Scientific Issues in Written Public Comments

Draft RoC Monograph on *ortho*-Toluidine

National Institute of Environmental Health Sciences

NTP Peer-Review Meeting
December 12-13, 2013

ortho-Toluidine: Public Comments

- Written public comments: 1 submission
  - Steven H. Wodka, attorney at law

ortho-Toluidine Public Comments: Scientific Issues

- Endorses listing *ortho*-toluidine as “known to be a human carcinogen”
- Disagrees with statements in Freeman report[1] regarding past and current occupational exposure
  - Standards pertaining to ventilation and lab coats and gloves protect workers against exposures
  - Use of *ortho*-toluidine in dye manufacturing has been largely banned
- Substance profile should clarify that the Occupational Safety and Health Administration’s permissible exposure limit of 5 ppm and the American Conference of Governmental Industrial Hygienists’ threshold limit value time-weighted-average of 2 ppm are “based on toxic effects other than cancer”

[1]*Freeman HS. (2012). Use of o-Toluidine in the Manufacture of Dyes and on the Potential for Exposure to Other Chemicals in the Processes Involving o-Toluidine.* (technical advisor report, ref. 92)

Scientific Issues in Written Public Comments

Draft RoC Monograph on Pentachlorophenol and By-Products of Its Synthesis

National Institute of Environmental Health Sciences

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Pentachlorophenol and By-Products of Its Synthesis: Public Comments

- Written public comments: 2 submissions
  - Herbert Estreicher, Ph.D., J.D. on behalf of the Pentachlorophenol Task Force
  - Robert Golden, Ph.D. and Elizabeth Delzell, Sc.D. on behalf of the Pentachlorophenol Task Force

Public Comments: Scientific Issues

- Disagree that pentachlorophenol and by-products of its synthesis is "known to be a human carcinogen"
  - Neither pentachlorophenol nor by-products of its synthesis are carcinogenic
- Disagree with conclusion of "significant exposure" in monograph
- Questions role of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in reaching listing decision
  - TCDD should not be considered a by-product of pentachlorophenol synthesis in the United States
  - TCDD should be treated as a confounder in the human studies
  - Already recognized as a known carcinogen by the International Agency for Research on Cancer
- Biological plausibility is not adequately addressed in the evaluation

Scientific Issues - Exposure

- Disagree with conclusion of “significant exposure” in monograph:

  “US exposure to pentachlorophenol and by-products of its synthesis is significant based on available biomonitoring data, its widespread past use as a pesticide, and current use in treated-wood products.”

- Current uses do not lead to significant exposures
  - Biomonitoring data: Detection of pentachlorophenol in urine does not definitively indicate exposure to only pentachlorophenol because pentachlorophenol is a metabolite of other chemicals
  - Presence of higher chlorinated dioxin congeners in populations near wood treatment facilities may be primarily a result of their continued presence in the soil from past use rather from a current active source
  - Exposure to pentachlorophenol has decreased due to restricted use and regulations requiring engineering controls and personal protective equipment for workers

Scientific Issue – Epidemiology Studies

- Disagree with conclusion of “sufficient evidence for the carcinogenicity from studies in humans” based on “consistent association between occupational exposure to pentachlorophenol and non-Hodgkin lymphoma…”
  - The epidemiology evidence for carcinogenicity is “inconclusive and limited”
    - Absence of strong associations in most of the studies and statistical imprecision in several key studies
    - Lack of consistency among the key studies
    - Inadequate evidence of a monotonic exposure-response trend
      - The exposure-response in Demers study (2006) could be due to exposure misclassification or residual confounding
      - No exposure-response found in Collins study (2009)
    - The possibility that the positive associations reported reflect residual confounding
    - The possibility that some of the positive associations reported reflect information bias
- Other studies beyond Demers and Collins add little to the assessment

Scientific Issues – Animal Studies

- Pure pentachlorophenol (>99% purity) is not carcinogenic
  - Stop-exposure study:
    - Malignant mesothelioma in the tunica vaginalis is specific to male F344 rats, which brings into question their relevance for extrapolation to other species, especially humans
    - Nasal tumors in male F344 rats may be due to direct inhalation and high-dose cytotoxicity of the 1000 ppm pentachlorophenol dose
- By-products of pentachlorophenol synthesis are not carcinogenic
  - Dermal exposure to hexachlorodioxin mixture was not carcinogenic in male and female mice
  - Dermal exposure is a relevant route of pentachlorophenol exposure for humans
  - Toxic Equivalence Factor for hexachlorodioxins is higher than for the hepta- and octa- dioxin by-products of pentachlorophenol synthesis
- Pentachlorophenol (~90% purity) is carcinogenic in animal studies, and these studies should not be given weight in the evaluation

Scientific Issues – Other Relevant Data

- Results from in *vivo* genotoxicity studies are overwhelmingly negative; therefore, it is implausible that early mutation plays a role in pentachlorophenol carcinogenicity
- Monograph does not address high-dose pentachlorophenol cytotoxicity-driven mode of action events [e.g., oxidative stress, induced DNA damage, and chronic inflammation] likely involved in animal carcinogenicity