NTP
National Toxicology Program

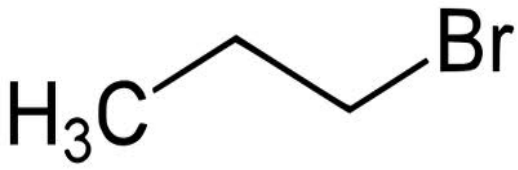
Report on Carcinogens Concept Review for 1-Bromopropane

Diane L. Spencer, M.S.
National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors Meeting
June 21 – 22, 2012

Background and Rationale

- Brominated hydrocarbon
- Solvent in variety of industrial applications



- Increased occupational usage and human exposure
- NTP 2-year bioassay: reported animal tumors
  (NTP Technical Report, August 2011)

Public comments

Federal Register notice January 2012:

Received one comment - provided current information and opinion on the NTP bioassay results and mode of action of 1-bromopropane

Human Exposure

Significant exposure in United States

- Used in several industrial processes
  - Degreaser for electronics and metal
  - Solvent vehicle for aerosolized adhesives (foam cushion manufacturing)
  - Spot remover in textile industry
  - Dry cleaning
  - Intermediate in synthesis of pharmaceuticals, insecticides, fragrances, flavors, other chemicals
- Measured in air in occupational settings where it is used and the metabolite *N*-acetyl-S-propylcysteine has been detected in urine of exposed workers
- High production volume chemical (EPA IUR)

  >1 million to 10 million pounds produced in 1998, 2002 and 2006

Inhalation is primary route – dermal exposure also possible

Increase in Occupational Use

- Use as an alternative solvent
  - Suspect carcinogens
    - Trichloroethylene (TCE)
    - Tetrachloroethylene (perc) – dry cleaning
    - Methylene chloride
  - Ozone-depleting chemicals (EPA Final Rule in 2007)
    - Methyl chloroform
    - CFC-113
- Currently not regulated by OSHA

Human Cancer Studies

- No epidemiological studies were identified that examined the relationship between human cancer and exposure specifically to 1-bromopropane.

- Because the increase in use (e.g., in dry cleaning) of 1-bromopropane is recent, epidemiological studies would not yet be able to evaluate cancer risk which is usually associated with a long latency period.

Cancer Studies in Experimental Animals

NTP identified treatment-related effects, due to inhalation of 1-bromopropane, in the 2-year bioassay:

	Rat	Mouse
Males	Large intestine adenoma (rare) Skin neoplasms	
Females	Large intestine adenoma (rare)	Lung (alveolar/bronchiolar) adenoma and carcinoma

Mechanistic and Other Relevant Data

Metabolism and mechanistic studies

- Absorbed in humans and rodents – inhalation, skin
- Metabolism
  - Undergoes an oxidative reaction by P450 enzymes (primarily CYP2E1) to form metabolites
  - Directly conjugates with glutathione to form metabolite *N*-acetyl-S-propylcysteine (biomarker of exposure)
  - Metabolites – more than 10 urinary metabolites identified
- Genotoxicity studies
  - *In vitro, in vivo* and in factory workers exposed to 1-bromopropane
- Immunosuppression due to 1-bromopropane exposure observed in both rats and mice

Key Scientific Questions and Issues Relevant for the Cancer Evaluation

- What is the level of evidence (sufficient or not sufficient) for the carcinogenicity of 1-bromopropane from studies in experimental animals? If sufficient, what are the target 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?

Proposed Approach for Conducting the Cancer Evaluation of 1-Bromopropane

- Scope
  - Review and assess scientific literature
  - Discuss scientific issues
  - Assess and integrate relevant scientific evidence
  - Apply RoC listing criteria to reach a preliminary listing recommendation
- Focus
  - On studies in experimental animals and mechanistic data

Obtaining Scientific and Public Input

- Scientific and technical expertise
  - Advisors external or internal to government (e.g., NIOSH)
    - Sources
      - Peer-reviewed literature databases
      - Recommendations from scientific community and public
  - Identify relevant literature
  - Review key sections of monograph
- Public input
  - Public comment is solicited throughout review process
    - Establish a webpage
      - Communicate status and relevant documents related to the monograph preparation
      - Mechanism to receive public input
  - Issues will be considered, specifically addressed and appropriate material incorporated

Draft RoC Monograph on 1-Brompropane

- Interagency review
- Release for public comment
- Peer review in public forum
  - Review panel of scientists from public and private sectors with expertise in disciplines such as:
    - Exposure assessment
    - Toxicology
    - Pathology
    - Genotoxicity
    - Mechanisms of carcinogenesis
  - Time will be set aside at this meeting to discuss scientific issues raised in the public comments.

Specific Charge Questions

1. Comment on whether the cited information suggests that exposures to the substance in the US are “significant” and whether the extent and nature of the scientific information on the carcinogenicity of the nominated substance are clearly described and adequate (studies in humans, animals, and/or mechanistic information) to support a RoC evaluation.

2. Advise as to whether the relevant scientific issues are identified. Are you aware of any other scientific issues that need to be considered during the evaluation?

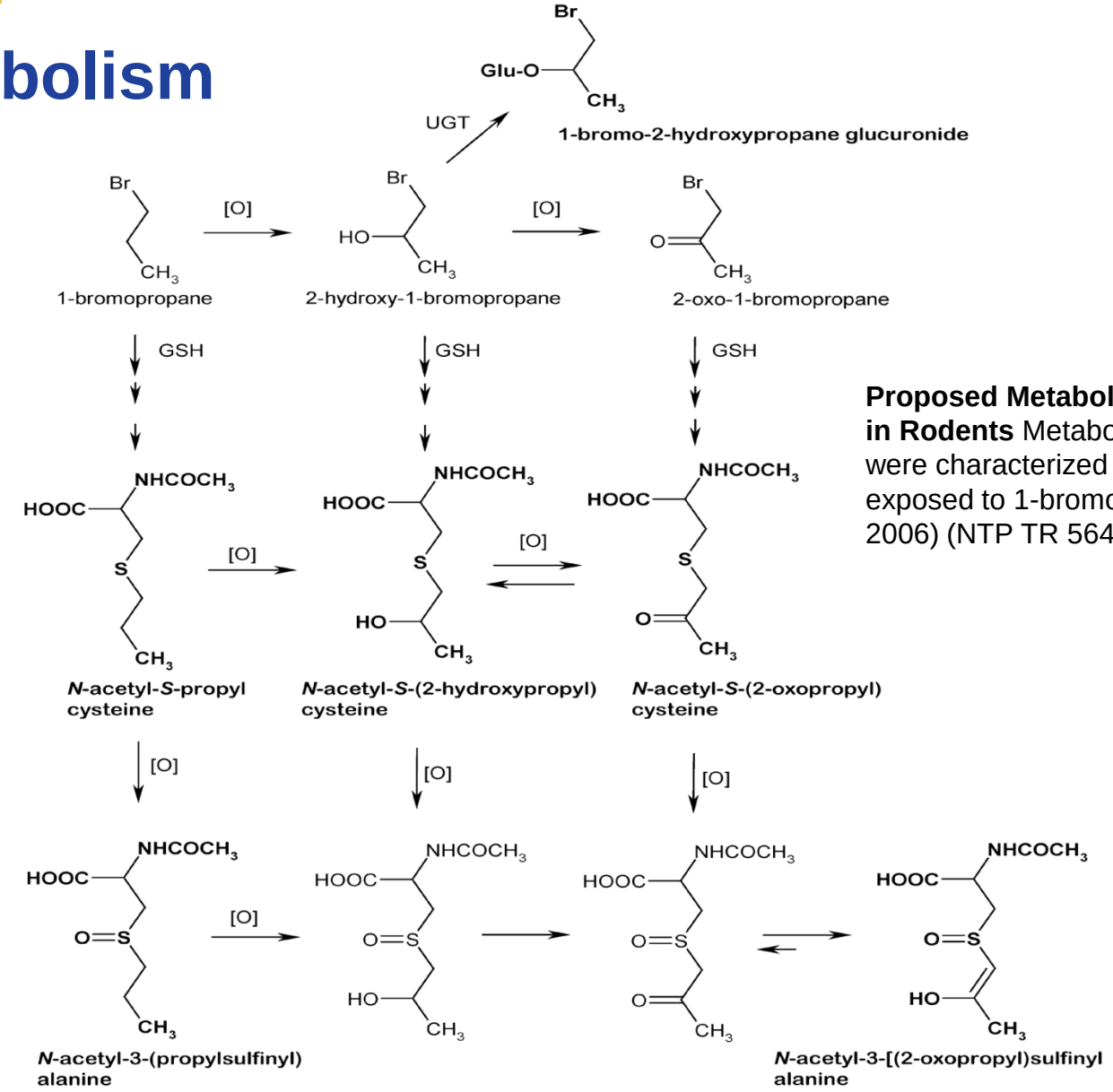
3. Comment on the proposed scope and focus for the cancer evaluation component of the draft RoC monograph.

4. Comment on the proposed approach for obtaining scientific and public input in development of the evaluation.

5. Rate the overall significance and public health impact of this evaluation as low, moderate, or high. NTP will use this rating in assessing the relative priority of evaluations of RoC candidate substances.

6. Provide any other comments you feel staff should consider in developing this evaluation.

Metabolism



Proposed Metabolism of 1-Bromopropane in Rodents Metabolites shown in bold font were characterized in urine from rodents exposed to 1-bromopropane (Garner *et al.*, 2006) (NTP TR 564 2011)

Occupational Exposure Guidelines/Regulations

- ACGIH (voluntary): 10 ppm (8 hr-TWA), considering 0.1 ppm because of other concerns (e.g., neurological, reproductive and developmental)
- Cal OSHA: 5 ppm – first and currently only legally enforceable standard for regulating 1-bromopropane in the US
- NIOSH: anticipate publishing a recommended exposure limit (REL) in the near future
- OSHA: no current permissible exposure limit (PEL) regulation

NTP Bioassay Results

NTP identified treatment-related effects

Rats

Male

- large intestine adenomas (rare)
- skin neoplasms (keratoacanthoma, squamous cell carcinoma, basal cell adenoma and carcinoma)
- malignant mesothelioma* (equivocal)
- Pancreatic islets (adenoma or carcinoma) [equivocal]

Female

- large intestine adenomas (rare)
- skin neoplasms [equivocal]

Mice

Male

- no evidence of carcinogenicity

Female

- lung (alveolar/bronchiolar) neoplasms

*tunica vaginalis of the epididymis