

Trichloroethylene Health Risk Assessment:

An update

Jim Cogliano, Cheryl Siegel Scott, Jane Caldwell

United States Environmental Protection Agency*
Office of Research and Development
National Center for Environmental Assessment

**The views expressed in this presentation are those of the authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.*

This assessment . . .

- Updates the cancer risk assessment of TCE.
- Develops an RfD and RfC for effects other than cancer.
- Demonstrates new directions in risk assessment:
 - New cancer guidelines.
 - Mode of action.
 - Toxicokinetic and mechanism-based modeling.
 - Uncertainty analysis--qualitative and quantitative.
 - Sensitive populations.
 - Differential risks to children.
 - Cumulative risks involving TCE.

This assessment does not . . .

- Change EPA's standards under its air, water, or waste programs.
- After the final assessment is released, EPA's regulatory programs may consider the findings of the new assessment and decide whether changes to their standards are warranted. Note that EPA's standards generally consider many other factors along with health risks.
- It would be premature to speculate at this time about the likelihood or timing of any potential changes to standards.

Recent developments

- External review draft released in September 2001.
- Public comment period (120 days) ended January 2002.
- Peer reviewed by EPA's Science Advisory Board in June 2002.
- Science Advisory Board's advice letter approved in October 2002.

Hazard conclusions

- TCE has multiple effects:
 - Several forms of cancer.
 - Also neurotoxicity, immunotoxicity, developmental toxicity, liver toxicity, kidney toxicity, and endocrine effects.
- TCE acts through multiple metabolites and metabolic pathways:
 - CYP450 metabolites include TCA, DCA.
 - GST metabolites include DCVC.
- TCE acts through multiple modes of action.

Dose-response results

- Based on multiple data sets – human and animal.
- Compares estimates for several adverse health effects.
- Makes extensive use of modeling:
 - Two toxicokinetic models to estimate internal dose.
 - Statistical analyses to calibrate the toxicokinetic models by fitting them to additional data sets.
 - Uncertainty analysis to discriminate between robust and uncertain modeling results.
 - “Benchmark dose” models for effects other than cancer.
 - Empirical models for human and animal cancer data.
 - Mechanism-based model for mouse liver tumors.

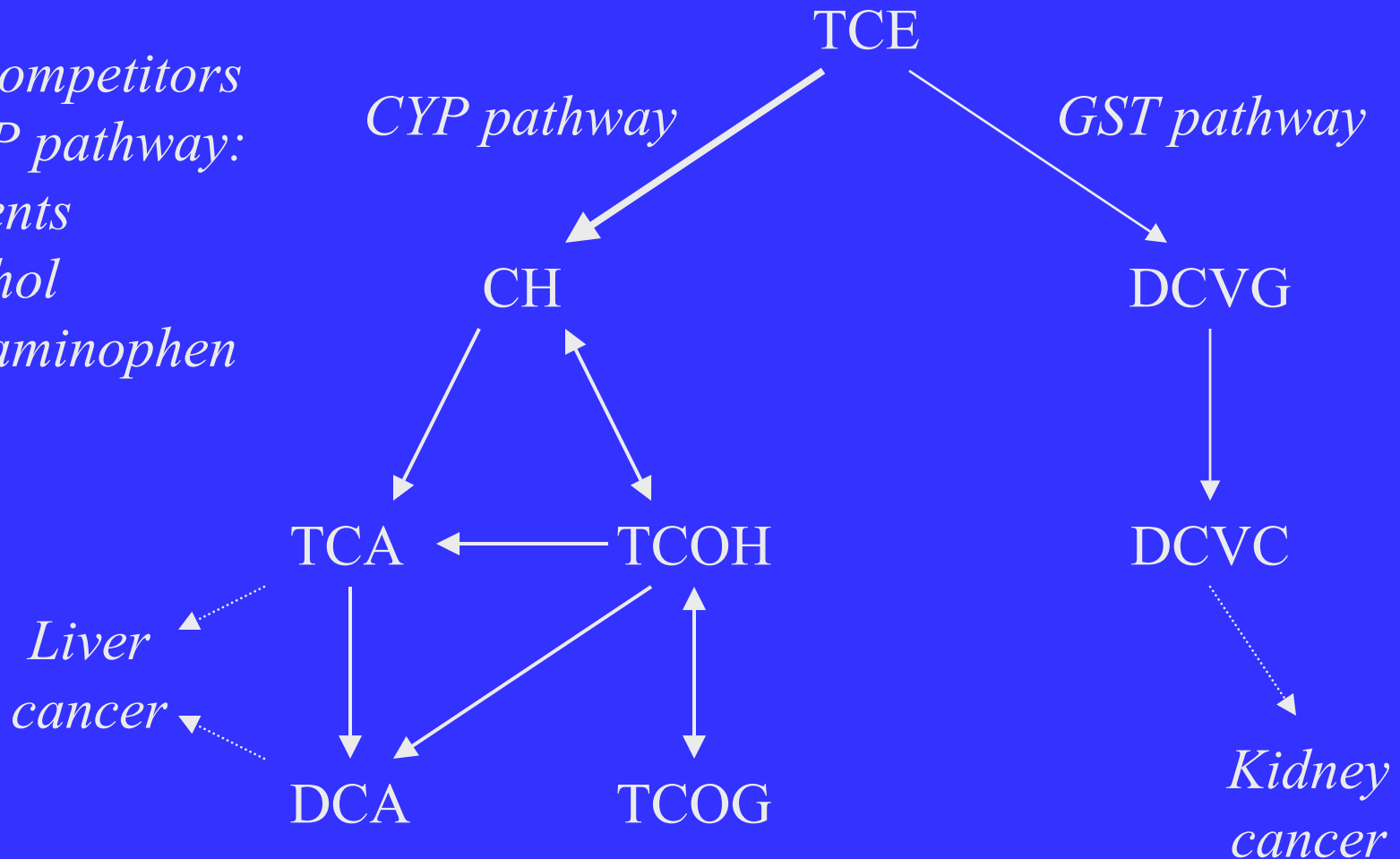
Cumulative risks involving TCE

- Among TCE's toxic metabolites are TCA and DCA.
- A direct source of exposure to TCA and DCA:
 - These are byproducts of drinking water chlorination.
- Indirect sources of exposure to TCA or DCA:
 - These are metabolites of some chlorinated solvents.
- The risk from TCE depends on:
 - Level of exposure to TCE.
 - Sources of direct exposure to TCE's metabolites.
 - Other compounds that produce these metabolites.
 - And more . . .

Cumulative exposures can alter TCE's metabolism

Some competitors for CYP pathway:

- Solvents*
- Alcohol*
- Acetaminophen*



Susceptible populations identified for TCE

- GST isozymes M1 and T1 confer susceptibility to kidney cancer.
- Diabetes: because TCE can disturb carbohydrate metabolism, and because diabetes causes induction of CYP2E1.
- Alcohol consumption: because of shared enzymatic pathways with TCE.
- High background exposure to TCE or its metabolites:
 - Solvent workers.
 - High levels of byproducts of drinking water chlorination.

Differential risks to children from TCE

- Differences in exposure:
 - Relative to body weight, children consume more air, water, food, and soil than do adults.
 - Nursing is an exposure pathway unique to children.
- Differences in toxicokinetics:
 - Slower clearance of the metabolite TCOH.
 - Potentially related to less-developed clearance enzymes.
- Differences in toxicodynamics:
 - Potentially greater sensitivity to neurotoxicants.

Draft advice letter from the SAB

- Commended EPA in several areas:
 - Risk to children and other susceptible populations.
 - Cumulative risk.
 - Examination of multiple kinds of evidence.
 - Assessment of health risks associated with TCE's metabolites.
 - Use of biologically based modeling.
 - Explicit recognition and acknowledgment of uncertainties.
 - Consideration of multiple datasets in deriving cancer slope factors.
- Suggested a separate chapter to serve as a model for children's risk assessments.
- Discussed several options for addressing cumulative risks.

Future developments

- EPA scientists will address the SAB's comments and public comments.
- A new final assessment will be placed on IRIS.