± 14.0
700	10		90.4 ± 21.6	31.0 ± 5.3**
0	10	3	119.7 ± 24.3	56.8 ± 18.8
1500	10		141 ± 58.5	30.2 ± 9.5*

Source: Ishidao *et al.* 2002.
AST = aspartate aminotransferase, ALT = alanine aminotransferase.
*$P < 0.05$ (compared with group controls).
**$P < 0.01$ (compared with group controls).

Immunotoxicity

1-Bromopropane has induced immunotoxic effects in mice (Lee *et al.* 2007a). T-dependent antibody response to sheep red blood cells, intracellular IL-2 production, and the absolute numbers of splenocyte subpopulations (total T-cells, $CD4^+$ cells, $CD8^+$ cells, macrophages, and B-cells) were all reduced in a dose-dependent manner. Thus, dose levels that resulted in decreased cellular glutathione and increased production of glutathione conjugate in spleen cells (see Table E-3) also suppressed immune function. These findings are consistent with studies that have shown immune function to be affected by intracellular glutathione (Dröge and Breitkreutz 2000). Studies in humans indicate that the immune system requires an optimal level of glutathione. Individuals with intermediate levels of glutathione generally have a higher number of $CD4^+$ T-cells than individuals with lower or higher intracellular glutathione levels. Some immune functions, such as DNA synthesis in lymphocytes, are very sensitive to reactive oxygen intermediates and are favored by high levels of glutathione while certain signal pathways are enhanced by oxidative conditions that are favored by low intracellular glutathione levels. IL-2-dependent functions (including T-cell proliferation, generation of $CD8^+$ T-cell blasts, cytotoxic T-cell activity, lymphokine-activated killer cells, and natural killer cells) are particularly sensitive and are inhibited by a partial depletion of intracellular glutathione levels (Dröge *et al.* 1994). Thus, the immunotoxicity of 1-bromopropane could be related to glutathione depletion from formation of glutathione conjugates and increased oxidative stress.

Anderson *et al.* (2010) also reported immunotoxic effects of inhaled 1-bromopropane in female $B6C3F_1$ mice and F344/N rats. Animals (8 per group) were placed in inhalation chambers and exposed to 0, 125, 250, or 500 ppm (mice) or 0, 250, 500, or 1,000 ppm (rats) for 6 hours/day, 5 days/week, for 4 or 10 weeks. Spleen immunoglobulin (IgM) responses to sheep red blood cells (plaque-forming cell assay) were significantly decreased in mice (all exposed groups) and in rats (high-dose group only) after exposure for 10 weeks (see Table E-7); however, the serum IgM response (ELISA assay) was not affected. Although the mechanism underlying these contradictory results is unknown, it has been observed following exposure to other chemicals (Johnson *et al.* 2000, Temple *et*

al. 1993). The sensitivities of these assays can vary depending on the compound being tested.

Table E-7. Suppression of splenic IgM response to sheep RBC in rodents after inhalation exposure to 1-bromopropane for 10 weeks

Exposure (ppm)	B6C3F$_1$ Mouse		Fisher 344 Rat	
	PFC/ 10^6 splenocytes	PFC/ spleen	PFC/ 10^6 splenocytes	PFC/ spleen
0	1752	449	309	142
125	1124*	263*	ND	ND
250	859*	181*	211	105
500	681*	144*	209	102
1000	ND	ND	164*	79*

Source: Anderson *et al.* 2010 (mean values from graphs in paper; actual data provided by authors).
IgM = immunoglobulin M; RBC = red blood cells; PFC = plaque-forming cell; ND = not done.
*$P < 0.05$ (compared with air control).

Total spleen cells and total T-cells (CD3+) were significantly reduced in mice (all exposed groups) and in high-dose rats after 4-weeks exposure (Anderson *et al.* 2010). This trend was not observed after 10-weeks exposure, with the exception of a decrease in total T-cells in high-dose rats. The apparent recovery of splenocyte numbers by the end of the 10-week exposure period might be due to the ability of 1-bromopropane to induce its own metabolism to increase production of CO_2 and other nontoxic metabolites. However, rats exposed to 500 or 1,000 ppm for 10 weeks also had a significant decrease in the $CD4^+/CD8^-$ T-cell subpopulation. There were no consistent changes in natural killer cell activity or biological alterations in B-cell or macrophage numbers in either species. These data suggest that T-cells are a possible target for 1-bromopropane immunotoxicity, which could increase the risk of infection.

An unusual non-neoplastic finding in rats in the 2-year carcinogenicity study was the presence of inflammatory lesions with Splendore-Hoeppli reaction material (Morgan *et al.* 2011, NTP 2011a). These lesions were exposure related and were more common in males than females. Although these lesions occurred primarily in the nose and skin, other sites were affected. Swabs were collected from abscesses on the tail, Harderian gland, head, and salivary glands from five rats and cultured under aerobic and anaerobic conditions and Splendore-Hoeppli bodies were later observed microscopically in these lesions. No bacterial growth occurred under anaerobic conditions, but *Pseudomonas aeruginosa* was observed in four of five aerobic cultures. Splendore-Hoeppli bodies may be formed by deposition of antigen-antibody complexes and debris from host inflammatory cells, or from glycoproteins, lipid, and calcium derived from host leukocytes. Infections from fungi, helminthes, or bacteria are the typical causative agents. Although immunosuppression might have contributed to the development of Splendore-Hoeppli bodies, it is not clear why these lesions occurred only in rats since mice were also immunosuppressed by exposure to 1-bromopropane in sub-chronic studies (Anderson *et al.* 2010).

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Part 2

Substance Profile

Proposed for the RoC

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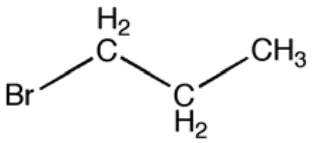
1-Bromopropane

CAS No. 106-94-5

Reasonably anticipated to be a human carcinogen[1]

First listed in the *Thirteenth Report on Carcinogens* (2014)

Also known as *n*-propyl bromide



Carcinogenicity

1-Bromopropane is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals. 1-Bromopropane, either directly or via reactive metabolites, causes molecular alterations that typically are associated with carcinogenesis, including genotoxicity, oxidative stress, and glutathione depletion. These alterations, observed mainly *in vitro* and in toxicity studies in rodents, are relevant to possible mechanisms of human carcinogenicity and support the relevance of the cancer studies in experimental animals to human carcinogenicity.

Cancer Studies in Experimental Animals

Inhalation exposure to 1-bromopropane caused tumors in two rodent species and at several different tissue sites, including one tissue site in rats at which tumors are rare (NTP 2011).

In male rats, 1-bromopropane caused significant dose-related increases in the incidences of several types of benign and/or malignant skin tumors (keratoacanthoma; keratoacanthoma and squamous-cell carcinoma combined; and keratoacanthoma, squamous-cell carcinoma, basal-cell adenoma, and basal-cell carcinoma combined). Both female and male rats showed an increased incidence of large-intestine tumors (adenoma of the colon and rectum), which are rare tumors in rats. In females, the incidence was dose-related and statistically significantly higher than in concurrent controls, and it exceeded the historical control range for all routes of exposure used in studies, including inhalation exposure. In males, the incidence of large-intestine adenoma was not significantly increased, but exceeded the historical control range for inhalation-exposure studies, and its occurrence was considered to be biologically significant because of the rarity of these tumors (which occurred in less than 0.2% of the historical controls). Although no carcinoma of the large intestine was observed in male or female rats in this study, adenoma of the large intestine has been shown to progress to carcinoma in other studies and forms a morphologic continuum with carcinoma (Deschner 1983, Chang 1984, Nigro 1985).

In female mice, 1-bromopropane caused significant dose-related increases in the incidence of benign and malignant lung tumors combined (alveolar/bronchiolar adenoma and carcinoma).

[1]NTP listing recommendation for the RoC.

These findings are supported by the observation of additional tumors in rats that may have been related to 1-bromopropane exposure, including malignant mesothelioma of the abdominal cavity and pancreatic islet tumors in males and skin tumors (squamous-cell papilloma, keratoacanthoma, and basal-cell adenoma or carcinoma) in females.

Other Relevant Data

1-Bromopropane is well absorbed following ingestion, inhalation, or dermal exposure. Occupational exposure occurs primarily by inhalation and dermal contact. Unmetabolized 1-bromopropane has been detected in the urine of exposed workers at levels significantly correlated with exposure to 1-bromopropane in air (Kawai *et al.* 2001, Ichihara *et al.* 2004).

1-Bromopropane is metabolized via several pathways; 16 urinary metabolites have been detected in rodents, and several other metabolites have been proposed (Jones and Walsh 1979, Ishidao *et al.* 2002, Garner *et al.* 2006). The primary metabolic pathways in rodents are oxidation reactions catalyzed by cytochrome P450 (primarily CYP2E1) and glutathione conjugation. The available data on human metabolism of 1-bromopropane, although limited, suggest that some of its metabolic pathways in humans are similar to those observed in rodents. Four mercapturic conjugates identified in the urine of rodents were also identified in the urine of workers exposed to 1-bromopropane (Hanley *et al.* 2009). The major metabolite, *N*-acetyl-*S*-(*n*-propyl)-L-cysteine, has been detected in the urine of exposed workers at levels that increased with increasing levels of 1-bromopropane in ambient air (Hanley and Dunn 2006, Valentine *et al.* 2007, Hanley *et al.* 2009, 2010). This metabolite is produced in humans by conjugation of 1-bromopropane with glutathione, and that reaction also releases free bromide ions, another useful biomarker for human exposure to 1-bromopropane (Jones and Walsh 1979, Hanley *et al.* 2006). No studies were identified that tested for the occurrence in humans of the oxidative metabolites that are obligate intermediates to the measured conjugates.

Studies on Mechanisms of Carcinogenesis

The mechanism(s) by which 1-bromopropane causes cancer are not known. However, exposure to 1-bromopropane has been shown to cause molecular alterations related to carcinogenicity, including genotoxicity (mutations and DNA damage), oxidative stress, glutathione depletion, and immunomodulation.

Studies have shown that 1-bromopropane can bind to macromolecules; it formed *S*-propylcysteine–globin adducts in exposed animals and humans (Valentine *et al.* 2007). Although 1-bromopropane did not induce mutations in bacteria under standard assay conditions, it did induce mutations in bacteria both with and without exogenous mammalian metabolic activation in the only reported study whose design was appropriate for testing a highly volatile chemical (Barber *et al.* 1981). It also caused mutations in cultured mammalian cells with or without mammalian metabolic activation (Elf Atochem 1996, as reviewed in NTP 2003) and DNA damage in cultured human cells without metabolic activation (Toraason *et al.* 2006). In addition, there is limited evidence of DNA damage in leukocytes from 1-bromopropane exposed workers (Toraason *et al.* 2006). In rodents exposed *in vivo*, 1-bromopropane did not increase micronucleus formation in bone marrow (Kim *et al.* 1998, as reviewed in NTP 2003) or peripheral blood erythrocytes (Elf Atochem 1996, cited in NTP 2003; NTP 2011) or cause dominant lethal

mutations. However, the dominant lethal mutation assay is generally regarded as relatively insensitive for the detection of mutagenic agents (Saito-Suzuki *et al.* 1982, Yu *et al.* 2008).

There is evidence that metabolic activation plays a role in the genotoxicity and toxicity of 1-bromopropane. Several reactive metabolites (or intermediates) of 1-bromopropane have been identified in rodents, including glycidol and α-bromohydrin, and propylene oxide has been proposed as a metabolite (Garner *et al.* 2006). These compounds cause genotoxic effects *in vitro*, including DNA adduct formation, mutations, and DNA or chromosome damage (Stolzenberg and Hine 1979, IARC 1994, 2000). Glycidol and propylene oxide cause cytogenetic effects *in vivo* and are carcinogenic in experimental animals, and both substances are listed in the Report on Carcinogens as *reasonably anticipated to be human carcinogens*. These reactive and genotoxic metabolites may be responsible for at least some of the carcinogenic effects of 1-bromopropane. As with 1-bromopropane, oral exposure to glycidol caused rare tumors of the large intestine in rats, as did oral exposure to two halogenated alkane analogues of 1-bromopropane, tribromomethane and bromodichloromethane (NTP 1987, 1989, 1990).

Chronic exposure to 1-bromopropane may produce levels of oxidative metabolites that exceed the glutathione-conjugating capacity or may inhibit enzymes required for glutathione synthesis. Because glutathione is an important cellular defense mechanism, reduced levels can lead to oxidative stress, increased toxicity, and carcinogenicity. Numerous studies have shown that 1-bromopropane induces both oxidative stress and glutathione depletion (Lee *et al.* 2005, 2007, 2010a, Liu *et al.* 2009, 2010, Huang *et al.* 2011). Studies with Cyp2e1$^{-/-}$ knockout mice, cytochrome P450 inhibitors, or a glutathione synthesis inhibitor showed that this metabolic activation pathway is involved in 1-bromopropane–induced toxicity, including neurological and reproductive effects, hepatotoxicity, and immunosuppression (NTP 2003, 2011, Lee *et al.* 2007, 2010a,b). Neurological effects of 1-bromopropane exposure have also been reported in humans (Li *et al.* 2010, Ichihara *et al.* 2012)

It is unclear whether induction of immunotoxicity by 1-bromopropane plays a role in tumor development. Recent studies have shown that 1-bromopropane causes immunosuppression in rodents (Lee *et al.* 2007, Anderson *et al.* 2010). In particular, it reduced the numbers of T cells and T-cell subpopulations. In addition, there is evidence that 1-bromopropane causes an inflammatory response. It induced dose-related increases in gene expression and production of proinflammatory cytokines in mouse macrophages (Han *et al.* 2008) and an inflammatory response in rats (NTP 2011). However, chronic respiratory inflammation and lung tumors were not associated in rodents; respiratory inflammation occurred in rats but not mice, whereas lung tumors occurred in mice but not rats.

Cancer Studies in Humans

No epidemiological studies or case reports were identified that evaluated the relationship between human cancer and exposure specifically to 1-bromopropane.

Properties

1-Bromopropane is a halogenated alkane that exists at room temperature as a colorless to pale-yellow volatile liquid with a strong, characteristic odor (NTP 2011). It is slightly

soluble in water and in most organic solvents, including acetone, ethanol, ether, benzene, chloroform, and carbon tetrachloride. It is less flammable than many other halogenated alkanes at room temperature. Thermal decomposition of 1-bromopropane produces hydrogen bromide. 1-Bromopropane can react with oxidizing agents to form hazardous flammable compounds and with water to produce acids. Physical and chemical properties of 1-bromopropane are listed in the following table.

Property	Information
Molecular weight	123.0[a]
Specific gravity	1.353 at 20°C/20°C[b]
Melting point	–110°C[a]
Boiling point	64.7°C[a]
Log K_{ow}	2.10[b]
Water solubility	2.45 g/L at 20°C[b]
Vapor pressure	110.8 mm Hg at 20°C[a]
Vapor density relative to air	4.25[b]

Sources: [a]NTP 2003, [b]HSDB 2006.

Use

1-Bromopropane is used primarily as a solvent cleaner in vapor and immersion degreasing operations to clean optics, electronics, and metals and as a solvent vehicle in industries using aerosol-applied adhesives, such as foam cushion manufacturing. However, its use as an aerosol solvent or adhesive could be affected by the proposed U.S. Environmental Protection Agency (EPA) rule that finds 1-bromopropane to be unacceptable for these uses (see Regulations). In recent years, 1-bromopropane usage has increased as a result of new industrial and commercial uses as a substitute for ozone-depleting chemicals or suspected carcinogens (e.g., as an alternative to tetrachloroethylene in the dry-cleaning industry) (Blando *et al.* 2010). 1-Bromopropane also has potential for use as a spot remover in the textile industry; however, an evaluation of 1-bromopropane as a substitute for trichloroethylene concluded that chronic toxicity data were insufficient, and use of 1-bromopropane was not recommended until more data were available (Mirza *et al.* 2000). In the past, 1-bromopropane was used primarily as a solvent for fats, waxes, and resins and as an intermediate in the synthesis of pharmaceuticals, insecticides, quaternary ammonium compounds, flavors, and fragrances in generally well-controlled, closed processes (Hanley *et al.* 2006, NTP 2003).

Production

1-Bromopropane is a high-production-volume chemical. In 2012, 1-bromopropane was manufactured by at least 21 companies worldwide, including at least one company in the United States (SRI 2012). Reported recent and historical volumes of U.S. production, imports, and exports of 1-bromopropane are listed in the following table.

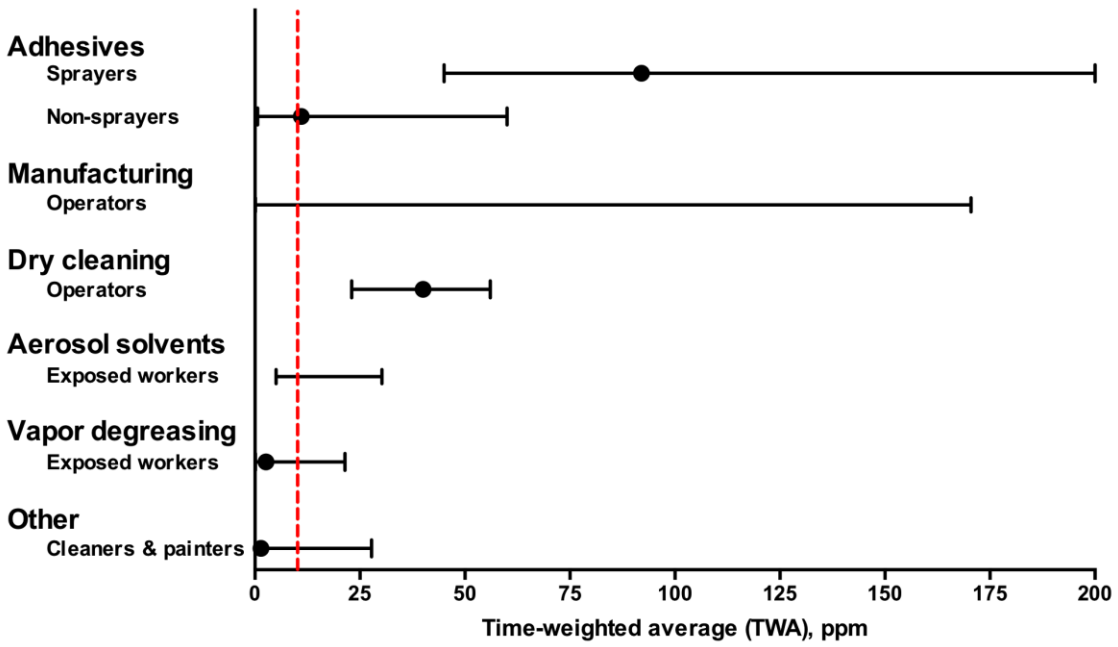
Category	Year	Quantity (lb)
Production + imports[a]	2006	> 1 million to 10 million
	1998, 2002	1 million to < 10 million
	1994	> 500K to 1 million
	1986, 1990	10K to 500K
U.S. imports:[b] recent	2011	10.3 million
historical	2007	10.9 million
U.S. exports:[b] recent	2011	15.1 million
historical	2007	8.8 million

Sources: [a]EPA 2012; EPA Chemical Data Reporting Rule, formerly the Inventory Update Rule.
[b]USITC 2012; reported as "brominated derivatives of acyclic hydrocarbons."

Exposure

A significant number of people in the United States are exposed to 1-bromopropane as a result of widespread usage, high production volume, and high levels of 1-bromopropane in commercial and industrial settings.

Occupational exposure to 1-bromopropane may occur through inhalation or dermal contact at workplaces where 1-bromopropane is produced or used (HSDB 2006). Concentrations of 1-bromopropane in air (8- to 12-hour time-weighted averages [TWAs]) from all studies identified across several U.S. industrial sectors ranged from not detected to 380 ppm, with the highest concentrations being for adhesive use and the lowest for vapor degreasing. Sprayers in the adhesive industry had the highest exposure, which ranged from 18 to 380 ppm across several studies. Exposure data for 1-bromopropane manufacturing were not available for the United States. Manufacturing exposure reported from China (Ichihara *et al.* 2004) ranged from not detectable to 170.5 ppm for processes that included adding materials to large reaction pots. However, production methods reported in a patent application by a U.S. manufacturer included numerous control processes to contain 1-bromopropane, which would likely reduce potential exposure substantially. The graph below shows TWA 1-bromopropane exposure levels from representative studies of adhesive application (Hanley *et al.* 2006), manufacturing (in China; Ichihara *et al.* 2004), dry cleaning (Eisenberg and Ramsey 2010), aerosol solvent use (Graul 2012), cleaning and painting in workshops using 1-bromopropane solvents (Kawai *et al.* 2001), and vapor degreasing (Hanley *et al.* 2010).



Time-weighted-average 1-bromopropane exposure levels as geometric means (Adhesives, Other, and Vap. Deg.); arithmetic mean (Dry Cln.); or not reported (Manuf. and Aer. Solv.). Note: the dashed, vertical line represents the ACGIH threshold limit value – time-weighted average (TLV-TWA) of 10 ppm.

Among workers at polyurethane foam furniture cushion manufacturing facilities, geometric mean values for daily urinary bromide excretion and urinary *N*-acetyl-*S*-propylcysteine concentrations were approximately 4 times as high for adhesive sprayers as for non-sprayers (Hanley *et al.* 2006, 2009). Concentrations of 1-bromopropane in exhaled breath also were consistently higher among sprayers than among workers performing other jobs. A National Institute for Occupational Safety and Health (NIOSH) Health Hazard Evaluation (HHE) of a furniture foam cushion manufacturing facility found the average difference between end-of-week and start-of-week serum bromide concentrations to be 23 mg/L for exposed workers, compared with 3 mg/L for unexposed workers (Harney *et al.* 2003). NIOSH HHEs and follow-ups at two facilities showed that 1-bromopropane air concentrations (TWAs) could be reduced by 80% or more through implementation of NIOSH recommendations for engineering controls, such as ventilation improvements and enclosure of spray tables (Reh *et al.* 2002).

The general population may be exposed to 1-bromopropane through inhalation of ambient air in the vicinity of industrial facilities where 1-bromopropane is used as an adhesive. EPA used air dispersion modeling to estimate 1-bromopropane concentrations in ambient air at a distance of 100 m from model facilities. The estimated concentrations were 0.138 mg/m^3 [0.0274 ppm] for facilities with average adhesive use and 1.38 mg/m^3 [0.274 ppm] for facilities with high adhesive use (Morris and Wolf 2003). EPA also estimated daily inhalation uptake of 1-bromopropane for a person living 100 m from a model facility to be 0.0537 mg/kg for average-adhesive-use facilities and 0.537 mg/kg for high-adhesive-use facilities.

Based on its production levels and industrial uses, 1-bromopropane may be released to the environment through various waste streams. 1-Bromopropane has been detected in temperate marine macroalgal tissue and is believed to be transported from these algae to the marine environment (HSDB 2006). No data on levels of 1-bromopropane in ambient

air, drinking water, surface water, soil, food, or consumer products and no data on non-occupational exposure to 1-bromopropane were found.

Regulations

California Occupational Safety and Health Standards Board (OSHSB)

Permissible exposure limit (PEL) = 5 ppm.

Environmental Protection Agency (EPA)

Significant New Alternatives Policy (SNAP) Program

The EPA SNAP program reviews alternatives to ozone-depleting substances and approves the use of alternatives that do not present substantially greater risk to the public health and environment than the substance they replace or other available substitutes. The EPA SNAP program has made the following determinations regarding various end uses of 1-bromopropane:

Solvent in industrial equipment for metals cleaning, electronics cleaning, or precision cleaning as a substitute for CFC–113 and methyl chloroform: acceptable (final rule).

Coatings as a substitute for CFC–113, HCFC–141b, and methyl chloroform: acceptable subject to the condition that use is limited to coatings facilities that have provided EPA data which demonstrate their ability to maintain acceptable workplace exposures (proposed rule).

Aerosol solvents as a substitute for CFC–113, HCFC–141b, and methyl chloroform: unacceptable (proposed rule).

Adhesives as a substitute for CFC–113, HCFC–141b, and methyl chloroform: unacceptable (proposed rule).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 10 ppm.

Environmental Protection Agency (EPA)

Acceptable exposure limit (8-hour time-weighted average) = 25 ppm.

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