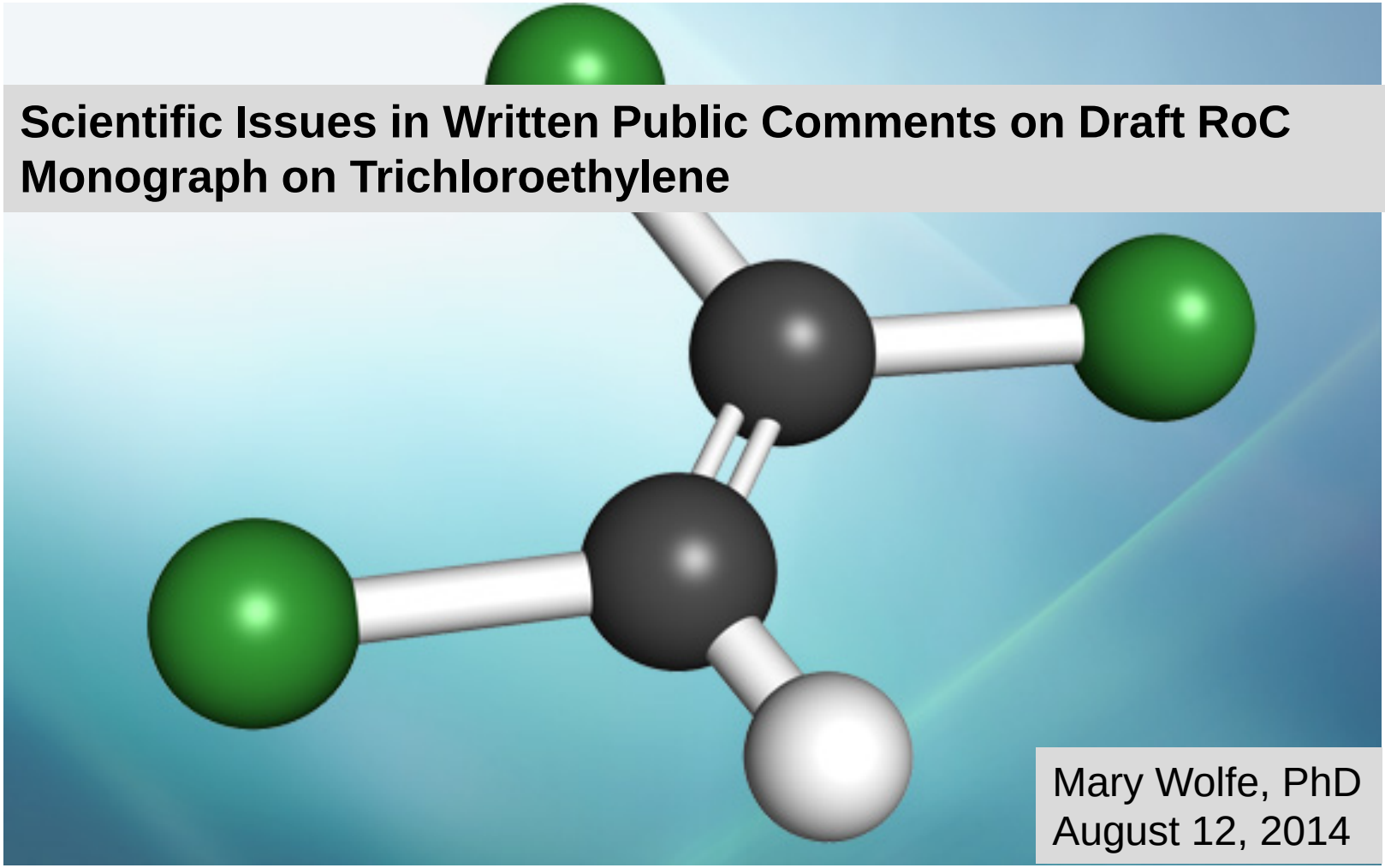
Scientific Issues in Written Public Comments on Draft RoC Monograph on Trichloroethylene



Mary Wolfe, PhD
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Public comments

- 1 Written public comment from Halogenated Solvents Industry Alliance (HSIA)
  - Believes there is a compelling case against changing the RoC listing of trichloroethylene (TCE) from *reasonably anticipated* to *known human carcinogen*

Epidemiological evidence for TCE and kidney cancer is weak and not sufficient

- NTP's assessment of the epidemiological data conflicts with the National Academy of Sciences' Camp Lejeune report
  - Report concluded limited or suggestive evidence of an association of TCE with kidney cancer
  - Increased risks of kidney cancer were found in studies with few subjects and varied quality of exposure data and methodology
- Weight-of-evidence analysis of the epidemiological data does not support the conclusion of "sufficient" evidence of a causal association
  - Limitations of studies include weak associations, potential for confounding, and exposure uncertainty
- Meta-relative risks (mRRs) from the meta-analyses cannot support a known human carcinogen classification
  - Meta-analysis as a tool cannot establish a causal relationship
  - mRRs are between 1.2 and 1.4
    - RRs less than 2 are not sufficient to establish causation

Toxicological data from rodent cancer studies are equivocal and inconsistent

- Evidence that TCE is a renal carcinogen in rodents is problematic
  - Renal tumors incidence is low in all three NTP studies, despite doses that were either at or exceeded the maximum tolerated dose (MTD)
  - Many studies have methodological problems
    - 1988 NTP studies were considered inadequate studies of carcinogenic activity by the authors
    - Oral and inhalation studies by Maltoni are controversial and used non-standard methodologies

Toxicokinetic and mechanistic data do not support the known human carcinogen classification

- Presumed mode of action (MoA)–glutathione conjugation–is based on flawed research
  - Research from 3 laboratories indicates a very low level of TCE metabolism via the glutathione conjugation pathway, which is lower in humans then rodents
  - Kidney toxicity in rats cannot be explained solely by the extent of DCVC production and activation
  - Kidney damage in humans is highly unlikely to occur at current occupational exposure levels and is of no concern for general population
- Genotoxicity is not a likely mechanism for kidney carcinogenicity
  - DCVC is weakly genotoxic *in vivo* and only low levels are produced
  - DCVC did not induce tumors in rats using a protocol expected to show tumor induction by a genotoxic MoA
  - DCVC activation is greater in mouse kidney than rat kidney, but TCE has not induced kidney tumors in mice