Preparation of the Draft RoC Monographs: *ortho*-Toluidine
Pentachlorophenol and By-Products of its Synthesis

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The Report on Carcinogens (RoC) is congressionally mandated

- Public Health Services Act, Section 301(b)(4) (1978, amended 1993)
  - Directs HHS Secretary to publish a list of carcinogens
- Preparation of the RoC is delegated to the National Toxicology Program (NTP)
- Identifies substances that pose a cancer hazard for people in the United States
  - Lists substances as “known” or “reasonably anticipated human carcinogens”
- Each edition of the report is cumulative
  - Most recent edition, 12th RoC, was published in June 2011

http://ntp.niehs.nih.gov/go/roc
Terminology

• Candidate substance
  – Substance selected for formal review

• Concept document
  – Contains rationale and proposed approach for a substance’s review

• Draft RoC monograph consists of two parts
  – Cancer evaluation component – contains the cancer assessment
  – Substance profile – contains the preliminary listing recommendation and scientific evidence that is key to the recommendation

• Report on Carcinogens
  – Compilation of substance profiles for each listed substance
ortho-Toluidine and pentachlorophenol* reviews: Completed steps

**ortho-toluidine monograph**

- Invite nominations
  - Interagency review
  - Public comment
  - Jan 20 2012: FR
- Develop draft concept
  - Public comment
  - Apr 25 2012: FR
- Draft concept reviews by BSC
  - June 21-22 public mtg
- NTP Director
  - Select candidate substance
- Complete draft monograph Aug 28, 2013

**Initiate cancer evaluation component**

- Technical advisors: dyes, ADME, and epidemiology experts
- Dye expert report
- Protocol: human studies
- Literature search strategy & list of references
- Prepare draft substance profile
- Interagency review
- Complete draft monograph Aug 28, 2013

**pentachlorophenol monograph**

- Invite nominations
  - Interagency review
  - Public comment
  - Jan 20 2012: FR
- Develop draft concept
  - Public comment
  - Apr 25 2012: FR
- Draft concept reviews by BSC
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**Initiate cancer evaluation component**

- Technical advisors: exposure, epidemiology, ADME, and toxicology experts
- Public webinar and informational group
- Protocol: human and animal studies
- Literature search strategy & references
- Prepare draft substance profile
- Interagency review
- Complete draft monograph Aug 28, 2013

*Includes by-products of its synthesis
Monograph contents: o-Toluidine and pentachlorophenol

**Cancer evaluation component**
- Literature-based assessment
  - Properties and Human Exposure
  - Disposition and Toxicokinetics
    - Absorption, distribution, metabolism, excretion
  - Cancer Studies in Humans
  - Cancer Studies in Experimental Animals
  - Other Relevant Data
    - Genotoxicity, mechanisms
  - Overall Cancer Evaluation

**Substance profile**
- Listing recommendation
  - Carcinogenicity: Key studies
  - Properties
  - Use
  - Production
  - Exposure
  - Regulations

**Appendices**
- Literature search strategy, data tables, quality questions, background information
Preparing the cancer evaluation component

1. Identify scientific issues and develop key questions (Concept document)
2. Identify and select literature: Systematic literature search (Appendix A and website)
3. Extract data/describe studies (Monograph sections and appendices)
4. Assess the quality of key studies (Appendices)
5. Synthesize the findings across studies and reach level of evidence conclusions for each discipline
6. Integrate the overall body of evidence and reach a preliminary RoC listing recommendation (Section 6)
Identifying the relevant literature

Web-based software
Inclusion/exclusion criteria
Multiple reviewers

Literature search: databases

General sources

Topic-specific searches

Excluded citations

1st level review (2277)

Selected citations: o-toluidine (1119)

Exposure (341) ADME (89) Human cancer (227) Exp. animal cancer (61) Genotoxicity (159) Toxicity (50) Mechanisms (436)

Excluded citations

2nd level review (full text)

Secondary Citations

Additional topics

Included citations (280)

Updated Searches
Assessing study quality

• Methods developed for evaluating study quality for the cancer studies in humans and experimental animals (Appendices)

• Protocols posted on each candidate substance’s website
  – Human cancer studies for both substances
  – Cancer studies in experimental animals for pentachlorophenol
Reaching a preliminary listing recommendation

Level of evidence: Human studies
- RoC listing criteria

Level of evidence: Experimental animals studies
- RoC listing criteria

Conclusions from mechanistic data

Preliminary listing recommendation
- RoC listing criteria
Evaluating whether there is significant exposure for U.S. residents

- Congressional mandate
  - 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

- Information on numbers of exposed people is usually not available; typically exposure has been inferred from data on the following:
  - Use, production volume, occupational monitoring, environmental (occurrence), estimated intake, and biomonitoring
  - Past cancer is relevant because cancer has a long latency period
  - Reviewers are asked to use their judgment as to whether the exposure information in the draft monographs supports NTP conclusion on U.S. exposure
Reaching a level of evidence conclusion of carcinogenicity from studies in humans

RoC listing criteria

• Sufficient evidence from studies in humans*: Causal relationship between exposure to the agent, substance, or mixture, and human cancer

• Limited evidence from studies in humans*: 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
Reaching a level of evidence carcinogenicity conclusion from studies in experimental animals

Sufficient evidence from studies in experimental animals defined by RoC listing criteria

- Increased incidence of malignant and/or a combination of malignant and benign tumors
  - In multiple species or at multiple tissue sites
  - By multiple routes of exposure
  - To an unusual degree with regard to incidence, site, or type of tumor, or age at onset
Evaluating and using the mechanistic data

• What are the potential mechanisms?
• Does the agent belong to a well-defined, structurally related class of substances whose members are listed in the RoC?
• What evidence do we have in humans and animals?
• How do we use mechanistic data?
  • Most of the time we have limited data
  • Is there convincing data that a substance operates by a mechanism that would cause cancer in humans?
  • Is there compelling data that a substance causes cancer by a mechanism that would not occur in humans?
Reaching a preliminary listing recommendation

Level of evidence: Human studies
  • RoC listing criteria

Level of evidence: Experimental animals studies
  • RoC listing criteria

Conclusions from mechanistic data

Preliminary listing recommendation
  RoC listing criteria
RoC listing criteria: Two listing 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
  - Sufficient evidence from studies in experimental animals
  - Less than sufficient evidence in humans or experimental animals
    - Agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous RoC as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen
    - **Convincing** relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans
RoC listing criteria: Guidance (final paragraph)

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.
ortho-Toluidine and pentachlorophenol reviews: Current step

**Nomination and Selection of Candidate Substances**
- Invite nominations to the RoC
  - Interagency review
  - Public comment
- Develop draft concept documents for substances proposed for evaluation
  - Public comment
  - Review of draft concept documents by NTP Board of Scientific Counselors*
    - (public meeting, public comment)
- NTP Director
  - Select candidate substances

**Scientific Evaluation of Candidate Substances**
- Prepare draft RoC Monograph for a candidate substance
  - (initiate cancer evaluation component)
  - External scientific input, as needed
    - (e.g., consultants, ad hoc presentations, expert panels*)
  - Public input
    - (e.g., listening session, comment)
- Interagency input
  - (complete cancer evaluation component and prepare draft substance profile)
  - Interagency review
- Complete draft RoC Monograph

**Public Release and Peer Review of Draft RoC Monographs**
- Release draft RoC Monograph
- Public comment
  - Peer review of draft RoC Monograph by NTP Peer-Review Panel*
    - (public meeting, public comment, peer-review report)
  - Interagency review
  - Complete draft RoC Monograph
  - Present information regarding the peer review and revised draft RoC Monograph to NTP Board of Scientific Counselors
    - (public meeting, public comment)
- NTP Director
  - Finalize RoC Monograph
    - (cancer evaluation component and substance profile)

**HHS Approval and Release of Latest Edition of the RoC**
- Submit recommended listing status for newly reviewed candidate substances
  - NTP Executive Committee
  - Approval of listing status by Secretary, HHS
    - (transmit latest edition of RoC to Congress and release to the public)

**Key**
- HHS = Health and Human Services
- NTP = National Toxicology Program
- RoC = Report on Carcinogens
* Federally chartered advisory groups
<table>
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<th>Charge</th>
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<tr>
<td>To comment on the draft cancer evaluation component, specifically,</td>
<td>Whether the scientific evidence supports the NTP’s conclusion on</td>
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<td>whether it is technically correct and clearly stated, whether the</td>
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<td>NTP has objectively presented and assessed the scientific evidence,</td>
<td>Whether the scientific evidence supports the NTP’s conclusion on</td>
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<td>and whether the scientific evidence is adequate for applying the</td>
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<td>scientific evidence supports the NTP’s preliminary listing decision</td>
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ortho-Toluidine and pentachlorophenol reviews: Next steps

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