Contaminated Water Supplies at Camp Lejeune, Assessing Potential Health Effects
National Research Council (2009)

BOX 1: Five Categories Used by IOM to Classify Associations

Sufficient Evidence of a Causal Relationship

Evidence from available studies is sufficient to conclude that a causal relationship exists between exposure to a specific agent and a specific health outcome in humans, and the evidence is supported by experimental data. The evidence fulfills the guidelines for sufficient evidence of an association (below) and satisfies several of the guidelines used to assess causality: strength of association, dose-response relationship, consistency of association, biologic plausibility, and temporal relationship.

Sufficient Evidence of an Association

Evidence from available studies is sufficient to conclude that there is a positive association. A consistent positive association has been observed between exposure to a specific agent and a specific health outcome in human studies in which chance and bias, including confounding, could be ruled out with reasonable confidence. For example, several high-quality studies report consistent positive associations, and the studies are sufficiently free of bias, including adequate control for confounding.

BOX 1 (cont.): Five Categories Used by IOM to Classify Associations

Limited/Suggestive Evidence of an Association

Evidence from available studies suggests an association between exposures to a specific agent and a specific health outcome in human studies, but the body of evidence is limited….

Inadequate/Insufficient Evidence to Determine Whether an Association Exists

Evidence from available studies is of insufficient quantity, quality, or consistency to permit a conclusion regarding the existence of an association between exposure to a specific agent and a specific health outcome in humans.

Limited/Suggestive Evidence of No Association

Evidence from well-conducted studies is consistent in not showing a positive association between exposure to a specific agent and a specific health outcome after exposure.

Source: Institute of Medicine. 2003. Gulf War and Health, Vol 2, Insecticides and Solvents. Washington, DC: National Academies Press.

BOX 2: Categorization of Health Outcomes Reviewed in Relation to TCE, PCE or Solvent Mixtures.

Sufficient Evidence of a Causal Relationship

NO OUTCOMES

Sufficient Evidence of an Association

NO OUTCOMES

Limited/Suggestive Evidence of an Association

Kidney cancer
Adult leukemia (solvent mixtures)
Multiple myeloma (solvent mixt.)
Myelodysplasic syndromes (solvent mixt.)
Scleroderma
Neurobehavioral effects (solvent mixt.)

Inadequate/Insufficient Evidence to Determine Whether an Association Exists

See list available via EPA SAB website – multiple cancer and non-cancer end-points.

Limited/Suggestive Evidence of No Association

NO OUTCOMES

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TCE Epidemiology: Comments to Meta-Analysis and Charbotel Study

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Strength of Epidemiologic Evidence is Overstated in EPA Assessment

- **EPA review concludes:**
  - Epidemiologic data robust and consistent
  - In some cases—strongly supportive of TCE carcinogenicity
- **Considering all factors: Epidemiologic data not robust, consistent, or strongly supportive**
  - Heterogeneity of findings
  - Limited exposure assessment
  - Dose-response not consistent across studies
  - Strength of association
  - Confounding

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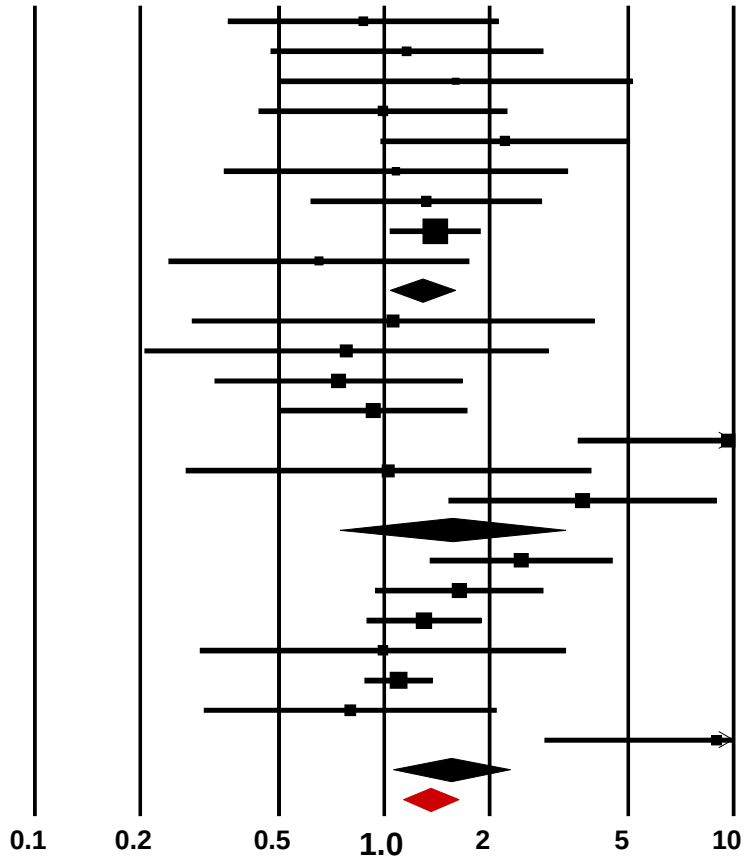
Meta-Analysis of Occupational TCE Exposure and Kidney Cancer: All Studies

Study Classification	Study name
Group I	Anttila 1995
Group I	Axelson 1994
Group I	Blair 1998
Group I	Boice 1999
Group I	Boice 2006
Group I	Hansen 2001
Group I	Morgan 1998
Group I	Raaschou-Nielsen 2003
Group I	Ritz 1999
	SRRE for Group I Cohort Studies* = 1.30 (1.04--1.61)
Group II	Blair 1989
Group II	Chang 2003
Group II	Costa 1989
Group II	Garabrant 1988
Group II	Henschler 1995
Group II	Selden and Ahlborg 1991
Group II	Sinks 1992
	SRRE for Group II Cohort Studies = 1.58 (0.75-3.32)
Case-Control	Bruning 2003
Case-Control	Charbotel 2006
Case-Control	Dosemeci 1999
Case-Control	Greenland 1994
Case-Control	Pesch 2000
Case-Control	Siemiatycki 1991
Case-Control	Vamvakas 1998
	SRRE for Case-control Studies = 1.57 (1.06-2.30)

SRRE for All Studies = 1.42 (1.13-1.77)
P-value for heterogeneity = 0.001



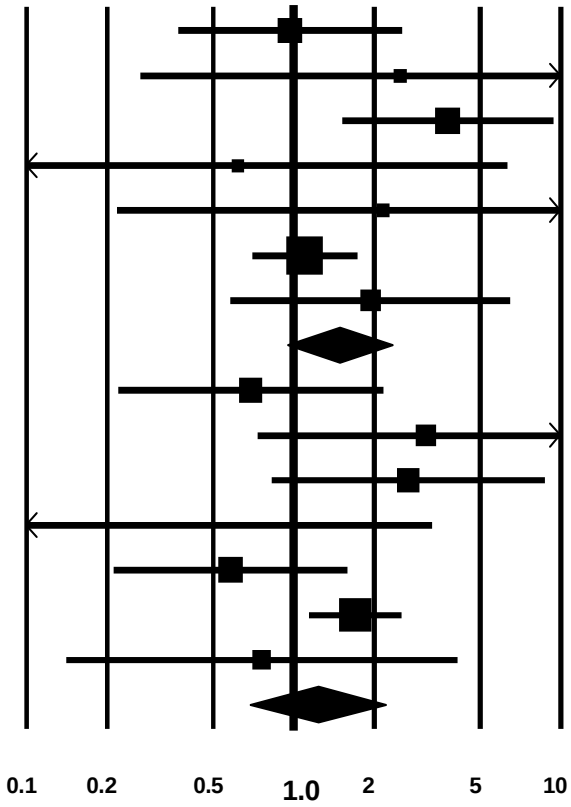
SRRE for All Studies (with cluster investigations removed: Henschler 1995, Vamvakas 1998, Sinks 1992) = 1.24 (1.06-1.45); P-value for heterogeneity = 0.616

* TCE-exposed subcohort data used when available for Group I cohort studies

Figure 3. Meta-Analysis of Occupational TCE Exposure and Kidney Cancer: Duration of Exposure/Employment

Study Name	Exposure Category
Boice 1999	Duration of Exposure: <1 yr
Boice 2006	Duration of Exposure: <4 yrs
Bruning 2003	Duration of Exposure: <10 yrs
Chang 2003	Duration of Employment: <1 yr
Costa 1988	Duration of Employment: <5 yrs
Raaschou-Nielsen 2003	Duration of Employment: <5 yrs
Ritz 1999	Duration of Exposure: 2-10 yrs
SRRE for Shortest Duration of Exposure/Employment = 1.50 (0.96-2.36)	
Boice 1999	Duration of Exposure: 5+ yrs
Boice 2006	Duration of Exposure: 4+ yrs
Bruning 2003	Duration of Exposure: 20+ yrs
Chang 2003	Duration of Employment: >5 yrs
Costa 1988	Duration of Employment: 15+ yrs
Raaschou-Nielsen 2003	Duration of Employment: 5+ yrs
Ritz 1999	Duration of Exposure: >10 yrs
SRRE for Longest Duration of Exposure/Employment = 1.24 (0.69-2.23)	

RR and 95% CI



P-Values for heterogeneity:
Shortest Duration = 0.272
Longest Duration = 0.085

Note:
Data for Ritz included kidney and bladder cancer cases; data for Costa included urinary system cases.

Charbotel Study—Significant Limitations for Use in Quantitative Risk Assessment

- **Representativeness**—one study: Is it representative of epidemiologic literature?
- **Semi-quantitative exposure classification**
  - Non-screw industry workers—much less precision, 40% of participants
  - Numerous work locations (750) can expect significant exposure variability
  - Self reported work history
- **Bottom line**
  - Should not use for quantitative risk assessment

Charbotel Study—Other Limitations

- **Improved on exposure assessment procedures for a subset of the study population, however ….**
- **Potential limitations:**
  - **Selection bias**—Cancers among screw cutting industry workers cancers more likely to be identified than other groups?
  - **Semi-quantitative exposure classification**
  - **Recall bias**—Self report of work history
  - **Confounding**—From other workplace exposures
  - **Control selection**—Hospital/clinic based controls
  - **Small numbers**—Relatively small numbers of exposed cases

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- Kelsh MA, Alexander DD, Mink PJ, Mandel JH. *Occupational Trichloroethylene Exposure and Kidney Cancer: A Meta-Analysis*. Epidemiology 2010: 21: 95–102.
- Alexander DD, Kelsh MA, Mink PJ, Mandel JH, Basu R, Weingart W. *A meta-analysis of occupational trichloroethylene exposure and liver cancer.* Int Arch Occup Environ Health 2007; 81(2):127–143.
- Mandel JH, Kelsh MA, Mink PJ, Alexander D, Kalmes RM, Weingart M, Yost L Goodman M. *Occupational trichloroethylene exposure and non-Hodgkins lymphoma: A meta-analysis and review.* Occup Environ Med 2006; 63(9):597–607.
- Alexander DD, Mink PJ, Mandel JH, Kelsh MA. *A meta-analysis of occupational trichloroethylene exposure and multiple myeloma or leukemia*. Occup Med 2006; 56(7):485–93.
- Mandel J and Kelsh MA. *A review of the epidemiology of trichloroethylene and kidney cancer.* Hum Ecol Risk Assessment 2001; 7(4):727–735.

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Experimental Animal Tumors from TCE

- EPA describes 4 primary tissues for cancer, only 1 or perhaps 2 of them, liver and lung tumors in mice, is biologically significant.
- EPA's text appears to overly discount the many negative data epicho& highlights marginal findings. Text is not dispassionate.
- For rat kidney tumors, of 74 doses, 4 expected as statistically significant by chance alone---1 or 2 found; 6 were judged to be biologically significant; 2 expected and only 1 judged at high doses.
- Liver tumors are biologically significant in mice of both sexes.
- TCE was negative for immune tumors; this should be unequivocally stated.
- Lung tumors in mice may be related to TCE; EPA needs to ferret out tumors due to epichlorohydin contamination before judging.

- **Conclusion: "suggestive evidence of carcinogenicity"**

Dose Response Assessment

EPA (2005) cancer guidelines (page 3-22) states that

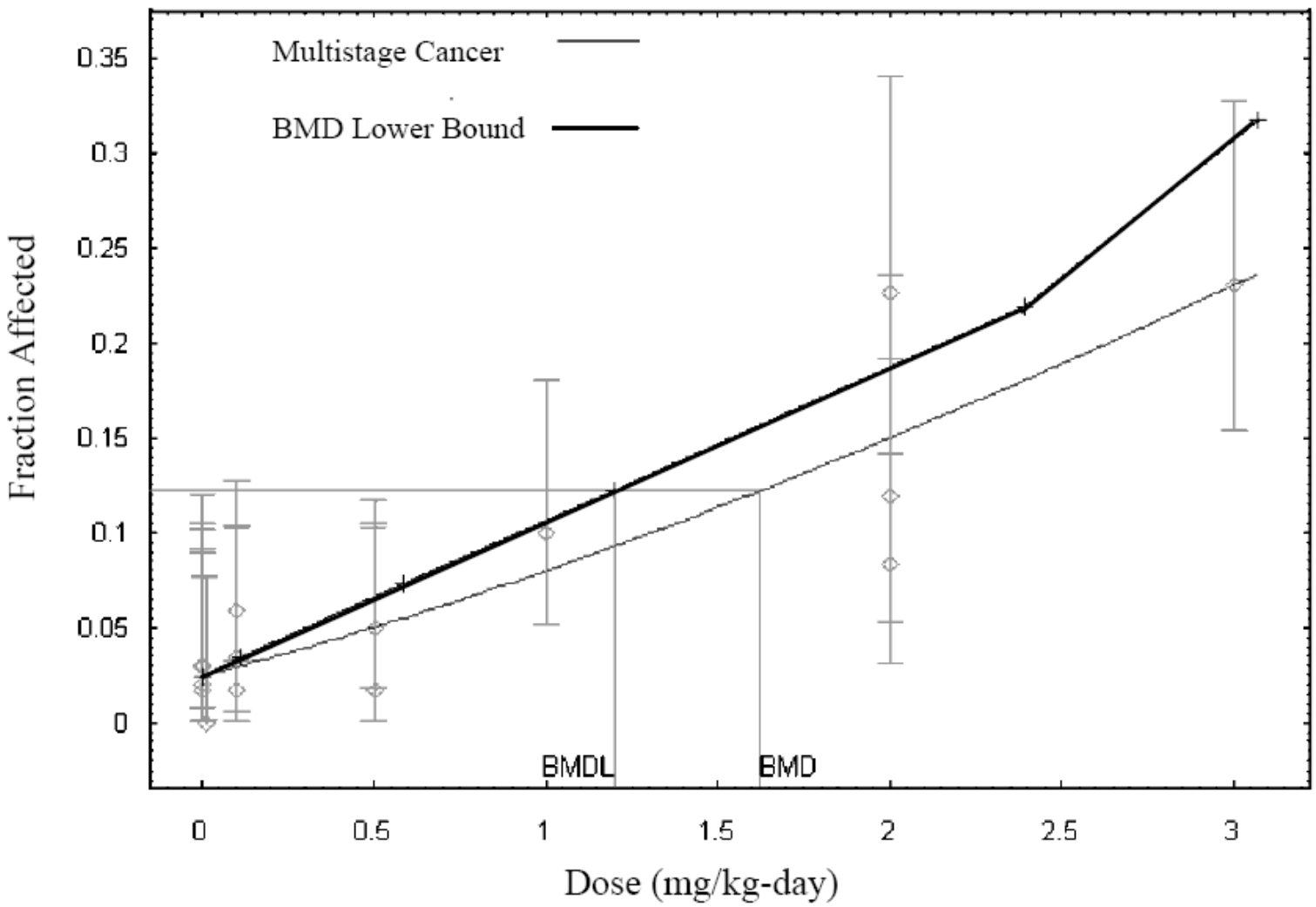
> "If there are multiple modes of action at a single tumor site, one linear and another nonlinear, then both approaches are used to decouple and consider the respective contributions of each mode of action in different dose ranges. For example, an agent can act predominantly through cytotoxicity at high doses and through mutagenicity at lower doses where cytotoxicity does not occur."

Kidney tumors are found sporadically and may have as their origin a genotoxicity endpoint, caused either by a metabolite of TCE or an endogenous mechanism.

A progressive, non-cancer kidney toxicity proceeds sporadic tumors in both dose and time at mid to higher doses in all, or perhaps nearly all, studies and after acute, subchronic and chronic exposures.

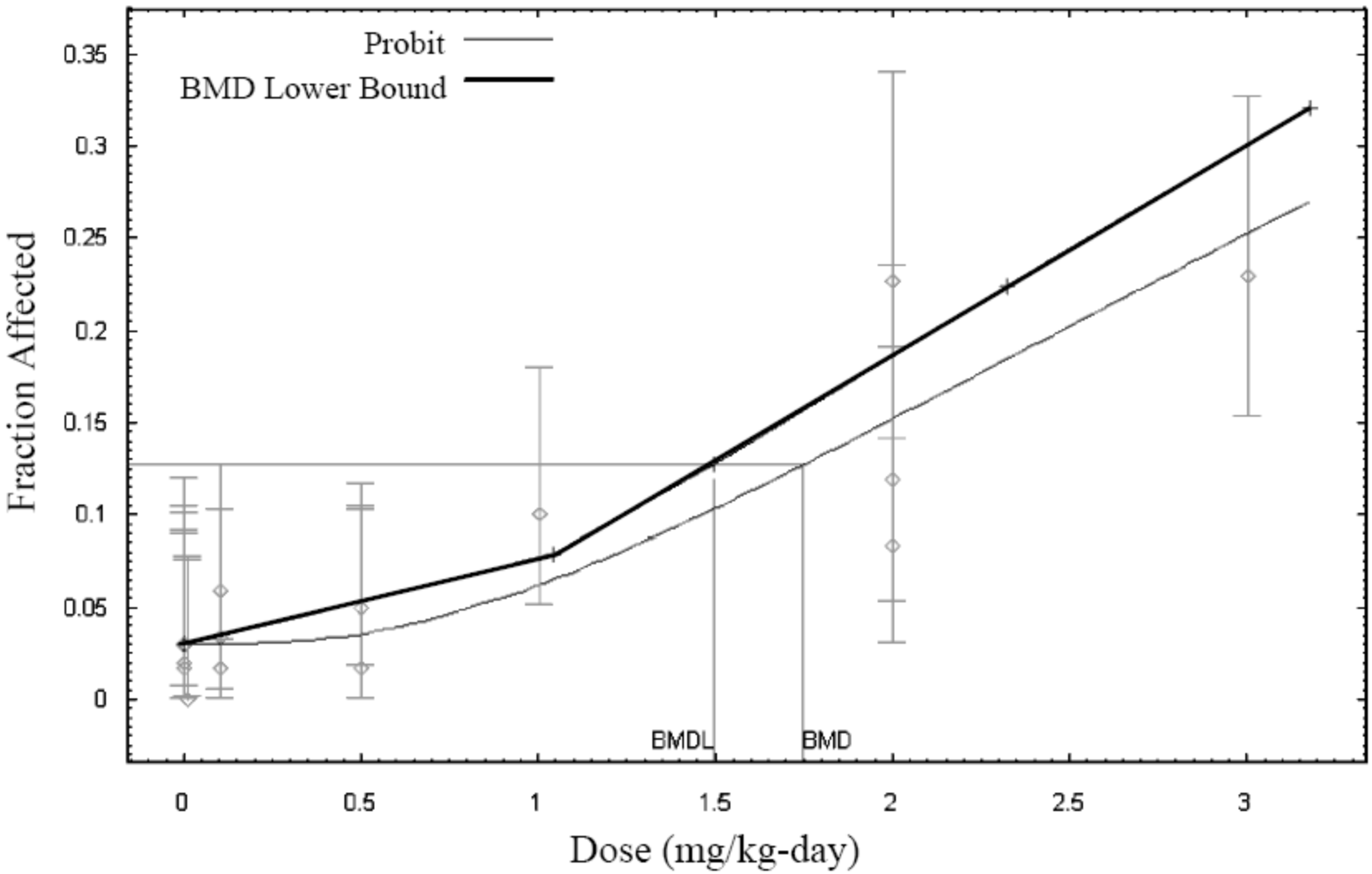
Conclusion: EPA could approach the dose response assessment as a dual mode of action.

Multistage model of acrylamide induced pooled-all thyroid tumor data, showing little change in slope between the low & high doses.

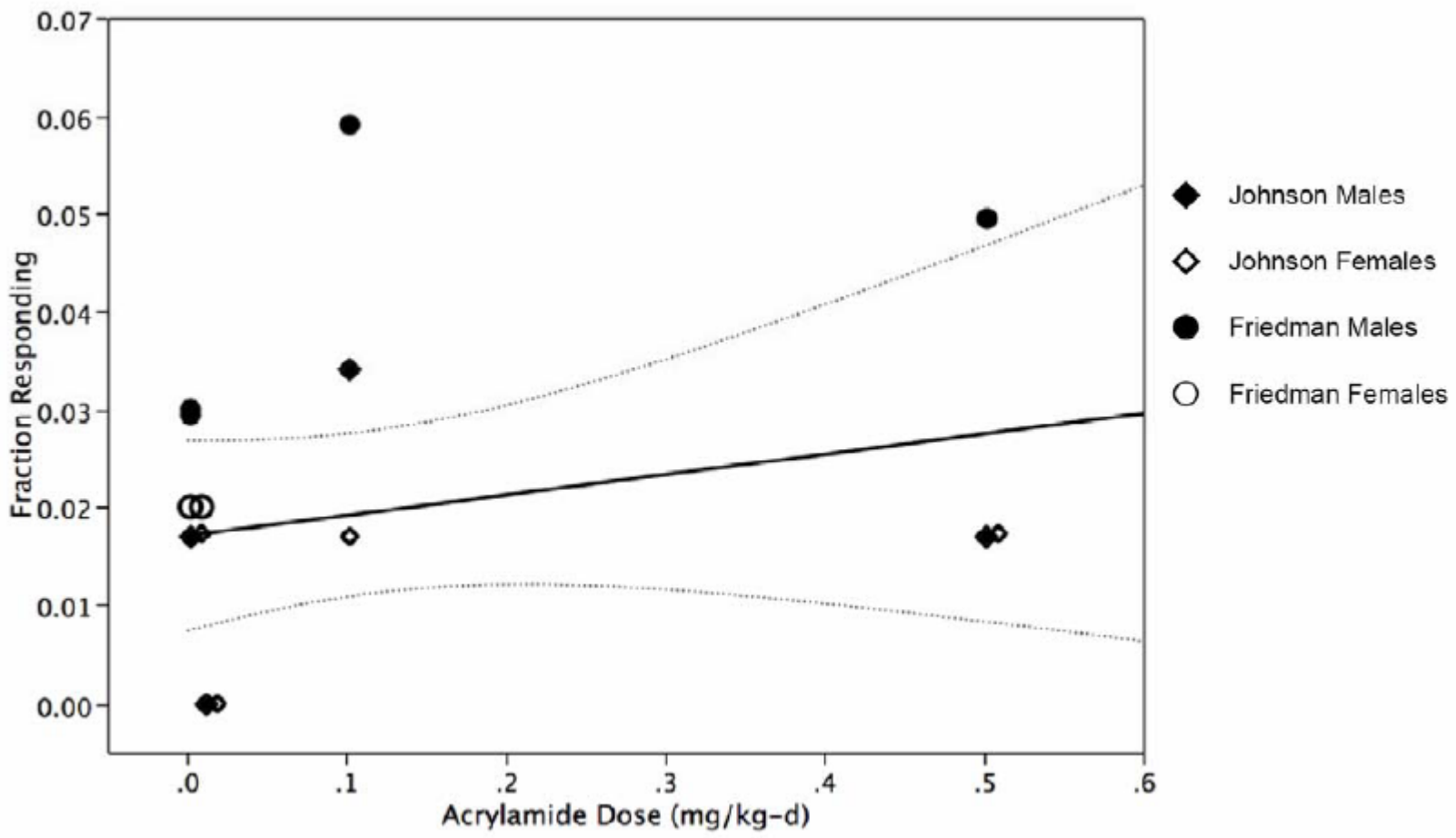


Dourson et al., 2008

Probit model of acrylamide induced pooled-all thyroid tumor data, showing little change in slope between the low & high doses.



Weighted linear regression on low-dose, pooled data with 95% confidence curves for the model. Data jittered to show all 14 data points.



- No sensitivity analysis was presented—should be conducted
  - Provide context for parameter uncertainty/variability
  - Identify key parameters for internal points of departure (iPODs)
- Uncertainties in GSH pathway parameters
  - 2.5%ile and 97.5%ile values of 0.11 and 3,700,000 mg/L for the Km for hepatic TCE GSH conjugation for mice
  - ~1000-fold difference in posterior median estimates of Km for hepatic GSH conjugation in humans vs. rats or mice, contrary to the understanding that similar enzymes are involved in TCE conjugation across species
  - Kim et al. (2009) posteriors (new, best-fit parameters) resulted in a substantially higher fraction of ingested TCE being predicted to be metabolized by the GSH pathway in mice (three-fold higher)
- Concerns about the human model at low concentrations
  - Fits to Chiu et al. (2007) data (lowest exposure concentration evaluated) had greatest residual error
  - Individuals in the Chiu et al. (2007) study were among the most likely to have individual parameter distributions that notably differ from the general population distribution.

TCE and Cardiac Defects

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Take Home Message

- The data on which EPA's assessment of TCE using heart defects as a major endpoint for setting the RfD and RfC are weak, incomplete and flawed and do not account for more robust data that show no increase in heart defects

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The human data are based on studies with inadequate exposure information

- Impossible to determine whether exposure occurred and, if so, to what levels of TCE
- Deficiencies in the human data include
  - Implausible background rates of cardiac malformations (Bove et al, 1995)
  - Differences in the outcome of various studies (Goldberg et al, 1990, versus the Baltimore Washington Infant Study – Wilson et al, 1998)

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All animal data reporting heart defects with TCE come from one laboratory - 1

- Data from that lab were accumulated over ten years (Johnson et al 2003; Dawson et al 1993)
- Deficiencies in study design and reporting make the interpretation of data tentative at best
- Major effect was increased incidence of atrial septal defects (or the foramen ovale, which closes around the time of birth)
- May be related to examination procedure or possible delays in development, rather than actual heart defects.

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All animal data reporting heart defects with TCE come from one laboratory - 2

- Two robust GLP studies found no effect on heart development (Fisher et al. 2001; Carney et al. 2006)
- Fisher et al (2001) included Dr. Paula Johnson as blinded evaluator, yet found no increase in cardiac defects
- Differences among the studies included source of animals, route of exposure and treatment days
- Preparation of heart dissections differed
  - Dawson et al (1993) and Johnson et al (2003) removed hearts first, then flushed with fixative
  - Fisher et al (2001) flushed hearts in situ with staining solution (1:3 hematoxylin-saline solution), perhaps a more physiologically normal situation, then removed hearts and immersion-fixed

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EPA's mechanistic argument is weak

- Results of human studies are insubstantial
- The animal data used by EPA are flawed
  - Better data were ignored
- In vitro/in ovo data are important parts of EPA's argument
  - Questionable relevance to environmental exposures
  - Absence of maternal influence

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Weight of evidence is ignored

- Proposed RfD relies only on positive studies
- Results of well conducted, robust GLP- and guideline compliant studies that found no impact on the heart are overlooked
- This is a “strength of evidence” approach rather than the more appropriate “weight of evidence” approach

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References

- Watson, RE, CF Jacobson, A Lavin Williams, WB Howard, and JM DeSesso (2006) Trichloroethylene-Contaminated Drinking Water and Congenital Heart Defects: A Critical Analysis of the Literature, *Reproductive Toxicology*, 21:117-147. (*e*-published 21 September 2005)

- Hardin BD, BJ Kelman, RL Brent (2005) Trichloroethylene and Dichloroethylene: A Critical Review of Teratogenicity, *Birth Defects Res A: Clin Mol Teratol*, 73: 931-955

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Comments from Lorenz Rhomberg

Gradient

on behalf of the Halogenated Solvents Industry Alliance

RfD/C Methods Issues

U.S. ENVIRONMENTAL PROTECTION AGENCY SCIENCE ADVISORY BOARD

Trichloroethylene (TCE) Review Panel

Public Meeting, May 10, 2010

TCE Rhomberg Slides

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Kidney Weight as Critical Endpoint

- Adverse?
- DCVC as internal dose?
  - Lash et al. (2000) suggest other metabolites for noncancer
- Inhalation RfC based largely on *oral* rat studies
- Very large impact of human-rat differences in modeled DCVC production
  - And on estimated inter-human variation in DCVC
  - Yet human DCVC production went from *less* than in rats to *much more* in modeling changes.
  - Sensitivity to this needs discussion – need to explain why and justify this as robust, if possible
  - ***Very important to be right about this!***

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See my written Comment #1 – p.28

Double-Counting Inter-Individual PK Variation

- For noncancer effects, observed (fitted) Rat DR reflects sensitivity variation among individual rats -- This variation has ***PK*** and ***PD*** components
- PoD reflects particularly sensitive rats -- partly for PK reasons (higher internal dose than average rat at that applied dose)
- But PoD extrapolated to Humans based on "standard" average rat and average human PK:
  - in effect, assumes that all variation in Rats is ***PD***, none in ***PK***
- Then allowance for Human variability uses 99th %-ile of PK to lower RfD/C from PoD:
  - in effect, assumes that all variation in Humans is ***PK***, none in ***PD***
- ***Real Question: What is ratio of 99th %-ile Human to 99th %-ile Rat?***
  - this requires modeling inter-individual variation in rats as well as humans, but was not done

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COMMENTS of PAUL DUGARD (Halogenated Solvents Industry Alliance) before EPA SCIENCE ADVISORY BOARD TRICHLOROETHYLENE PANEL May 10, 2010

NUMERICAL BASES FOR REGULATIONS 1.

RfC

EPA Recommends: 1ppb (5µg/m^3). Based on KIDNEY WEIGHT (rat 28-day)

***Problems:* Wrong assumption of GST in man, PBPK uncertainties.**

Supporting studies:

Kidney toxicity (long term). *Problems:* GST in man, PBPK uncertainties

Cardiac defects. *Problems:* Poor study design and conduct. No dose response.

Thymus weight (mouse, 30 week). *Problems:* Not reported in other studies. Adversity of effect?

RfD

EPA Recommends: 0.4µg/kg-day. Based on KIDNEY WEIGHT (rat 28-day)

***Problems:* Wrong assumption of GST in man, PBPK uncertainties.**

Supporting studies:

As above – same objections

Developmental Immunotoxicity (Peden-Adams et al). *Concern:* Unique study with effects at very low dose. Needs confirmation before primary determinant of RfD.

NUMERICAL BASES FOR REGULATIONS 2.

Inhalation Cancer Slope Factor (Unit Risk)

EPA Recommends: **Risk of $2x10^{-2}$ per ppm (or $4x10^{-6}$ per µg/m^3) for 70 yr exposure.**

1 in one million (lifetime) equivalent to continuous exposure of 0.05 ppb or 0.25 µg/m^3

Based on Charbotel et al epidemiology study (kidney cancer). As analyzed in comments by Kelsh and Alexander, this study is unsuitable for setting cancer slope factors. Questionable factor of 4 (increase) for multiple tumor types.

Support: Kidney tumors in rat studies. *Problems:* GST assumption in man, PBPK

Lymphomas (mouse) and testicular tumors (rat) not suitable for setting cancer slope factors in their own right.

Oral Cancer Slope Factor

EPA Recommends: **Risk of $5x10^{-2}$ per mg/kg-day for 70 yr exposure.**

Based on Charbotel et al: Concerns as above.

Support: Kidney tumors in rat studies. *Problems:* GST assumptions in man, PBPK

Testicular tumors (rat): Low concern endpoint.

Mouse liver tumors: Should be non-linear calculation