Process for Preparing the Draft RoC Monograph on Antimony Trioxide

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Office of the Report on Carcinogens
National Institute of Environmental Health Sciences
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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
Process for the Preparation of the RoC

Select substances for evaluation

- Invite nominations
- Conduct scoping and problem formulation activities
  - Scientific and/or public input as needed
- Develop draft concepts
  - 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
- Interagency review of NTP listing recommendation
  - Scientific and/or public input as needed

Peer review and finalize RoC monographs

- Release draft RoC monograph
  - Public comment
  - Expert peer review draft RoC monograph
  - NTP Peer review panel* or letter review
  - 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
  - NTP Executive Committee
  - Secretary, HSS reviews and approves
  - 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
Process for the Preparation of the RoC

Opportunity for Public Comment

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Peer Review: Current Step

Process for the Preparation of the RoC

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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

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

1 public comment:
International Antimony Association
Select Antimony Trioxide for Evaluation

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

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
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

Process for preparing draft monograph on antimony trioxide
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 *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
**Prepare Draft RoC Monograph**

Evaluate whether a significant number of U.S. residents are exposed to antimony trioxide

<table>
<thead>
<tr>
<th>Congressional mandate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Publish a report that lists substances which are <em>known</em> or <em>reasonably anticipated to be human carcinogens</em> and to which a significant number of persons residing in the United States are exposed.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Evaluate data (Section 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past and present exposure inferred using data on consumption, use, environmental and occupational exposure</td>
</tr>
<tr>
<td>Workers are typically exposed to high levels</td>
</tr>
<tr>
<td>Not a formal exposure assessment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reviewer instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
</tr>
</tbody>
</table>
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.

**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>Primary evidence</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</td>
<td>Lung and stomach cancer</td>
</tr>
<tr>
<td></td>
<td>antimony compounds</td>
<td></td>
</tr>
</tbody>
</table>

**Supporting evidence (mechanistic and other relevant data)**

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental animal studies</td>
<td>Carcinogenicity and biological effects related to carcinogenicity or toxicity</td>
</tr>
<tr>
<td>Human studies</td>
<td>Biological effects related to carcinogenicity or toxicity</td>
</tr>
<tr>
<td>\textit{In vitro} studies</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

<table>
<thead>
<tr>
<th>Selection of studies</th>
<th>Data extraction</th>
<th>Evaluation of study quality</th>
<th>Level of evidence conclusions</th>
<th>Overall cancer evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systematic literature search</td>
<td>Table Builder</td>
<td>Formal framework for human and animal cancer studies</td>
<td>Human cancer studies</td>
<td>Human cancer studies</td>
</tr>
<tr>
<td>Inclusion/Exclusion Criteria</td>
<td>Result and appendix tables</td>
<td></td>
<td>Experimental animal cancer studies</td>
<td>Animal cancer studies</td>
</tr>
<tr>
<td>Literature tagging using HAWC</td>
<td></td>
<td></td>
<td>RoC handbook</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RoC listing criteria</td>
<td>Mechanistic and other relevant data</td>
</tr>
</tbody>
</table>
Literature tagging was done using HAWC

Health Assessment Workspace Collaborative: Online collaborate workspace
https://hawcproject.org
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
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
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
RoC Listing Criteria

Reach level of evidence from studies in experimental animals

**Sufficient evidence**

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

<table>
<thead>
<tr>
<th>Sufficient evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Causal relationship between exposure to the agent, substance, or mixture, and human cancer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Limited evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded</td>
</tr>
</tbody>
</table>

*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.

**Evaluate Cancer Hazards**

- **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
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.
Acknowledgments

Monograph Preparation

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