Report on Carcinogens
Cumene
Concept Review

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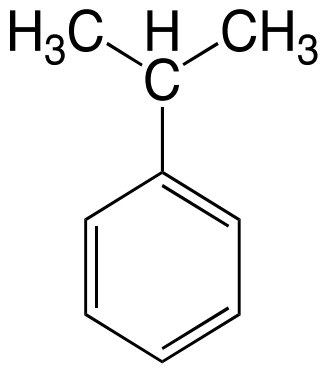
Cumene



- Cumene is a liquid with a gasoline-like odor.
  - Component of fossil fuels.
  - Primarily used in the synthesis of acetone and phenol.
- Proposed as a candidate substance for the RoC.
  - Widespread current and past U.S. exposure.
  - An adequate database of studies in animals for evaluation of its potential carcinogenicity.

Cumene - U.S. Exposure

- No public comments were received on RoC cumene nomination or concept.
- Authoritative Review: IARC (2012) classification as possibly carcinogenic to humans (Group 2B).
- Environmental Exposures
  - Contaminated air from combustion (e.g., motor exhaust) and evaporation (e.g., gasoline and kerosene fumes) of fossil fuels.
  - Release with production, use, and transport.
  - Tobacco products and some foods.
  - Primary route of exposure: inhalation of ambient air.

Cumene - U.S. Exposure

- Occupational Exposures – production processes such as chemical syntheses, petroleum refining, rubber vulcanization, solvent and paint manufacture, and in pharmaceutical and textile industries.
  - Primary routes of exposure – inhalation or dermal exposures in workplaces.
  - Some of the highest levels of exposure during car repair work.
- U.S. Production
  - > 1 billion pounds per year
  - 2.29 billion pounds imported; 127 million pounds exported (2011)

Cancer Studies

- No epidemiological studies on human cancer and exposure specifically to cumene.
- One experimental animal study
  - NTP Technical Report (2009) – 2 yr. carcinogenesis studies of cumene in F344/N rats and B6C3F_1 mice (inhalation studies)
    - Rats – Adenoma of respiratory epithelium (m,f); Renal tubule adenoma or carcinoma (m)
      - Interstitial cell adenoma of testes (m) may have been exposure-related.
    - Mice – Alveolar/bronchiolar carcinoma (m,f) and adenoma (m); Hepatocellular adenoma or carcinoma combined (f)
      - Hemangiosarcoma in the spleen (m), adenoma of the thyroid gland (m), hepatocellular adenoma or carcinoma (combined) (f) may have been exposure-related.

Other Relevant Data

- Metabolism
  - P450 oxidation of alkane group or benzene ring
  - 16 metabolites identified
    - Urine and Bile- 2-phenyl-2-propanol glucuronide
    - Expired Air- cumene and α–methylstyrene
- Genotoxicity studies
  - Cumene and α–methylstyrene have been tested *in vitro* and *in vivo* for genotoxicity.
  - Mouse lung tumors induced by cumene exposure tested for mutations in *K-ras* and *p53* and loss of heterozygosity.

Potential Mechanisms of Carcinogenesis

- Genetic or epigenetic effects.
- Species- and sex-specific accumulation of α_{2u}-globulin in kidneys of male rats.
- Formation of cytotoxic metabolites by CYP2F-specific mechanism.
  - *cyp2f2* mouse lung
  - CYP2F4 rat nasal cavity
  - No specific enzymes involved in cumene metabolism have been identified.

Key Scientific Questions Relevant for Cancer Evaluation

- What is the level of evidence (sufficient or not sufficient) for the carcinogenicity of cumene from animal studies? What are the tissue sites?
- What are the potential modes of action by which cumene may cause cancer? Is there evidence that the mode of action is not relevant to humans?
  - What is the level of evidence that renal tumors in male rats are caused by an α_{2u}-globulin-associated nephropathy? Are there other potential mechanisms?

Major Scientific Issues and Proposed Approach

- Renal tumors in male rats are proposed to be caused by a species- and sex-specific mechanism, α_{2u}-globulin nephropathy.
- Convene a group of NTP scientists with specific expertise on cumene to independently evaluate data relevant to cumene exposure in adult male rats using IARC criteria and US EPA sequence of events for α_{2u}-globulin nephropathy.

Proposed Approaches for Obtaining Public Input

- Public comments requested on the nomination and draft concept.
- RoC webpage for candidate substances under review.
  - Communicate status and relevant documents related to the monograph preparation.
  - Provide information on public meetings.
  - Mechanism to receive public input.
    - New literature
    - Suggestions for scientific advisors
    - Scientific issues
- Future forums may be convened to address any additional scientific issues.

Next Steps

- The draft RoC monograph will undergo interagency review and be released for public comment.
- NTP will convene a peer-review panel to review the monograph on cumene.
- The panel will consist of members with expertise related to the cancer hazard evaluation such as: toxicology and cancer assessment in experimental animals, inhalation toxicology, pathology, general metabolism/tissue-specific metabolism of alkylbenzenes, genotoxicity, and mechanisms of carcinogenesis.
- Time will be set aside at the peer-review meeting for a discussion of scientific issues raised in public comments.

Specific Charge Questions

1. Comment on whether the cited information suggests that exposures to the substance in the US 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. 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.