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National Toxicology Program

Report on the Draft RoC Monograph Peer-Review Panel Meeting December 12–13, 2013

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NTP Board of Scientific Counselors
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Objective

- To provide the NTP Board of Scientific Counselors (BSC) with information regarding the peer review of draft Report on Carcinogens(RoC) monographs for two candidate substances:
  - *ortho*-Toluidine
  - Pentachlorophenol and by-products of its synthesis (hereinafter called PCP)
- Peer-review meeting: December 12–13, 2013 at NIEHS.

Peer-review panel meeting information available at http://ntp.niehs.nih.gov/go/38854

Outline

- Background information: RoC and the two candidate substances.
- Steps in the review process and public comments.
- Draft RoC monographs and listing recommendations.
- Peer-review panel meeting.
  - Members and charge.
  - Panel's recommendations.
- Steps subsequent to the peer-review meeting.
  - Peer-review report, NTP response, and revised monograph.
  - Next steps after the NTP BSC meeting.

The RoC is congressionally mandated

- Public Health Services Act, Section 301(b)(4) (1978, amended 1993).
  - Directs HHS Secretary to publish a list of carcinogens.
- The NTP prepares the RoC for the Secretary.
- Identifies substances that pose a cancer hazard.
  - Lists substances as "*known*" or *"reasonably anticipated human carcinogens."*
  - Significant number of people residing in the United States are exposed.
- Each edition of the report is cumulative.
  - Most recent edition, 12th RoC, was published in June 2011.

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

Candidate substances: *ortho*-Toluidine

- Aromatic amine used to make dyes, rubber chemicals, and herbicides.
- The highest exposure to *ortho*-toluidine occurs to people who are exposed (via inhalation or through the skin) in workplaces that use it.
- People are exposed to lower levels of *ortho*-toluidine in their everyday lives from consumer products, medical products, cigarette smoke, and possibly the environment.
- Listed in the RoC since 1983 as *reasonably anticipated to be a human carcinogen.*
- Additional cancer studies in humans published since that time.
- Project leader: Dr. Ruth Lunn.

http://ntp.niehs.nih.gov/go/37898

Candidate substances: PCP

- Pesticide used as a wood preservative; since 1987 its use has been restricted to commercial use.
- By-products formed during its synthesis include mostly other chlorinated phenols and higher-chlorinated dioxins and furans.
- Virtually everyone who is exposed to pentachlorophenol is exposed to its by-products.
- Available database is mostly of humans and animals exposed to the mixture.
- Project leader: Dr. Gloria Jahnke.

http://ntp.niehs.nih.gov/go/37897

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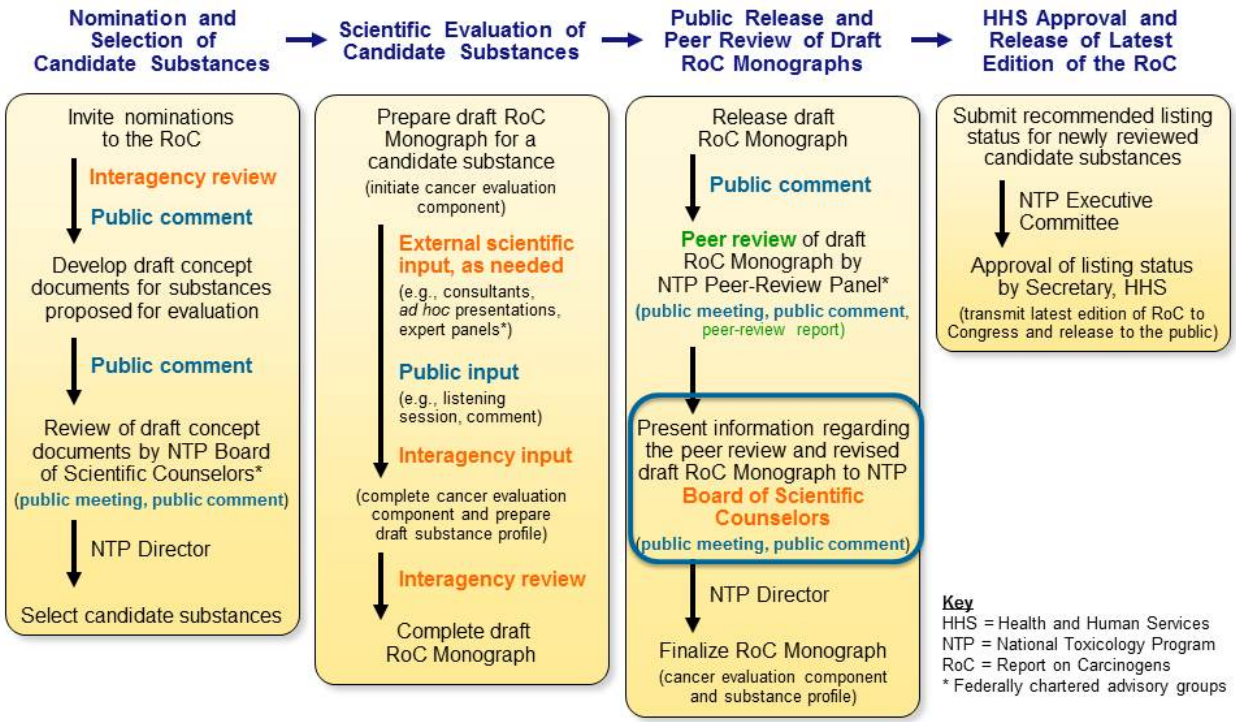
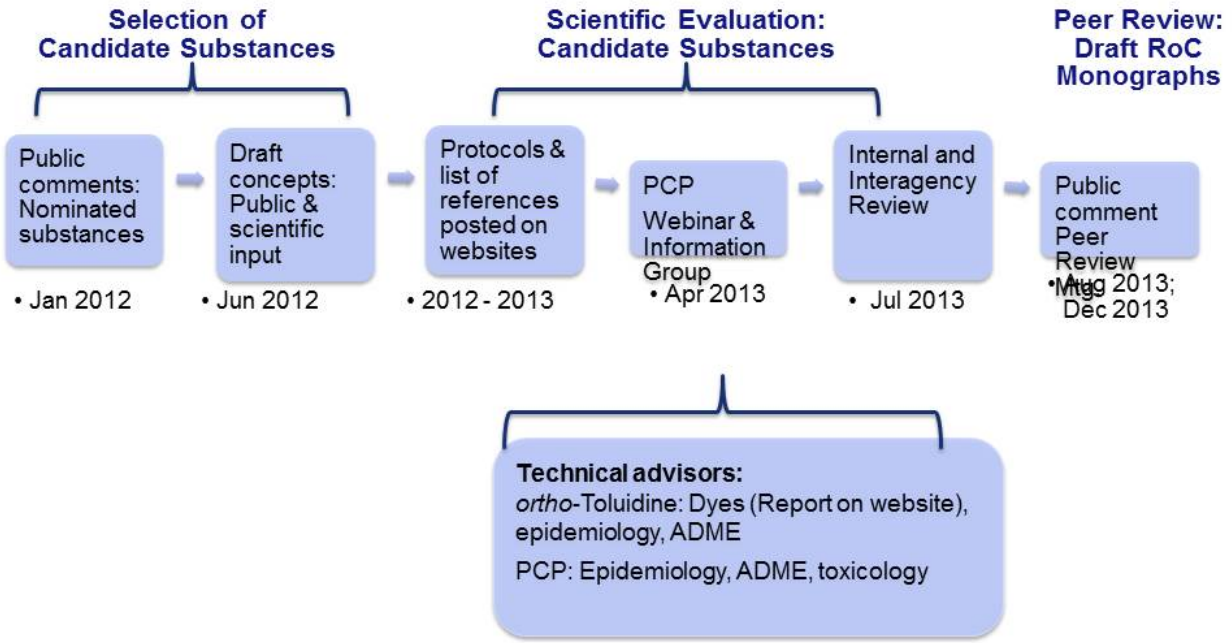
Review of *ortho*-Toluidine and PCP: Review Process and Public Comments

Process for Preparation of the RoC



Key steps in the review of *ortho*-toluidine and PCP



Multiple opportunities for public comments

Step	*o*-Toluidine	PCP
Nomination	1	1
Draft concept	0	0
Public webinar	NA	oral + written follow-up
Website submission	0	0
Draft monograph (written)	1	3
Draft monograph (oral)	0	1

- Time was set aside at the peer-review meeting to discuss scientific issues raised in the public comments.

http://ntp.niehs.nih.gov/go/37663

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Review of *ortho*-Toluidine and PCP: Draft RoC Monographs and Listing Recommendations

A RoC monograph consists of two parts

Cancer Evaluation Component
Literature-based assessment

- Properties and Human Exposure
- Disposition and Toxicokinetics
- Human Cancer Studies
- Cancer Studies in Experimental Animals
- Other Relevant Data
- Overall Cancer Evaluation
- Appendices
  Literature search strategy, data tables, quality questions, background information

Substance Profile
Listing recommendation

- Carcinogenicity: Key studies
- Properties
- Use
- Production
- Exposure
- Regulations

RoC recommendations: Level of evidence and evaluation of mechanistic data

- Level of evidence conclusions in humans based on RoC listing criteria: Inadequate (i.e., not limited or sufficient), limited, sufficient.
- Level of evidence conclusions in experimental animals based on RoC listing criteria: Sufficient, not sufficient.
- Mechanistic data considerations (most cases limited data).
  - Compelling data that a substance causes cancer by a mechanism that would not occur in humans.
  - Convincing data that a substance operates by a mechanism indicating that it would cause cancer in humans.

RoC Listing criteria available at http://ntp.niehs.nih.gov/go/15209

RoC conclusions: Preliminary listing recommendation

- *Known to be a human carcinogen*
  - Sufficient evidence of carcinogenicity from studies in humans (mechanistic studies in human tissue or cells can contribute to the evaluation).
- *Reasonably anticipated to be a human carcinogen*
  - Limited evidence of carcinogenicity from studies in humans.
  - Sufficient evidence of carcinogenicity from studies in experimental animals.
  - Convincing mechanistic data.

RoC Listing criteria available at http://ntp.niehs.nih.gov/go/15209

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Review of *ortho*-Toluidine and PCP: Peer-Review Meeting

December 12–13, 2013, NIEHS

ortho-Toluidine and PCP Peer-review Panel

Member	Affiliation
Kenneth McMartin, PhD (Chair)	Louisiana State University Health Sciences Center
Stelvio M. Bandiera, PhD	University of British Columbia
Laura Beane-Freeman, PhD	National Cancer Institute
Stephen Nesnow, PhD	Independent Consultant
Gabriele Sabbioni, PhD*	Tulane University
Martha Sandy, PhD	California Environmental Protection Agency
MaryJane Selgrade, PhD, ATS	ICF International
Allan Smith, MD, PhD	University of California, Berkeley
Glenn Talaska, PhD	University of Cincinnati
Paul Villeneuve, PhD	Carleton University
Elizabeth Ward, PhD	American Cancer Society
Shelia Zahm, ScD	Independent Consultant

**ortho*-Toluidine only

Peer-review panel: Charge and actions for each draft monograph (*ortho*-toluidine and PCP)

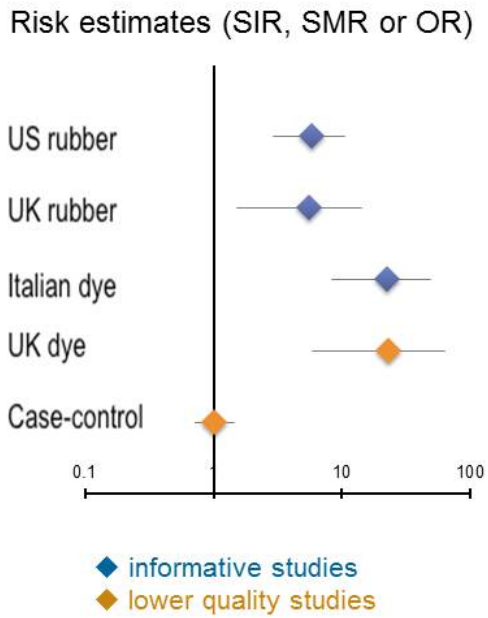
- Charge
  - To comment on the draft cancer evaluation component, specifically, whether it is technically correct and clearly stated, whether the NTP has objectively presented and assessed the scientific evidence, and whether the scientific evidence is adequate for applying the listing criteria.
  - To comment on the draft substance profile, specifically, whether the scientific justification presented in the substance profile supports the NTP's preliminary policy decision on the RoC listing status of the candidate substance.
- Actions (votes)
  - Whether the scientific evidence supports the NTP's conclusion on the level of evidence for carcinogenicity from cancer studies in human and experimental animal studies of the substance.
  - Whether the scientific evidence supports the NTP's preliminary listing decision for the substance in the RoC.

ortho-Toluidine: Actions

NTP Draft Recommendations	Basis	Panel
Significant number of persons in the United States are exposed to *ortho*-toluidine.	Widespread exposure. Occupational exposure.	Agreed.
Sufficient evidence of carcinogenicity from studies in humans.	Causes urinary bladder cancer in humans.	Agreed.
Sufficient evidence of carcinogenicity from studies in experimental animals.	Causes tumors at several tissues sites in rats and mice. *Rat tissue sites*: Urinary bladder, connective tissue, subcutaneous tissue, mesothelium. *Mouse tissue sites*: Blood vessel and liver. *Supporting evidence*: Mammary gland fibroadenoma in rats.	Agreed.

Sufficient evidence of carcinogenicity from studies in humans: *ortho*-Toluidine causes urinary bladder cancer

- Consistent findings across studies.
- Risks of urinary bladder cancer increased with increasing level or longer duration of exposure to *ortho*-toluidine.
- Large magnitudes of effect across studies.
- Reasonably rule out confounding and biases.
- Panel agreed with draft conclusions.



ortho-Toluidine: Actions

NTP Draft Recommendations	Basis	Panel
Preliminary listing recommendation: *ortho*-Toluidine is known to be a human carcinogen.	Studies showing it causes urinary bladder cancer in humans together with: • Studies showing it causes cancer in experimental animals, including urinary bladder (indicating tumor-site concordance). • Biological plausibility of mechanisms of its carcinogenicity in humans.	Agreed.

PCP: Actions

NTP conclusions in draft monograph	Basis	Panel
Significant number of persons in the United States are exposed to PCP.	Widespread past and present exposure. Occupational & environmental Biomonitoring data.	Agreed.
Sufficient evidence of carcinogenicity from studies in experimental animals.	Causes tumors at several tissue sites in mice and rats. *Rat tissue sites*: nose, mesothelium (stop exposure study only). *Mouse tissue sites*: liver, adrenal gland, blood vessels.	Agreed.
Sufficient evidence of carcinogenicity from studies in humans.	Causes NHL in humans.	Panel recommended conclusion of limited evidence.

Limited evidence of carcinogenicity of PCP from studies in humans

- Evidence suggests that an association of exposure to PCP and increased risk of NHL is credible.
  - Increased risks of NHL found in several studies but the strength of the evidence varies across studies.
  - Statistically significant exposure-response relationship with exposure duration found in a high-quality study.
- Causal relationship has not been demonstrated.
  - Evidence is based on a small number of high-quality studies with relatively moderate risk estimates (~ 2-fold).
  - Alternative explanations (such as chance, bias and confounding) cannot be adequately excluded.

PCP: Panel's additional recommendations and actions

- Additional Panel recommendation: Sufficient evidence for PCP by itself in experimental animals.
  - Studies in rats using "pure" PCP (not sufficient evidence by itself).
  - Studies in mice using Dowicide EC (90% pure).
- NTP does not believe the body of evidence is sufficient to make a conclusion on PCP alone.
  - Dowicide EC still has low levels of dioxins and contains tetrachlorophenol (10%) which has not been tested in experimental animals.
  - "Pure" pentachlorophenol studies are in rats, and Dowicide EC studies are in mice, which limits direct comparison.
- NTP agrees with the Panel's recommendation that pentachlorphenol and by-products of its synthesis should be listed in the RoC as *reasonably anticipated to be a human carcinogen*.

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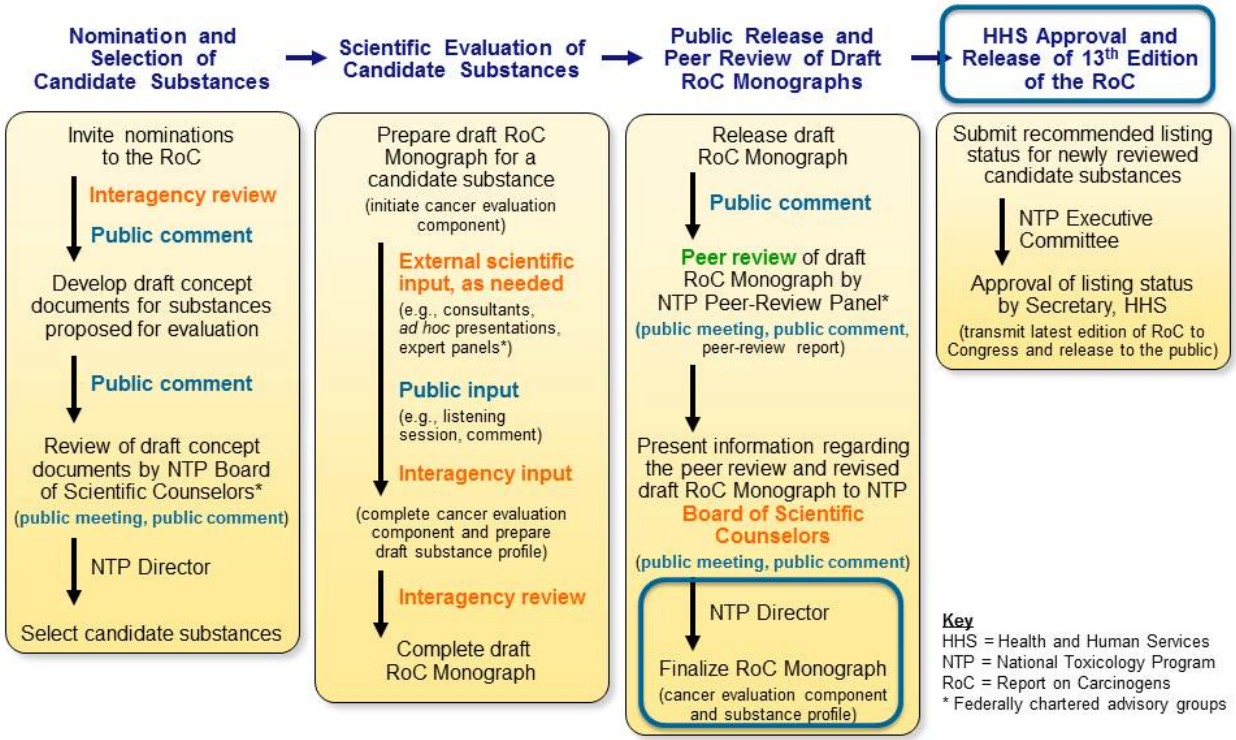
Review of *ortho*-Toluidine and PCP: Steps Subsequent to the Peer-Review Meeting

Peer-review report and NTP responses

- Peer-review report
  - Recommendations concerning NTP's draft conclusions and scientific issues supporting the recommendations (e.g., mainly actions).
  - Scientific and technical peer-review comments to improve the technical accuracy, clarity, and objectivity of the monograph (charge questions).
  - In general, the Panel thought the approaches for evaluating the cancer studies were systematic and transparent.
- NTP response to the peer-review report
  - NTP addressed both types of comments in its written response.
  - Provides the NTP's rationale for accepting/not accepting peer review recommendations.
- Revised draft monographs
  - NTP revised the draft monographs for *ortho*-toluidine and PCP based on the peer-review comments.

Next steps



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

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