NTP
National Toxicology Program

Report on Carcinogens Draft Concept for *ortho*-Toluidine

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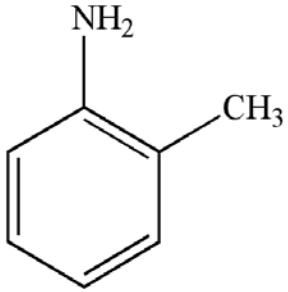
ortho-Toluidine is proposed for re-review for the RoC



- Aromatic amine used to make dyes, rubber chemicals and herbicides
- Listed in the RoC since 1983 as *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals
- Numerous human cancer studies published since 1983
  - IARC concluded *ortho*-toluidine is carcinogenic to humans (2010, 2012)
- Significant U.S. exposure
- Public comment received to date supports nomination

People in the United States are or have been exposed to *ortho*-toluidine

- Is there significant U.S exposure to *ortho*-toluidine?
  - High production volume chemical (10 million to < 50 million lbs.)
  - Wide-spread usage
  - Biomonitoring data: Detected in blood, breast milk and urine in humans
- Where are people exposed to *ortho*-toluidine?
  - Workplace: production, or use to produce dyes, pigments, rubber chemicals or pesticide intermediates
  - Consumer products, tobacco smoke and medical products
  - Environment: 6,900 to 55,000 lb/yr released in the U.S. between 1988 and 2009
- How are people exposed to *ortho*-toluidine?
  - Inhalation and skin contact

ortho-Toluidine causes cancer in experimental animals

- Original listing
  - Dietary exposure
  - Tumors found at multiple sites in two rodent species
- Two studies published since original listing
  - NTP TOX report (feed) in male rats: early onset of mesothelioma of the epididymis
  - Tumors observed in chronic studies in rodents(subcutaneous injection) and dogs (feed and gavage)

	Rat	**Mice**
Both sexes	Sarcoma: spleen and other organs	Hemangioma, hemangio-sarcoma
Males only	Fibroma, mesothelioma: abdominal cavity, epididymis	
Females only	Urinary bladder tumors, mammary gland tumors	Liver tumors

Human cancer studies focus on urinary bladder cancer

- Studies (primarily case-reports) available at the time of first listing were inadequate to evaluate potential cancer risk
- Studies published since first listing:
  - Two population-based case control studies: childhood leukemia, and urinary bladder cancer
  - Several cohort studies (mortality, incidence or both) of workers in five different industries:
    - Magenta manufacturing
    - Aniline dye production
    - Bromoindigo or thioindigo dye production
    - 4-chloro-*ortho*-toluidine production and processing
    - Rubber chemicals production
- Workers exposed to multiple chemicals, some of which are suspected carcinogens

Mechanistic and other relevant data

- Metabolism in rats
  - *N*-acetylation and hydroxylation at the 4-position are the major metabolic pathways
  - Other pathways:
    - Oxidation of the amino and methyl group
    - Hydroxylation at the 6-position
- Metabolism in humans
  - *N*-acetyl-*ortho*-Toluidine has been detected in exposed humans
- Key mechanistic data
  - Adducts (DNA or hemoglobin) found in rodents and people exposed to *ortho*-toluidine
  - *ortho*-Toluidine releasing adducts found in human urinary bladder tissue or tumors (source of exposure not known)
  - Large database available on genetic effects

Key questions and issues relevant for evaluating human and mechanistic data

- Human cancer studies
  - What is the level of evidence (sufficient, limited, or inadequate) for the carcinogenicity of *ortho*-toluidine from studies in humans?
  - What are the potential confounders for evaluating urinary bladder cancer risk in these studies?
  - Can the relationship between bladder cancer risk and exposure to *ortho*-toluidine be explained by exposure to these substances?
- Mechanistic data
  - What are the potential mechanisms by which *ortho*-toluidine may cause cancer?
  - Is there evidence that these mechanisms occur in humans? If so, what is the level of evidence?

Scope and focus of the draft monograph

- Focus: human cancer studies and mechanistic data
  - Mechanistic studies in experimental animals and humans will be evaluated
- Integrate the findings from the animal studies into the overall synthesis of cancer studies in humans and mechanistic data
  - Will not reevaluate the level of evidence (sufficient or non-sufficient) of cancer studies in experimental animals because no new studies were identified that would change the conclusions made in 1983
- Special topics
  - Concise summary of toxicological and epidemiological data on co-exposures identified in the epidemiologic studies
- IARC (2010, 2012) used as a resource
  - Some chapters of the monograph (such as exposure) will be limited to brief reviews or updates of information in the 12th RoC

Proposed approaches for obtaining 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
- Future forums may be convened to address any additional scientific issues

Scientific input: Technical advisors

- Scientific experts in dye chemistry and/or manufacturing
  - Sources for identifying advisors: Web searches, textile schools, dye industry
  - Purpose: Provide information on current and historical use of *ortho*-toluidine to manufacture various dyes, such as magenta
- Technical advisors (internal and/or external to the government)
  - Knowledge related to *ortho*-toluidine, dyes or arylamines
  - Expertise in industrial hygiene, epidemiology and cancer mechanisms
  - Sources for identifying advisors: Literature database, recommendations from scientific community and the public
  - Purpose: Review list of citations and specific chapters of the monograph

Public release and peer review of the draft monograph

- Interagency review and release of the draft monograph for public comment
- Peer-review by external scientific panel
  - Epidemiology, exposure assessment, toxicology, genetic damage, mechanisms of carcinogenesis, urinary bladder cancer, and biotransformation of aromatic amines
- 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.