Process for Preparing the Draft RoC Monograph on Antimony Trioxide

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National Institute of Environmental Health Sciences
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Antimony Trioxide Peer Review Meeting

Outline

Background on Report on Carcinogens (RoC)

Select antimony trioxide for evaluation for the RoC

Develop draft RoC monograph

Evaluate cancer hazards and overview of RoC listing criteria

Next steps
The Report on Carcinogens (RoC) is congressionally mandated

• Identifies substances that pose a cancer hazard to people residing in the United States
  – Two listing categories: known and reasonably anticipated to be a human carcinogen

• Substance profile is written for each listing
  – Listing status, scientific information key to listing and data on properties, uses, production, exposure, and regulations to limit exposure

• Each edition of the report is cumulative

• NTP prepares the RoC for the Secretary of the Department of Health and Human Services using a four-part formal process and established listing criteria

http://ntp.niehs.nih.gov/go/roc
Four-Part Process

Process for the Preparation of the RoC

Select substances for evaluation

- Invite nominations
- Conduct scoping and problem formulation activities
- Develop draft concepts
  - Scientific and/or public input as needed
  - Public comment
  - NTP BSC review (public meeting & comment)
  - NTP Director
- Finalize concepts and select substances for review

Prepare draft RoC monographs

- Develop protocol as needed
- Develop draft RoC monograph
  - Scientific and/or public input as needed
- Interagency review of NTP listing recommendation

Peer review and finalize RoC monographs

- Release draft RoC monograph
  - Public comment
  - Scientific and/or public input as needed
- Present summary of peer review; prepare revised draft RoC monograph
- NTP BSC (public meeting)
- NTP Director
- Finalize RoC monograph

Publish and release RoC

- Submit recommended listing status of new substances
- Secretary, HSS reviews and approves
- NTP Executive Committee
- Publish and release RoC

Key
BSC = Board of Scientific Counselors
HHS = Health and Human Services
NTP = National Toxicology Program
RoC = Report on Carcinogens
* Federally chartered advisory groups

https://ntp.niehs.nih.gov/go/rocprocess
Opportunity for Public Comment

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  - Expert peer review draft RoC monograph
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Process for the Preparation of the RoC

Peer Review: Current Step

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https://ntp.niehs.nih.gov/go/rocprocess
Select Antimony Trioxide for Evaluation

- Invite nominations
  - Conduct scoping and problem formulation activities
    - Request for Information
      - September 2016
  - Develop draft concepts
    - Public comment
      - NTP BSC review
        - December 2016
    - NTP Director
  - Finalize concepts and select substances for review

RoC Nomination: NIOSH
Deferred because of inadequate database

NTP 2-year bioassays nomination: CPSC

Draft technical report on antimony trioxide was peer reviewed in 2016 and finalized in 2017
Select Antimony Trioxide for Evaluation

Invite nominations

Conduct scoping and problem formulation activities

Request for Information
September 2016

Develop draft concepts

Public comment
NTP BSC review
December 2016

NTP Director

Finalize concepts and select substances for review

1 public comment:
International Antimony Association
Potential public health concern

- Adequate database of cancer studies in experimental animals
- Evidence for occupational exposure in the United States
- Interest reinitiated by 2016 NTP technical report on 2-year bioassays

Select Antimony Trioxide for Evaluation

Invite nominations

Conduct scoping and problem formulation activities

Request for Information
September 2016

Develop draft concepts

2 public comments
NTP BSC review
December 2016

NTP Director

Finalize concepts and select substances for review
Prepare Draft RoC Monograph

Process for preparing draft monograph on antimony trioxide

- Develop protocol and post on RoC website
  - Technical advisors
  - Develop draft RoC monograph
    - Technical advisors
  - Interagency review of NTP listing recommendation

Methods for preparing the monograph such as approaches for evaluating study quality and integrating data
Research Questions

• Are or were a significant number of people in the United States exposed to antimony trioxide?

• Is antimony trioxide known or reasonably anticipated to be a human carcinogen (as defined by the RoC listing criteria)?

Scope of the monograph

• Antimony trioxide is converted \textit{in vitro} and \textit{in vivo} to other antimony forms and vice versa

• Information on other antimony compounds may help inform the potential carcinogenicity of antimony trioxide
Publish a report that lists substances which are known or reasonably anticipated to be human carcinogens and to which a significant number of persons residing in the United States are exposed.

Past and present exposure inferred using data on consumption, use, environmental and occupational exposure
- Workers are typically exposed to high levels
- Not a formal exposure assessment

Use their judgment as to whether the exposure information in the draft monograph supports the NTP conclusion that a significant number of U.S. residents are exposed to antimony trioxide
Antimony trioxide is converted in vitro and in vivo to other antimony forms and vice versa.

Information on other antimony compounds may help inform the potential carcinogenicity of antimony trioxide.

Inadequate database on other antimony compounds to evaluate the potential carcinogenicity.

Research Questions

- Are a significant number of people in the United States exposed to antimony trioxide?
- Is antimony trioxide known or reasonably anticipated to be a human carcinogen (as defined by the RoC listing criteria)?

Scope of the monograph

- Antimony trioxide is converted in vitro and in vivo to other antimony forms and vice versa.
- Information on other antimony compounds may help inform the potential carcinogenicity of antimony trioxide.
- Inadequate database on other antimony compounds to evaluate the potential carcinogenicity.
## Framework for evaluating research question

<table>
<thead>
<tr>
<th>Scientific evidence stream</th>
<th>Exposure</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary evidence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experimental animal studies</td>
<td>Antimony trioxide</td>
<td>All reported neoplasms</td>
</tr>
<tr>
<td>Human epidemiology studies</td>
<td>Antimony trioxide and other antimony compounds</td>
<td>Lung and stomach cancer</td>
</tr>
<tr>
<td><strong>Supporting evidence (mechanistic and other relevant data)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experimental animal studies</td>
<td>Antimony (III) compounds</td>
<td>Carcinogenicity and biological effects related to carcinogenicity or toxicity</td>
</tr>
<tr>
<td>Human studies</td>
<td>Antimony (III) compounds</td>
<td>Biological effects related to carcinogenicity or toxicity</td>
</tr>
<tr>
<td>In vitro studies</td>
<td>Antimony (III) compounds</td>
<td>Biological effects related to carcinogenicity or toxicity</td>
</tr>
</tbody>
</table>

Analogous to "PECO" Statement, P = population replaced by evidence stream, E = exposure, O = outcome, C= comparator – unexposed for all evidence streams, O = outcome
Evaluate Cancer Hazards

Cancer hazard conclusions are reached using systematic review methods and the RoC listing criteria

Selection of studies
- Systematic literature search
- Inclusion/Exclusion Criteria
- Literature tagging using HAWC

Data extraction
- Table Builder
- Result and appendix tables

Evaluation of study quality
- Formal framework for human and animal cancer studies

Level of evidence conclusions
- Human cancer studies
- Experimental animal cancer studies
- RoC handbook
- RoC listing criteria

Overall cancer evaluation
- Human cancer studies
- Animal cancer studies
- Mechanistic and other relevant data

Cancer hazard conclusions are reached using systematic review methods and the RoC listing criteria.
Literature tagging was done using HAWC

Health Assessment Workspace Collaborative: On line collaborate workspace
https://hawcproject.org
Cancer hazard conclusions are reached using systematic review methods and the RoC listing criteria.
Data was systematically extracted and study quality is assessed using a web-based management system.

Tables developed for both animal and human cancer studies.

Accordion design for each study element.

Result modules.

Output into Word tables or Excel.
Cancer hazard conclusions are reached using systematic review methods and the RoC listing criteria.
• Increased incidence of malignant and/or a combination of malignant and benign tumors
  • In multiple species or at multiple tissue sites OR
  • By multiple routes of exposure OR
  • To an unusual degree with regard to incidence, site, or type of tumor, or age at onset

Sufficient evidence
RoC Listing Criteria

Reach level of evidence conclusion for carcinogenicity from studies in humans*

**Sufficient evidence**

- Causal relationship between exposure to the agent, substance, or mixture, and human cancer

**Limited evidence**

- Causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded

*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.
Cancer hazard conclusions are reached using systematic review methods and the RoC listing criteria.

### Selection of studies
- Systematic literature search
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### Data extraction
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### Evaluation of study quality
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### Level of evidence conclusions
- Human cancer studies
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- RoC listing criteria

### Overall cancer evaluation
- Human cancer studies
- Animal cancer studies
- Mechanistic and other relevant data
RoC Listing Criteria: Two Categories

**Known to be a human carcinogen**

- Sufficient evidence of carcinogenicity from studies in humans

**Reasonably anticipated to be a human carcinogen**

- Limited evidence from studies in humans
- OR

- Sufficient evidence from studies in experimental animals
- OR

- Belongs to well-defined structurally related class of substances listed in the RoC or demonstrates convincing mechanistic evidence

Conclusions based on scientific judgment considering all relevant information such as chemical structure, metabolism, pharmacokinetics, genetic effects, and mechanisms of action.
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**Monograph Preparation**

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Ella Darden (ILS)
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**Other Support**
Susan Dakin (contractor*)
Andy Shapiro (DNTP/NIEHS): Table builder and HAWC

*Contract Support
<table>
<thead>
<tr>
<th>Charge</th>
<th>Actions (votes)</th>
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<tbody>
<tr>
<td>Comment on whether the Draft RoC Monograph on Antimony Trioxide is technically correct, clearly stated, and objectively presented.</td>
<td>Whether the scientific evidence supports the NTP's conclusions on the level of evidence for carcinogenicity from cancer studies in animals and human for antimony trioxide.</td>
</tr>
<tr>
<td>Provide opinion on whether there is currently or was in the past significant human exposure to antimony trioxide.</td>
<td>Whether the scientific evidence supports NTP’s preliminary policy decision on the listing status of antimony trioxide in the RoC.</td>
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