United States Environmental Protection Agency

# U.S. EPA's Draft Toxicological Review of Trichloroethylene (TCE)

Presentation for the
Science Advisory Board

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# Importance of Final TCE Assessment to Environmental Protection

- **Widely used as degreaser, chemical intermediate and extractant, component of some consumer products.**
- **Common environmental contaminant**
  - Designated Hazardous Air Pollutant
  - Common groundwater and drinking water contaminant
  - Found at >1500 hazardous waste sites
  - Released to indoor air via vapor intrusion
- **Regulatory standards**
  - MCL in drinking water is 5 ppb
  - No federal air concentration standard (some state standards exist)
- **Important assessment/needed information**
- **Goal: Complete TCE assessment and provide high quality risk information to EPA programs and regions and other stakeholders**

# Some Key Milestones:
## Development of Draft TCE Assessment

- **TCE IRIS Assessment posted, cancer assessment only, March 1987**
- **Removed from IRIS for further review, July 1989**
- **EPA Symposium on New TCE Science, February 2004**
- **Four issue papers submitted to NAS in preparation for science consultation, February 2005:**
  - Issues in Trichloroethylene Pharmacokinetics
  - Interactions of Trichloroethylene, Its Metabolites, and Other Chemical Exposures
  - Role of Peroxisome Proliferator-Activated Receptor Agonism and Cell Signaling in Trichloroethylene Toxicity
  - Issues in Trichloroethylene Cancer Epidemiology
- **NAS Report on Key Scientific Issues, July 2006**
- **Draft assessment provided for public review and comment (90 days) and start of independent external peer review, November 2009**

# Key Features:
## Draft TCE Assessment

- **Comprehensive review of studies of TCE and TCE metabolites**
- **Toxicity review organized by tissue/system**
- **Multiple lines of evidence supporting major conclusions of hazard characterization and dose-response assessment**
  - Human epidemiologic data
  - Animal toxicity data
  - Mechanistic data
  - State-of-the-art quantitative analyses
    - *PBPK modeling*
    - *Meta-analysis of cancer epidemiology*
    - *Benchmark dose modeling*
    - *Uncertainty and variability analyses*

# Key Science Issues

- **Toxicokinetics and PBPK modeling**
  - Flux of TCE GSH Conjugation
    - *Several orders of magnitude less TCE GSH conjugation than oxidation has been postulated based on inferences from urinary measures*
    - *Re-examination of in vitro and in vivo data suggests substantially greater TCE GSH conjugation, at least in humans, though still less than oxidation*
    - *Data incorporated into PBPK modeling to provide quantitative estimates*
- **Draft Hazard Identification: Non-cancer**
  - Fetal cardiac defects
    - *The epidemiological studies, while individually limited, are as a whole suggestive of elevated risks*
    - *Significant effects in rats at low drinking water exposures in Dawson/Johnson studies, though these studies have a number of limitations*
    - *Other studies in rats did not report cardiac defects, though could be due to experimental design differences (e.g., exposure routes, exposure periods, and/or dissection methods)*
    - *Biological plausibility supported by other data*

# Key Science Issues (continued)

- **Draft Hazard Identification: Cancer**
  - Draft Carcinogenicity Characterization as *Carcinogenic to humans*
    - *Primary evidence: Convincing epidemiologic data on TCE and kidney cancer (per Cancer Guidelines [U.S. EPA, 2005])*
    - *Supporting evidence:*
      - Epidemiologic data on lymphomas and liver cancer.
      - Numerous positive rodent bioassays (e.g., rat kidney, mouse liver, mouse lymphoma), toxicokinetic data, and mechanistic data.
  - Meta-analysis of cancer epidemiology
    - *NRC (2006) report recommended a new meta-analysis of cancer epidemiology as <u>part</u> of EPA's overall evaluation of TCE carcinogenicity.*
    - *EPA conducted meta-analysis for kidney cancer, lymphomas, and liver cancer in accordance with NRC recommendations*
      - Focused on higher-quality studies to reduce selection bias and measurement error.
      - Supports association for kidney cancer, robust under different assumptions, with no evidence of heterogeneity or potential publication bias.
      - Supports association for lymphomas, robust under different assumptions, with some evidence of heterogeneity ($p$=0.10) and potential publication bias.
      - More limited evidence for liver cancer, due to fewer studies and fewer observed events.

# Key Science Issues (continued)

- **Mode of Action (MOA)**
  - Mutagenic MOA operative for kidney tumors
    - *Genotoxicity: Predominance of positive genotoxicity and mutagenicity for GSH conjugation metabolites*
    - *Toxicokinetics: Delivery to and in situ formation in the kidney*
    - *VHL mutations: inadequate evidence to either confirm or refute role in TCE-induced kidney carcinogenesis*
    - *MOA related to cytotoxicity/proliferation cannot be ruled out, but insufficient evidence for causal role at this time.*
  - Inadequate evidence for PPARα as the predominant MOA for liver tumors

# Key Science Issues (continued)

- **Dose-Response Assessment**
  - Critical endpoints/studies for non-cancer RfD and RfC
    - *Kidney: becomes a critical endpoint due to inferences as to flux of GSH conjugation*
    - *Fetal cardiac defects: only Johnson study is suitable for dose-response analysis*
    - *Immunotoxicity/developmental immunotoxicity: based on a number of recent studies*
    - *Single RfD and RfC based on multiple studies/endpoints.*
  - Cancer dose-response based on epidemiologic data
    - *Use of Charbotel et al. (2006) study for estimating kidney cancer risk*
    - *Adjustments for lymphoma and liver cancer based on relative risks from meta-analysis and from Raaschou-Nielsen et al. (2003).*
    - *Support from similar (within an order of magnitude) estimates based on rodent bioassays.*
    - *Age-dependant adjustment factor applied to kidney cancer risk*
  - Use of PBPK model for addressing interspecies extrapolation, human variability (for non-cancer), and route-to-route extrapolation

# Requests to the Panel

- **Narrow set of key, clear, specific recommendations that will help EPA complete this important assessment expeditiously**
- **Specific requests:**
  - Concise, brief report
  - Focus on key issues
  - Highlight the specific improvements that could be made to this document so that it may be completed
  - Timely delivery of panel's final report
- **EPA may revisit TCE toxicity in the future:**
  - What research will, a decade from now, support a better assessment?
  - What research will reduce reliance on defaults and reduce qualitative and quantitative uncertainty?
- **Thank you for your time**