Report on Carcinogens (RoC) Concept: 1-Bromopropane

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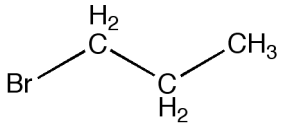

1. Rationale

1-Bromopropane (CASRN 106-94-5) is a brominated hydrocarbon that is currently used as a solvent in a variety of industrial and commercial applications. 1-Bromopropane has been selected as a candidate substance[1] for the RoC due to the potential for substantial human exposure to 1-bromopropane, and an adequate database to evaluate its potential carcinogenicity. 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. Occupational exposure data are available from several published studies and indicate that workers can be exposed to high levels of 1-bromopropane. 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. We are not aware of any organization that has conducted a cancer evaluation of 1-bromopropane.

In January 2012, the National Toxicology Program (NTP) solicited information on 1-bromopropane and other nominated substances (77FR2728, see *http://ntp.niehs.nih.gov/go/rocnom* for comments) and received one public comment that provided relevant information on the production, increases in use and human exposure, and current recommended occupational limits to 1-bromopropane. The public comment also asserted that there is no scientific reason to assume that the mode of action of 1-bromopropane for tumor induction in experimental animals is not relevant to humans.

The ORoC presented the draft concept document for 1-bromopropane to the NTP Board of Scientific Counselors (BSC) at the June 21-22, 2012 meeting[2] which provided an opportunity for written and oral public comments. No public comments were received. The

[1]The scientific evaluation of 1-bromopropane will be captured in the draft RoC monograph, which consists of a cancer evaluation component and a draft substance profile (for more details, see *http://ntp.niehs.nih.gov/go/rocprocess*). The proposed approach, delineated in this concept document, for preparing the cancer evaluation of the draft monograph is tailored to the nature, extent, and complexity of the scientific information on this chemical. This concept document also discusses information supporting the rationale and the proposed approach including (1) data on human exposure, (2) an overview of the nature and extent of the scientific information for evaluating carcinogenicity in humans and/or animals, (3) scientific issues and questions relevant to the evaluation of 1-bromopropane carcinogenicity, and (4) the proposed approach for conducting the scientific evaluation including the literature search strategy, the scope and focus of the monograph, and the approaches for obtaining scientific and public input to address the key scientific questions and issues.

[2]Information on the NTP BSC June 21-22, 2012 meeting is available at *http://ntp.niehs.nih.gov/go/9741*.

NTP Director approved 1-bromopropane as a candidate substance, and this concept was finalized based on review of the BSC's comments. The concept may be revised again if new information on 1-bromopropane would lead to a change in the proposed approach for conducting the cancer evaluation.

2. Overview of Data Related to Human Exposure

There is significant exposure to 1-bromopropane for U.S. workers, inferred by the various uses, production volume, and high levels of the substance measured in some commercial and industrial settings.

1-Bromopropane is a high production volume chemical in the United States with annual production in recent years ranging from 1 million to 10 million pounds as reported for 1998, 2002, and 2006 (EPA 2012). 1-Bromopropane is produced by reacting propanol with excess hydrogen bromide gas; this also results in small amounts (< 1%) of by-products, including 2-bromopropane, 1-propanol and di-*n*-propyl ether (NTP 2011a).

1-Bromopropane is used as a solvent cleaner to degrease electronics, precision optics, and metals, as a solvent vehicle in industries that use aerosolized adhesives (e.g., foam cushion manufacturing), as a spot remover in the textile industry, and as a solvent in the dry cleaning industry. In many industrial applications, 1-bromopropane has seen a recent increase in usage as an alternative to substances that have been identified as suspect carcinogens or ozone-depleting chemicals. For example, it is used to replace chlorinated solvents such as trichloroethylene, tetrachloroethylene (perc, primarily used in the dry cleaning industry; IARC 1995, Blando *et al.* 2009), and methylene chloride, all of which are listed in the RoC as *reasonably anticipated to be human carcinogens* (NTP 2011b). The U.S. Environmental Protection Agency issued a Final Rule in 2007 officially accepting 1-bromopropane as an alternative to two ozone-depleting chemicals, methylchloroform (1,1,1-trichloroethane) and chlorofluorocarbon-113 (CFC-113), when used as a solvent in industrial cleaning applications (EPA 2007a). However, there is currently a proposed EPA rule that 1-bromopropane be deemed unacceptable as a substitute solvent when used in aerosols and spray adhesives, because it poses "unacceptable risks to human health in this end use compared to other available alternatives" (EPA 2007b). Other uses for 1-bromopropane are as a solvent for fats, waxes, or resins, and as an intermediate in the synthesis of pharmaceuticals, insecticides, flavors, or fragrances; these are generally well-controlled, closed processes, unlike the above-mentioned newer applications, which can result in increased worker exposure (Akron 2010, NTP 2003).

Occupational exposure to workers is the major source of exposure to 1-bromopropane, through its production and use in various industries and applications. Inhalation is the primary route of human exposure to 1-bromopropane, though dermal exposure is also possible.

There are currently only limited standards or recommendations for limiting worker exposure to 1-bromopropane in the United States. There is neither an OSHA Permissible Exposure Limit (PEL), nor a NIOSH Recommended Exposure Limit for 1-bromopropane. The only, legally enforceable, occupational standard for regulating 1-bromopropane in the United States is a California OSHA PEL of 5 ppm. In 2005, the American Conference of Governmental Industrial Hygienists (ACGIH) published a recommended guideline for a Threshold Limit Value (TLV) for 1-bromopropane as 10 ppm, 8-hour time-weighted average

(TWA) (ACGIH 2005); however, it is currently under consideration by the ACGIH to lower the TLV to 0.1 ppm.

In the United States, levels of 1-bromopropane have been measured in the air in several different industries and were reported to be up to 54 ppm in dry cleaning businesses (Blando *et al.* 2010), as high as 143 ppm in manufacturing facilities that provided some exhaust ventilation, as high as 247 ppm in an adhesive spray facility with no ventilation for workers (NCDOL 2008), and as high as 381.2 ppm in a foam fabricator facility (Reh *et al.* 2002). Exposure to 1-bromopropane is higher among sprayers (92 ppm, geometric mean) in the adhesive industry than non-sprayers in the same industry (GM = 11 ppm), (Hanley *et al.* 2006) and workers in the vapor degreasing and cleaning industry (GM = 2.6 ppm) (Hanley *et al.* 2010).

Potential biological indices of exposure to 1-bromopropane include measurements of bromide ion [$Br^{(-)}$], *N*-acetyl-*S*-(*n*-propyl)-L-cysteine (AcPrCys), and 1-bromopropane in urine, and serum bromide level (Hanley 2006, 2009, Cheever *et al.* 2009, Mathias 2012). Serum bromide levels ranged from 17 to 1,700 mg/L among adhesive application workers exposed to 1-bromopropane and employed in several factories in the United States (Harney *et al.* 2003, Majersik *et al.* 2007, Raymond and Ford 2007).

3. Overview of the Scientific Information Regarding Carcinogenicity

3.1. Human cancer studies

No epidemiological studies have been identified that examined the relationship between human cancer and exposure specifically to 1-bromopropane. 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 a long latency period.

3.2. Cancer studies in experimental animals

One study on the carcinogenic effect of 1-bromopropane in animals was identified from the peer-reviewed literature. 1-Bromopropane was tested for carcinogenicity in a 2-year inhalation (whole body) study conducted by the NTP in both sexes of $B6C3F_1$ mice and F344/N rats (NTP 2011a, Morgan *et al.* 2011). Both male and female rats developed rare adenomas of the large intestine and had an increased incidence of epithelial neoplasms of the skin. Female mice treated with 1-bromopropane showed an increased incidence of lung alveolar/bronchiolar adenoma and carcinoma, but no increase in tumor incidence was observed in male mice.

3.3. Mechanistic and other relevant data

1-Bromopropane is absorbed in animals by all routes of exposure and is absorbed in humans exposed occupationally, generally by inhalation (NTP 2011a) but also dermally (Frasch *et al.* 2011). From metabolism studies in rats and mice, 1-bromopropane can directly conjugate with glutathione forming *N*-acetyl-*S*-propylcysteine, or may first be oxidized by P450 enzymes, primarily CYP2E1, to reactive intermediates that can also be oxidized by P450 enzymes and/or conjugated with glutathione. More than 10 urinary metabolites have been identified, primarily as mercapturic acids derived from glutathione conjugates (NTP 2011a, Garner *et al.* 2006). Mice have been shown to have a greater capacity to oxidatively metabolize 1-bromopropane than rats, due to species differences in cytochrome activity and glutathione detoxification capacity (Garner *et al.* 2007).

1-Bromopropane can form covalent adducts with globin and neurofilaments in rats, and several of its urinary metabolites or postulated metabolites – bromoacetone, glycidol, propylene oxide, and α-bromohydrin – have been shown to react with DNA or protein (Jones and Walsh 1979, Ishidao *et al.* 2002, Garner *et al.* 2006, 2007, Ghanayem and Hoffler 2007, Lee *et al.* 2010). Glycidol, a primary metabolite, and propylene oxide, a postulated metabolite, are each listed in the RoC as *reasonably anticipated to be a human carcinogen* (NTP 2011b). 1-Bromopropane has been tested for genotoxicity *in vitro*, *in vivo*, and in exposed workers (NTP 2011a, Barber *et al.* 1981, Toraason *et al.* 2006).

1-Bromopropane has caused neurological, developmental, reproductive, immunological, and hepatotoxic effects in rodents and neurological and possible reproductive effects in humans (NTP 2003, 2011a, Lee *et al.* 2007, 2010). In the NTP (2011a) 2-year inhalation study, non-neoplastic lesions were increased in 1-bromopropane-exposed rats (nose, larynx, and trachea) and mice (nose, larynx, trachea, and lung). In addition, predominantly in the nose and skin of exposed rats, there was an exposure-related increase in unusual inflammatory lesions containing Splendore-Hoeppli material, indicative of immunosuppression (NTP 2011a, Morgan *et al.* 2011). 1-Bromopropane was shown to cause immunosuppression in rats and mice after whole-body inhalation exposure, as evidenced by decreases in total spleen cells and T-cells and in IgM response to sheep red blood cells (Anderson *et al.* 2010).

4. Key Scientific Questions and Issues Relevant for the Cancer Evaluation

The key questions and issues for the review of 1-bromopropane concern the evaluation of studies in experimental animals and mechanistic data.

- 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?
  - What is the level of evidence for these mechanisms (strong, moderate, weak) in experimental animals?
  - Are there mechanistic data to suggest that the cancer findings in experimental animals are not relevant to humans?
  - Could the reported alterations in immune surveillance in rodents lead to an increased incidence of tumors?

5. Proposed Approach for Conducting the Cancer Evaluation

5.1. Scope and focus of the draft RoC monograph

ORoC will prepare the draft RoC monograph on 1-bromopropane, which will consist of two parts, the cancer evaluation and the substance profile. The cancer evaluation component of the draft monograph will review and assess the scientific literature, provide a discussion of scientific issues, and assess and integrate the relevant scientific evidence, applying the listing criteria to reach a preliminary RoC listing recommendation[3]. The substance profile of the draft monograph will give the NTP's preliminary listing recommendation and a summary of the key supportive evidence. Details on the methods for writing the draft RoC

[3]A listing recommendation can be not to list, to list as *reasonably anticipated to be a human carcinogen*, or to list as *known to be a human carcinogen*.

monograph and topics typically covered in the monograph are outlined in the NTP process for the preparation of the RoC (*http://ntp.niehs.nih.gov/go/rocprocess*).

The cancer evaluation component of the draft monograph will focus on studies of 1-bromopropane in experimental animals and mechanistic data. The monograph will also discuss literature related to immunosuppression and cancer development. In addition, human and animal studies of non-cancerous endpoints, such as neurological or reproductive/developmental toxicity, and studies of structurally related compounds and metabolites, may be informative regarding the mechanism of action of 1-bromopropane. Details of the preliminary literature search strategy, including data sources and literature search terms, are discussed in the 1-bromopropane literature search strategy (see Appendix 1).

5.2. Proposed approach for obtaining scientific and public input

Public comments on scientific issues have been requested on 1-bromopropane at several times prior to the development of the draft RoC monograph including the request for information on the nomination and the request for comment on the draft concept. The ORoC will consider this information and experts suggested by the public[4] in drafting the cancer evaluation component of the draft monograph. The ORoC will create a webpage for the candidate substances currently under review. The webpage will typically include the following: (1) RoC documents related to the review of the substance (e.g., concept document, draft RoC monograph), (2) citations for references identified from literature searches, (3) public comments, (4) an input box for the public to provide information (such as new literature) or comments (such as the identification of additional scientific issues), and (5) information on public meetings or listening sessions. The NTP will communicate when new information is added or updated (such as updated literature searches) to the website via the NTP list serve. Additional scientific issues may be identified during the preparation of the monograph. Future forums (such as a listening session) for receiving public comment on any additional scientific issues may be considered depending on public interest; these would be announced via a Federal Register notice, the NTP list serve[5] and the RoC website.

ORoC will consult with appropriate advisors, external or internal to the government (such as NIOSH), with knowledge related to 1-bromopropane. Sources for identifying these advisors include, but are not limited to, peer-reviewed literature databases and recommendations from the scientific community and the public. Advisors with knowledge of animal carcinogenesis, genotoxicity, and mechanistic studies will be consulted to critically review the ORoC assessment of the available studies, to help identify relevant literature, and to provide critical comments on the ORoC assessment of key sections of the monograph.

[4]Federal Register notice and public comments are available at *http://ntp.niehs.nih.gov/go/rocnom*.

[5]Persons can subscribe to the NTP list serve free-of-charge at *http://ntp.niehs.nih.gov/go/getnews.*

6. Public Release and Peer Review of the Draft Monograph

Once completed, the draft RoC monograph on 1-bromopropane will undergo interagency review followed by release for public comment and public peer review. The NTP will convene an external scientific panel[6] to peer review the draft monograph in a public forum.

Members of the panel will be from the public and private sectors with expertise in disciplines related to the cancer evaluation of 1-bromopropane, such as exposure assessment, pathology, toxicology, genotoxicity and mechanisms of carcinogenesis. The NTP will set aside time at the peer-review meeting for a discussion of scientific issues raised in the public comments.

[6]NTP panels are federally chartered technical and scientific advisory groups convened as needed to provide advice on specific scientific issues and peer review. Members of NTP panels are scientists with relevant expertise and knowledge from the public and private sectors. The final selection of membership is based upon providing a balanced and unbiased group of highly qualified individuals and is made in accordance with Federal Advisory Committee Act and HHS implementing guidelines; *http://ntp.niehs.nih.gov/go/166*.

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Appendix 1

Preliminary Literature Search Strategy: 1-Bromopropane

This document identifies the data sources, search terms and preliminary search strategies for identifying literature for the draft RoC monograph on 1-bromopropane. The literature search will be updated approximately every three months, and prior to submitting the draft monograph for interagency review. Additional literature searches will be conducted as needed to identify information to address scientific issues that arise during the review. Citations retrieved from literature searches will be uploaded to web-based systematic review software and screened using inclusion and exclusion criteria. Multi-level reviews of the literature are conducted with initial reviews based on titles and abstracts only and subsequent reviews based on full-text searches.

1. Data Sources

Identification of synonyms and metabolites for 1-bromopropane (CASRN 106-94-5)

- *Synonyms*- IARC and National Library of Medicine databases (e.g., ChemIDplus, Hazardous Substances Data Bank)
- *Metabolites*- Cheever *et al.* 2009, Jones and Walsh 1979, Garner *et al.* 2006, Ghanayem and Hoffler 2007, Ishidao *et al.* 2002, Mathias *et al.* 2012. A total of ten potential metabolites of 1-bromopropane (not including Phase II conjugated metabolites) have been identified. These include six brominated metabolites and four debrominated metabolites.

Citation databases (searches titles, abstracts, and key words)

- PubMed
- Web of Science
- Scopus

Additional data sources:

- Authoritative reviews or general sources for exposure and other information (e.g., Toxnet; U.S. Government agencies websites, publications and databases; International Agency for Research on Cancer monographs)
- Citations in authoritative reviews, and primary references located by literature search
- QUOSA library of occupational case-control studies (full-text search for 1-bromopropane and CAS RN: 106-94-5)

2. Preliminary Literature Searches

Because the literature database for studies on 1-bromopropane is not extensive, the approach for conducting the literature search in the three major databases (see Data Sources, Section 1) consists of a combination of general searches (for all literature on 1-bromopropane *per se*) and topic-specific searches (for information related to the carcinogenicity of 1-bromopropane and to four debrominated metabolites of 1-bromopropane, the six brominated metabolites of 1-bromopropane, and its chemical class) (see Table 1). (Initial searches for four debrominated metabolites of 1-bromopropane and for its chemical class brought up several thousand references). These topic-specific searches are constructed to answer key questions in the monograph, as a result not all chemical-specific searches are combined with all topics covered by the monograph. For

example, searches for metabolites of 1-bromopropane would not be combined with exposure-related terms because information on exposure to these metabolites is beyond the scope of this document. Search terms for specific topics have been developed in consultation with an information specialist.

Searches for human cancer studies are somewhat unique because they involve the identification of search terms for exposure scenarios in which people might be exposed to 1-bromopropane in combination with search terms specific for 1-bromopropane. Thus, additional strategies were developed to search for relevant cancer studies with potential exposure 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 have most likely been exposed to other solvents such as tetrachloroethylene.

A full-text search of PDFs retrieved by QUOSA from a search in the three major databases for publications on the aerospace/aircraft industry (manufacturing, maintenance, etc.) where 1-bromopropane might be used as a degreaser did not identify any papers that specifically mentioned 1-bromopropane. Searches using 1-bromopropane synonyms also did not identify any human cancer studies.

Additional literature searches will be conducted to identify literature related to immunosuppression and cancer development.

Table 1: Preliminary 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 their synonyms	bromoalkanes, alkyl bromides, haloalkanes, alkyl halides	Cancer Studies in Experimental Animals Genotoxicity Toxicity Mechanism
1-Bromopropane brominated 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 metabolites and their synonyms	propylene oxide, *n*-propanol, glycidol, and 3-hydroxypropionate	Cancer Studies in Experimental Animals (for the mechanistic section) Genotoxicity Toxicity Mechanism

[a]Search terms for each topic were developed in consultation with an information specialist.