Report on Carcinogens
Draft Concept for
Trichloroethylene

Ruth M. Lunn, DrPH
National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors Meeting
June 21 – 22, 2012
Trichloroethylene is proposed for re-review for the RoC

- Chlorinated alkene used primarily as a metal degreaser
- Widespread exposure: present in the environment, food, numerous consumer products, and the workplace
- Listed in the RoC since 2000 as reasonably anticipated to be a human carcinogen
  - Sufficient evidence of carcinogenicity from studies in experimental animals
  - Limited evidence from studies in humans
- Over 20 cancer studies in humans published since 2000
Several recent evaluations of TCE and cancer have been conducted

• NRC: Assessing the human health risks of trichloroethylene: Key scientific issues (2006)
  • Strong evidence: exposure to high levels of TCE is associated with increased rates of kidney cancer

  • Carcinogenic to humans: convincing epidemiologic evidence of a causal association between human exposure and kidney cancer

  • Limited evidence: association between exposure to TCE and kidney cancer
Public comments

• One public comment received on NTP request for information on several nominations
• Disagreed with EPA conclusions on carcinogenicity
  • Limitations in the epidemiologic studies
  • Magnitudes of the meta-risk estimates were small
People are potentially exposed to TCE by multiple routes and in multiple settings

- Ubiquitous in environment: atmosphere, soil, ground, surface and drinking water, and food (μg to 10 μg/day)
  - Inhalation of outdoor/indoor air
  - Volatilization from tap and shower water
  - Ingestion of drinking water and food
  - Dermally from bathing water
- Highest levels of exposure found in the workplace (~38 ppm)
  - Primarily used in metal degreasing industries; also used as a solvent in other applications such as adhesives, paints, varnishes
  - Previous uses: dry cleaning industry, pesticides, drugs and food
  - Use declined since 1970’s
- TCE is a high production volume chemical (100-500 million lb/yr)
Cancer sites of concern are non-Hodgkin’s lymphoma and cancers of the kidney and liver

• Original listing: limited evidence in humans
  – non-Hodgkin’s lymphoma (NHL), liver cancer, kidney cancer
  – Potential confounding from exposure to other solvents could not be ruled out

• Current literature database: over 75 studies
  – Cohort studies: aircraft and aerospace workers, workers in other TCE-exposed industries such as electronics, paperboard, or cardboard manufacturers, and biomonitoring studies
  – Hospital-and population-based case-control studies of occupational exposure to TCE
  – Geographically based studies of environmental exposure to TCE
  – Recent meta-analyses: NHL, multiple myeloma, leukemia and cancers of the liver and kidney
TCE causes cancer in experimental animals

- Original listing based on increases of tumor incidence at multiple sites in two rodent species by two routes of exposure

- Two studies published since original listing
  - Drinking water study in mice: liver tumors
  - Intraperitoneal injection in neonatal mice: no increases in tumor incidence

<table>
<thead>
<tr>
<th>Route</th>
<th>Rat</th>
<th>Mice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhalation</td>
<td>Males Kidney, testicular</td>
<td>Both sexes Liver, lung Females Lymphoma,</td>
</tr>
<tr>
<td>Gavage</td>
<td>Males Kidney, testicular</td>
<td>Both sexes Liver</td>
</tr>
</tbody>
</table>
TCE metabolism occurs by two major pathways

- **Oxidative (Cyp 2E1)**
  - Lung toxicity: TCA, DCA
  - Liver toxicity and tumors: CH, TCA, DCA

- **Glutathione conjugation**
  - Kidney toxicity: DCVC
  - Mutagenicity: DCVC, DCVG

- Detected in humans
  - TCA, DCA, TCOH, NAcDCVC, DCVG
Proposed mechanisms for TCE potential carcinogenicity

- Large database of studies evaluating potential mode of action for liver and kidney cancer
  - Mutagenicity
    - Studies measuring mutations in the von Hippel-Lindau (VHL) tumor-suppressor gene in renal tumors
  - Cytotoxicity
  - Oxidative damage
  - Alpha activation (PPARα) (liver and kidney cancer)
  - $\alpha_2u$-globulin-related nephropathy (kidney cancer)
- Paucity of mechanistic data for TCE-induced lymphoma in rodents and humans
  - Numerous studies in humans and laboratory animals evaluating immune effects of TCE
  - Altered immunity is proposed to be a risk factor for NHL
Cancer evaluation will focus on human and mechanistic data for specific endpoints

- Assessment limited to non-Hodgkin’s lymphoma, kidney cancer, and liver cancer
  - Identified as cancer sites of potential concern in several, comprehensive reviews and 2000 RoC evaluation
  - Concordance with experimental animal data

- Assessment will be on the human cancer studies and mechanistic data
  - Mechanistic studies in experimental animals and humans will be evaluated

- Findings from the animal studies will be integrated into the overall synthesis of cancer studies in humans and mechanistic data
  - Accept the RoC conclusions (2000) of sufficient evidence in experimental animals
  - Studies published after the 2000 are consistent with this conclusion
Key questions and issues

• Human cancer studies
  – What is the level of evidence (sufficient, limited) for the carcinogenicity of TCE from studies in humans?
  – What are the major strengths and limitations in the individual studies and how do they affect the findings?

• Mechanistic data
  – What are the potential mechanisms by which TCE may cause lymphoma and cancers of the kidney and liver?
  – Is there evidence that the mechanisms by which TCE causes cancer in experimental animals may not occur in humans?
    • If so, what is the level of evidence (strong, moderate, weak)?
  – Is there mechanistic evidence in humans that would support the associations observed in some human cancer studies?
    • If so, what is the level of evidence (strong, moderate, weak)?
  – Is there any evidence that TCE-induced immunologic effects are related to cancer (such as lymphoma or liver cancer) development?
ORoC will use a variety of sequential approaches to receive scientific and public input

- Public comments requested on the nomination and draft concept
- Establish a website
  - Communicate status and relevant documents related to the monograph preparation
  - Mechanism to receive public input
- Identify appropriate technical advisors
  - External or internal to the government, with expertise in TCE who will serve as consultants in developing the monograph
  - Sources for identifying advisors: Literature database, recommendations from scientific community and the public
- Listening session to receive comments on inclusions of topics and preliminary list of references
  - Announced via Federal Register
  - Example of topics are specific modes of action
ORoC will convene web-based symposims on each of the three cancer sites

- Each symposium will consist of invited speakers presenting their views on the strength of evidence for the association between TCE and cancer
  - Two talks that address the strength and limitations of the epidemiologic studies and two that address mechanistic data
- Speakers
  - Industry, environmental advocacy groups, academia, labor unions, research organizations, or government agencies
  - Any real or apparent conflicts of interest will be disclosed
- Discussion of the key issues led by ORoC technical advisors and staff
- Opportunity for the public to submit questions for the speakers
Public release and peer review of the draft monograph

• Interagency review and public release of draft RoC monograph
• Expert panel with expertise on relevant topics such as epidemiology, exposure assessment, kidney cancer, liver cancer, and non-Hodgkin’s lymphoma, toxicology, PPARα activation, and mechanisms of carcinogenesis
• Time set aside for addressing issues raised by the public
Specific charge questions

1. Comment on whether the cited information suggests that exposures to the substance in the United States 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. The 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.