Trichloroethylene (TCE) Basics

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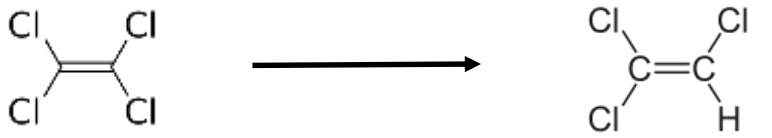
Outline

- Why do we care so much about TCE?
- Where do we find TCE?
  - Historic uses
  - Current uses
- Toxicology
  - Absorption, distribution, metabolism, and elimination (ADME)
  - Carcinogenicity – kidney, non-Hodgkin's lymphoma, liver
    - Camp Lejeune, NC, and cancer clusters
  - Non-carcinogenic effects
    - CNS, kidney, liver, immune system, respiratory tract, reproductive system
    - Developmental
      - Cardiac……source of controversy and short-term exposure maximum limits
      - Immune suppression
- Changes in TCE reference levels over time
  - 20 years in the making, the EPA IRIS final report released 2011 is changing the regulatory action levels for allowable TCE exposure

Why do we care so much about TCE?

- Ubiquitous and environmentally persistent contaminant
  - Soil and groundwater contamination
    - Present at >50% of Superfund sites
    - Present at hundreds of military bases (Camp Lejeune, NC)
- TCE has a high vapor pressure (~ 3 times that of water)
  - Inhalation exposure is common
- TCE has a short in vivo half-life
  - Difficult to measure and track individual exposure
- Difficult to remediate
  - As a dense non-aqueous phase liquid (DNAPL), TCE forms plumes beneath aquifers, yet has significant aqueous solubility (1gm/L at 25°C)
  - TCE plumes migrate and contaminant aquifers over large distances
- Obvious acute exposure effects in adults (CNS symptoms) only occur at very high levels
  - TCE “seems” safe at low levels

Where do we find TCE?



toxic metabolites

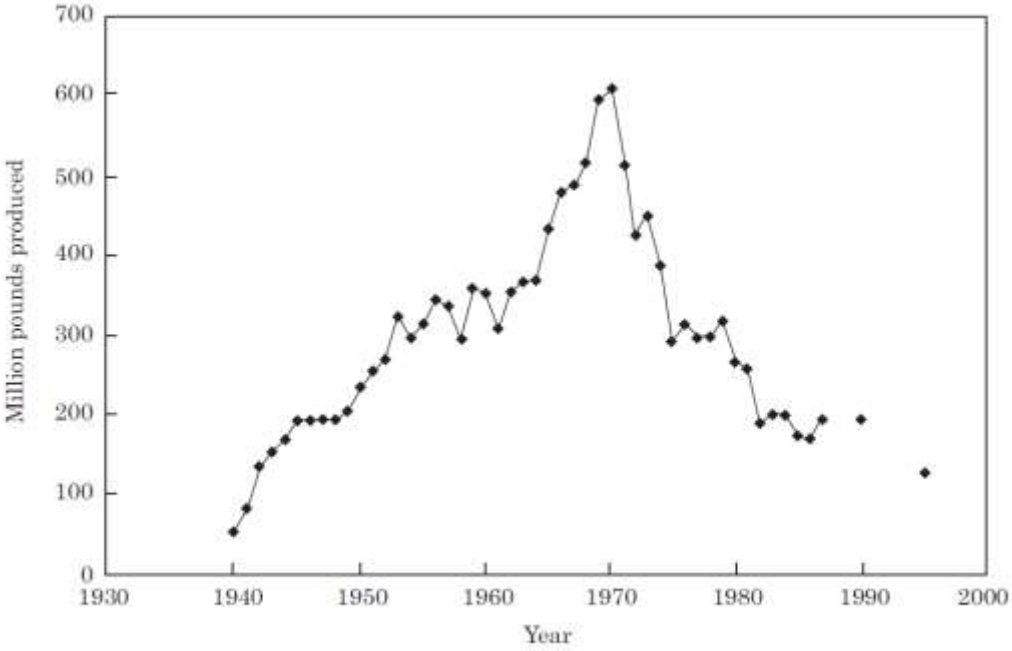


Figure 1. United States production of trichloroethylene (TCE).

Journal of Environmental Forensics (2000) **1**, 83–93

HISTORICAL

Because of its central nervous system depressant activity, TCE was used as an anesthetic in the first half of the 20th century.

Mainly used as a degreasing agent by the military and manufacturers (including the semiconductor industry) in the mid-20th century, with dumping of waste contaminated with TCE into the ground a common practice.

TCE is a major breakdown product of tetrachloroethylene, a commonly used chemical in dry cleaning.

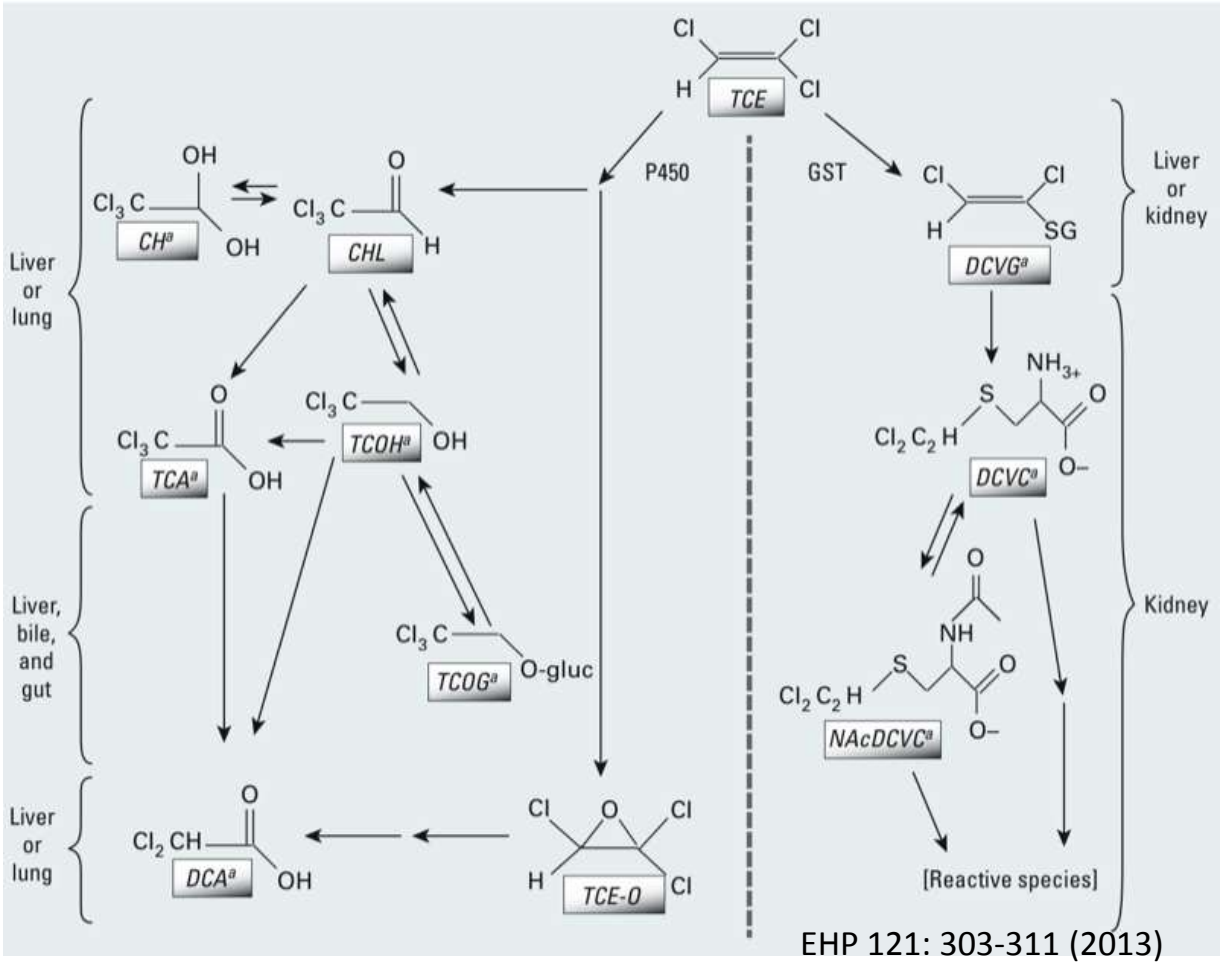
CURRENT

Most TCE in the US is now used in the manufacture of the refrigerant hydrofluorocarbon-134a, and exposure is of little concern in this controlled setting.

Exposures in small degreasing facilities and dry cleaning settings are of significant concern because of the lack of engineering controls.

Exposure also occurs through consumer products (e.g., gun cleaners).

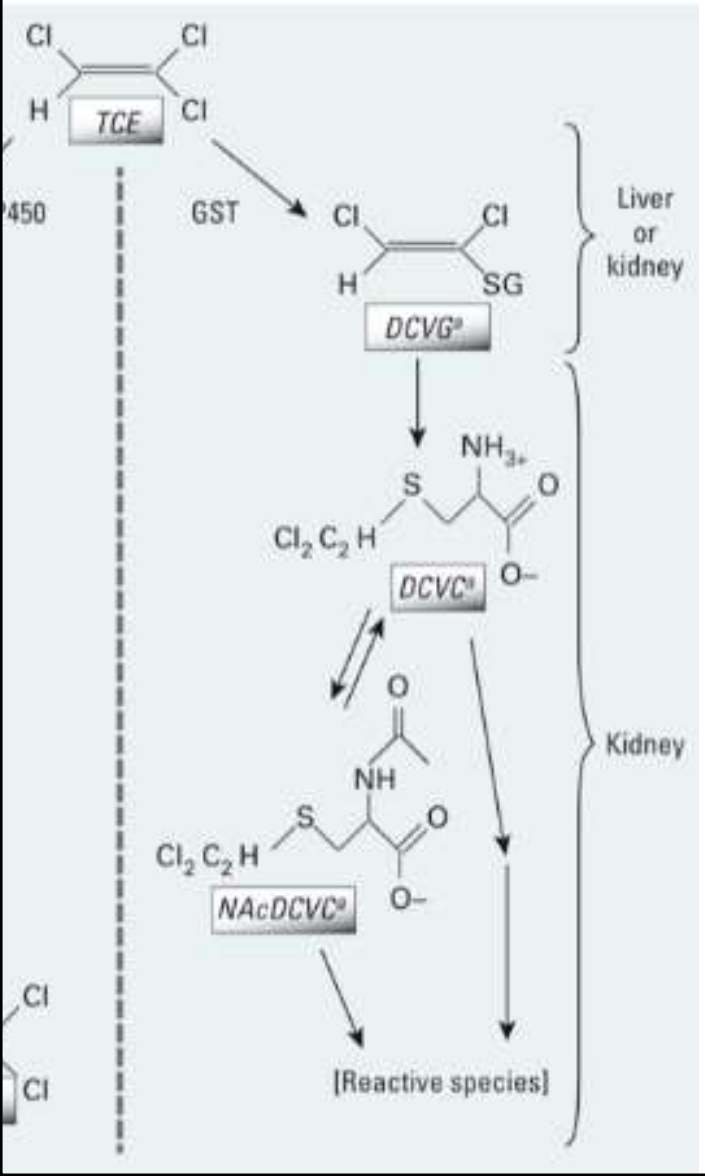
Toxicology – Absorption, distribution, metabolism, and elimination



EHP 121: 303-311 (2013)

- Absorption is rapid and occurs through skin, inhalation (showering, vapor intrusion), and orally (drinking water)
- Distribution is rapid and to all tissues, including CNS
- Metabolism is oxidative (p450) and through glutathione S-transferases
- Elimination occurs into the urine (high kidney exposure to active metabolites) and through the lungs

Toxicology – Metabolism details

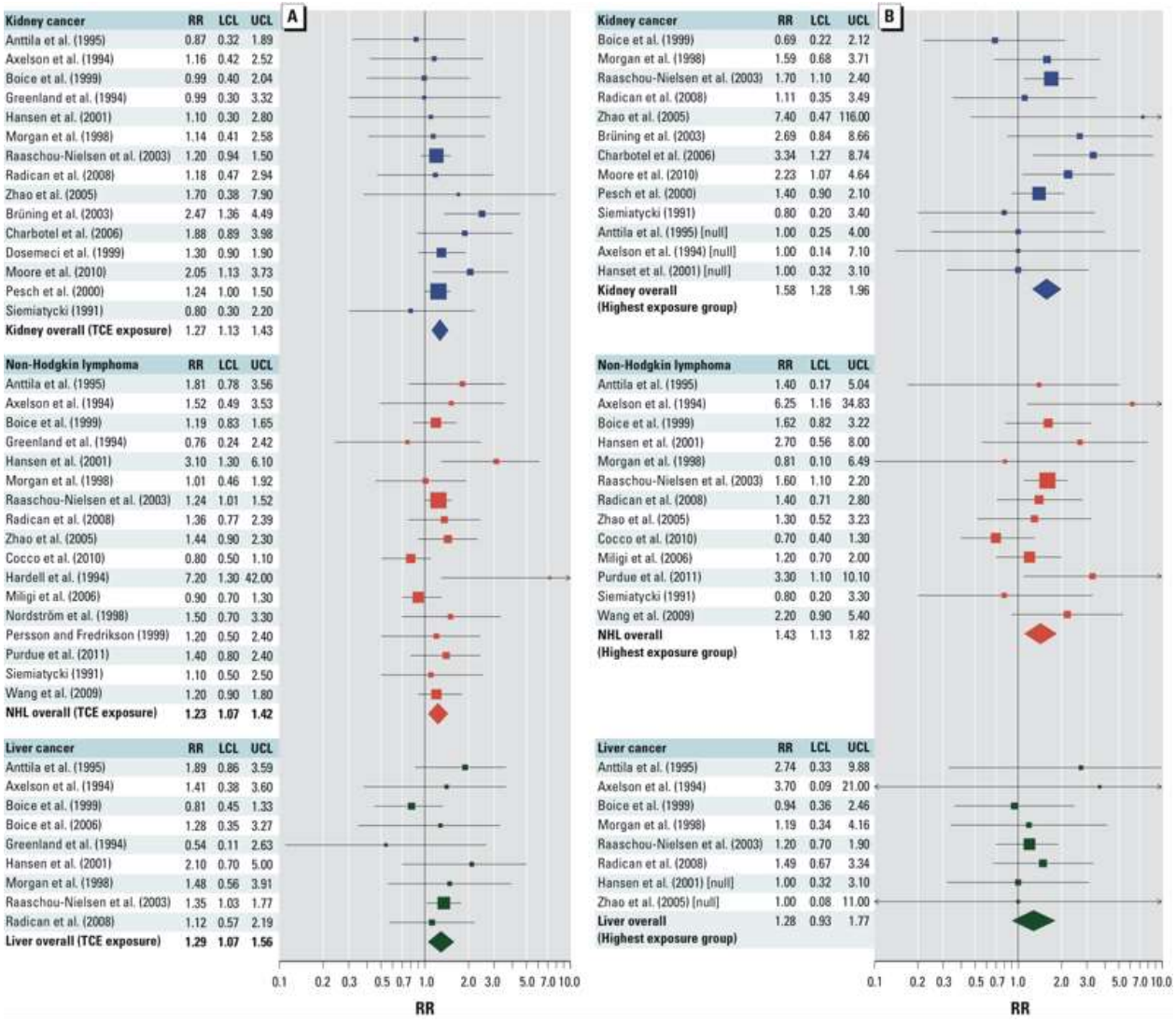


Metabolic capability is associated with risk of kidney cancer following TCE exposure

- People who lack the glutathione S-transferase GSTT1 have decreased reductive glutathione-dependent metabolism of TCE and are protected from developing TCE-induced kidney cancer
- People with certain polymorphisms of renal cysteine conjugate β-lyase (CCBL1) form more highly reactive cysteine S-conjugates such as S-(1,2,dichlorovinyl-L-cytseine) and S-(1,2,2-trichlorovinyl-L-cysteine) and are more likely to develop renal carcinoma

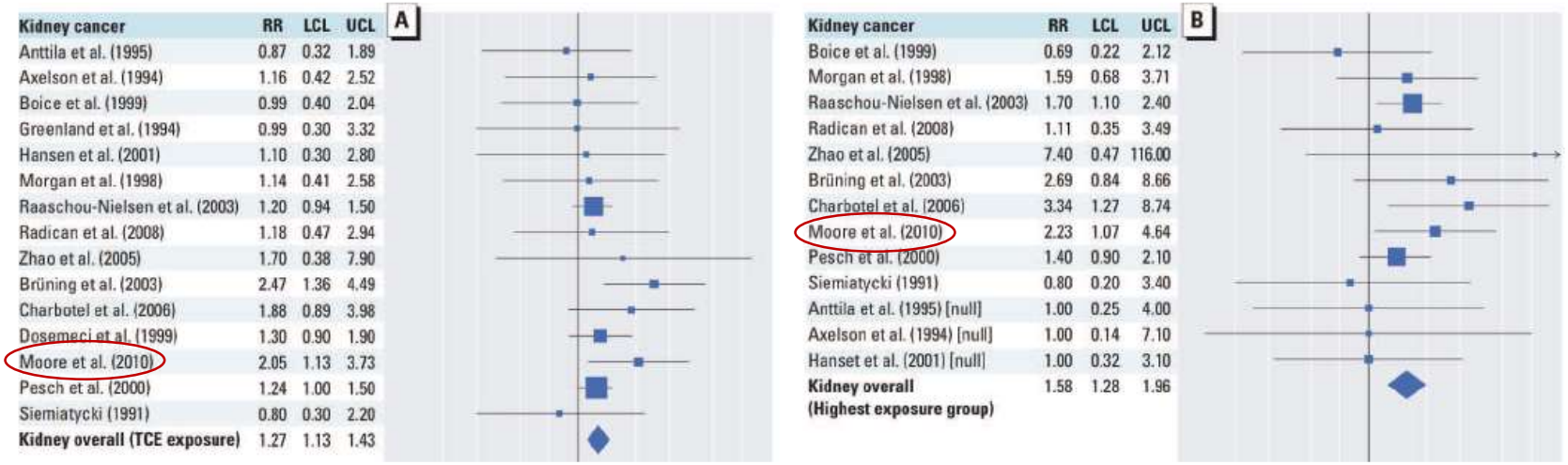
Toxicology – Carcinogenicity

Forest plots of cancer studies using random effects models for overall (i.e., “ever” or “any”) TCE exposure (*A*), and highest TCE exposure groups (*B*). The meta-analysis summary of effects estimates produced an overall assessment of relative risk (RRm; diamonds) with values plotted with 95% CIs (LCL, lower confidence limit; UCL, upper confidence limit) for each cancer type. Symbol sizes reflect relative weight of the studies.



EHP 121: 303-311 (2013)

Toxicology – Carcinogenicity



Kidney cancer	RR	LCL	UCL
Anttila et al. (1995)	0.87	0.32	1.89
Axelson et al. (1994)	1.16	0.42	2.52
Boice et al. (1999)	0.99	0.40	2.04
Greenland et al. (1994)	0.99	0.30	3.32
Hansen et al. (2001)	1.10	0.30	2.80
Morgan et al. (1998)	1.14	0.41	2.58
Raaschou-Nielsen et al. (2003)	1.20	0.94	1.50
Radican et al. (2008)	1.18	0.47	2.94
Zhao et al. (2005)	1.70	0.38	7.90
Brüning et al. (2003)	2.47	1.36	4.49
Charbotel et al. (2006)	1.88	0.89	3.98
Dosemeci et al. (1999)	1.30	0.90	1.90
Moore et al. (2010)	2.05	1.13	3.73
Pesch et al. (2000)	1.24	1.00	1.50
Siemiatycki (1991)	0.80	0.30	2.20
Kidney overall (TCE exposure)	1.27	1.13	1.43

A

Kidney cancer	RR	LCL	UCL
Boice et al. (1999)	0.69	0.22	2.12
Morgan et al. (1998)	1.59	0.68	3.71
Raaschou-Nielsen et al. (2003)	1.70	1.10	2.40
Radican et al. (2008)	1.11	0.35	3.49
Zhao et al. (2005)	7.40	0.47	116.00
Brüning et al. (2003)	2.69	0.84	8.66
Charbotel et al. (2006)	3.34	1.27	8.74
Moore et al. (2010)	2.23	1.07	4.64
Pesch et al. (2000)	1.40	0.90	2.10
Siemiatycki (1991)	0.80	0.20	3.40
Anttila et al. (1995) [null]	1.00	0.25	4.00
Axelson et al. (1994) [null]	1.00	0.14	7.10
Hanset et al. (2001) [null]	1.00	0.32	3.10
Kidney overall (Highest exposure group)	1.58	1.28	1.96

B

ALL THE RELATIVE RISKS ARE SMALL. KIDNEY CANCER IS THE REGULATORY DRIVER FOR CANCER RISK ASSESSMENT, BECAUSE OF THE QUALITY OF THE STUDIES AND HIGH PROBABILITY OF AN EFFECT.

EHP 121: 303-311 (2013)

Toxicology – Carcinogenicity

Table 1. Primary components for a causality determination based on the epidemiologic database for TCE.

Consideration	Summary of weight of evidence
Consistency of observed association	• Strong evidence of consistency for kidney cancer (consistently elevated RRs). Meta-analysis yielded robust, statistically significant summary RR, with no evidence of heterogeneity or potential publication bias. • Moderate evidence of consistency for NHL (consistently elevated RRs); RR estimates more variable compared with kidney cancer. Meta-analysis yielded robust, statistically significant summary RR, with some heterogeneity (not statistically significant) and some evidence for potential publication bias. • Limited evidence of consistency for liver cancer (fewer studies overall, more variable results). Meta-analysis showed no evidence of heterogeneity or potential publication bias, but the statistical significance of the summary estimate depends on the large study by Raaschou-Nielsen et al. (2003).
Strength of observed association	• Strength of association is modest. Other known or suspected risk factors (smoking, body mass index, hypertension, or coexposure to other occupational agents such as cutting or petroleum oils) cannot fully explain the observed elevations in kidney cancer RRs. The alternative explanation of smoking was ruled out by the finding of no increased risk of lung cancer. Indirect examination of some specific risk factors for liver cancer or NHL did not suggest confounding as an alternative explanation.
Specificity	• Limited evidence suggesting that particular von Hippel-Lindau mutations in kidney tumors may be caused by TCE (Brauch et al. 1999, 2004; Brüning et al. 1997; Nickerson et al. 2008; Schraml et al. 1999); additional research addressing this issue is warranted.
Biological gradient (exposure–response relationship)	• Only a few epidemiologic studies examined exposure–response relationships. Studies with well-designed exposure assessments reported a statistically significant trend of increasing risk of kidney cancer (Charbotel et al. 2006; Moore et al. 2010; Zhao et al. 2005) or NHL (Purdue et al. 2011) with increasing TCE exposure. Further support was provided by the meta-analyses; higher summary RR estimates for kidney cancer and NHL were observed for the highest exposure groups than for overall TCE exposure, taking possible reporting bias into account. Liver cancer studies generally had few cases, limiting the ability to assess exposure–response relationships. The meta-analysis for liver cancer did not provide support for a biological gradient (lower summary RR estimate for highest exposure groups than for overall TCE exposure, taking possible reporting bias into account).
Biological plausibility and coherence	• TCE metabolism results in reactive, genotoxic, and/or toxicologically active metabolites at target sites in humans and in rodent test species. • The active GSTT1 enzyme in humans was associated with increased kidney cancer risk, whereas the lack of active enzyme was associated with no increased risk (Moore et al. 2010). • TCE is carcinogenic in rodents; cancer types with increased incidences include kidney, liver, and lymphohematopoietic cancers. • A mutagenic mode of action is considered operative for TCE-induced kidney tumors, based on mutagenicity of GSH-conjugation metabolites and the toxicokinetic availability of these metabolites to the target tissue. • Modes of action are not established for other rodent cancer findings; human relevance is not precluded by any hypothesized modes of action due to inadequate support.

NHL, non-Hodgkin lymphoma. Data from U.S. EPA (2011d).

EHP 121: 303-311 (2013)

Using a weight of evidence approach, TCE is characterized as carcinogenic to humans by all routes of exposure, based on convincing evidence of a causal association between TCE exposure in humans and kidney cancer. Additional support for carcinogenicity is found from evidence of an association between TCE exposure and non-Hodgkin's lymphoma and liver cancer in humans, animal studies, and mechanistic data supporting a mutagenic mode of action for kidney tumors.

Toxicology – Case study

Camp Lajeune, NC

- Base water supply contaminated with TCE, PERC, and benzene between 1950s-1980s
- Contamination detected in early 1980s
- Early failure to act on reports by USMC and Navy
- Activism by soldiers and their families
- Interventions to address contaminated water supplies
- Political response to support exposed personnel

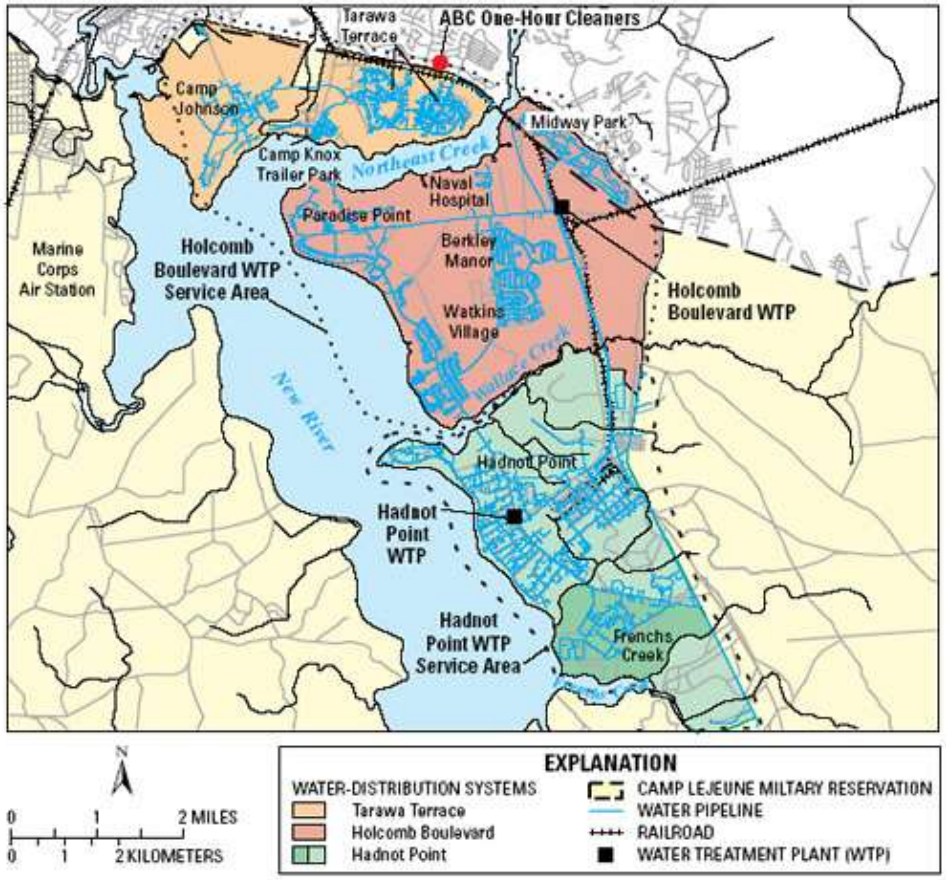
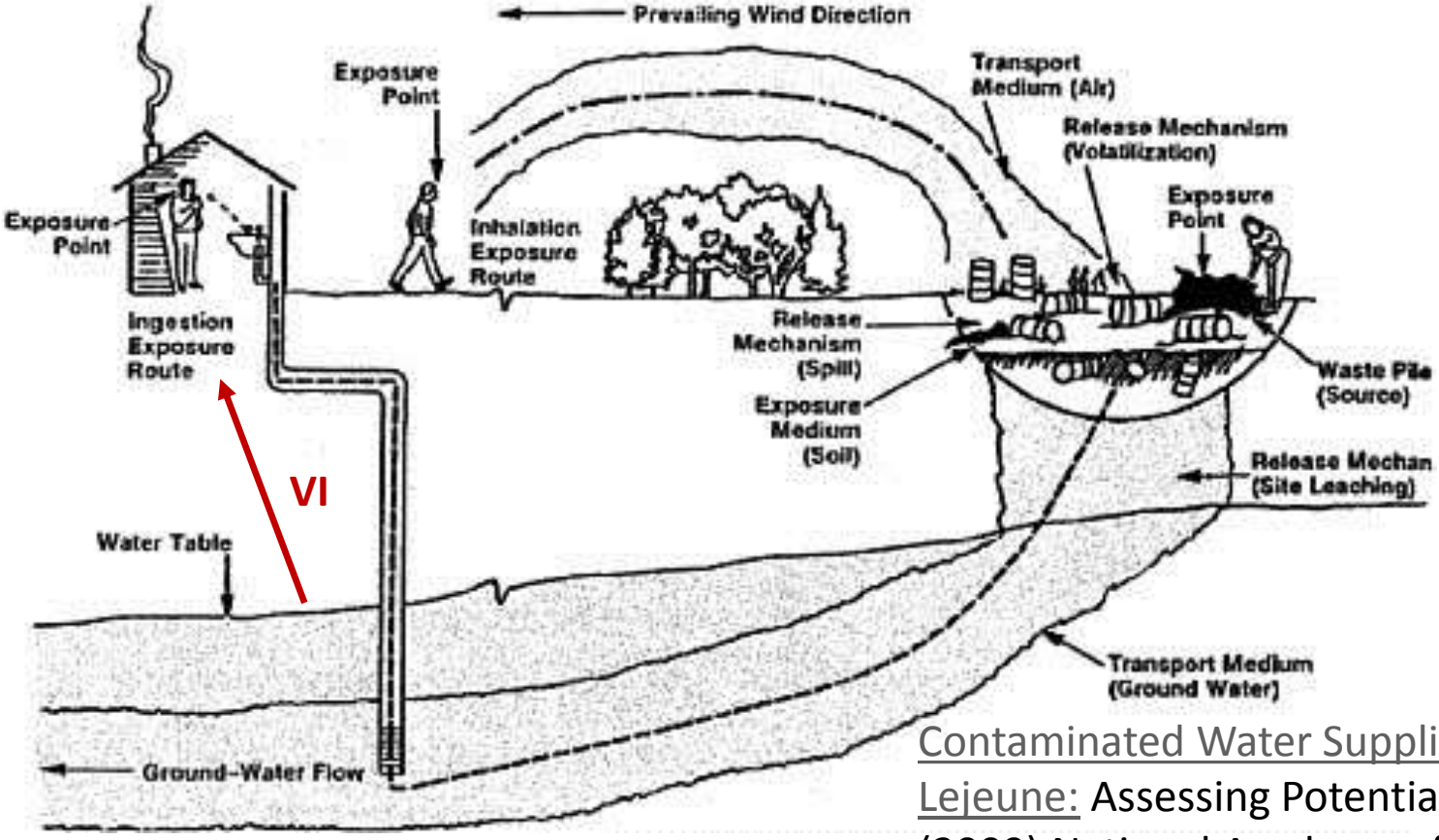


Figure 2. Present-day (2004) water-distribution systems serving Hadnot Point, Holcomb Boulevard, and Tarawa Terrace areas of U.S. Marine Corps Base, Camp Lejeune, North Carolina.

Toxicology – Case study

"Indoor air can become contaminated because of volatilization from contaminated water supplies and use of certain consumer products. Vapor intrusion through walls and floors can be a source of indoor exposure in buildings near contaminated groundwater."



Contaminated Water Supplies at Camp Lejeune: Assessing Potential Health Effects (2009) National Academy of Sciences

Toxicology – Case study

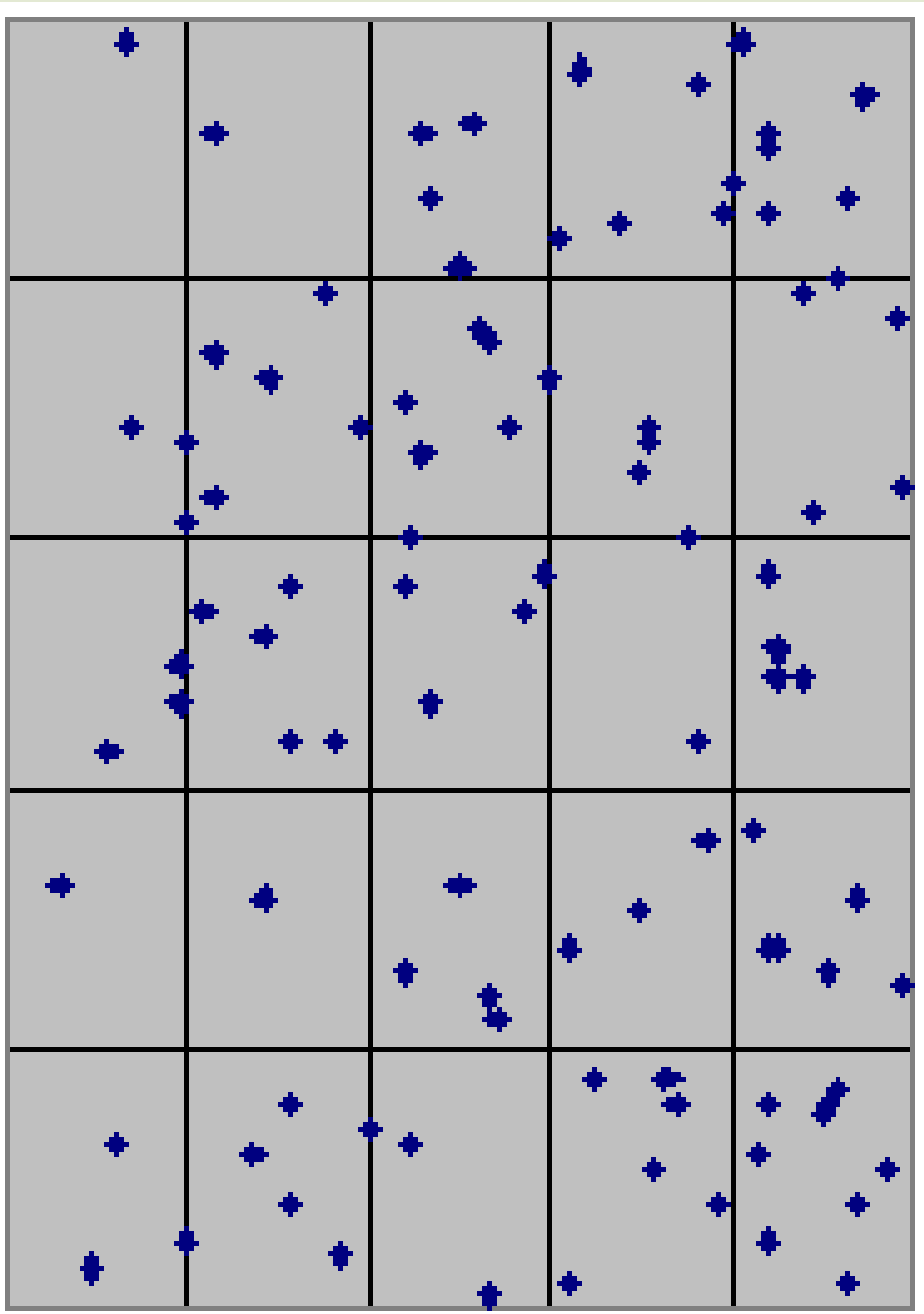
In 2012 the US Congress passed a bill, signed by President Obama, called the Janey Ensminger Act in honor of Jerry Ensminger and his daughter Janey who died of cancer at age 9, authorizing medical care to military and family members who had resided at the base between 1957 and 1987 and developed conditions linked to the water contamination. The measure applies to up to 750,000 people.

Covered ailments

- Esophagial cancer
- Lung cancer
- Breast cancer
- Bladder cancer
- Kidney cancer
- Leukemia
- Multiple myeloma
- Non-Hodgkin's lymphoma
- Myleodysplasic syndromes
- Renal toxicity
- Hepatic steatosis
- Female infertility
- Miscarriage
- Scleroderma
- Neurobehavioral effects

Clusters

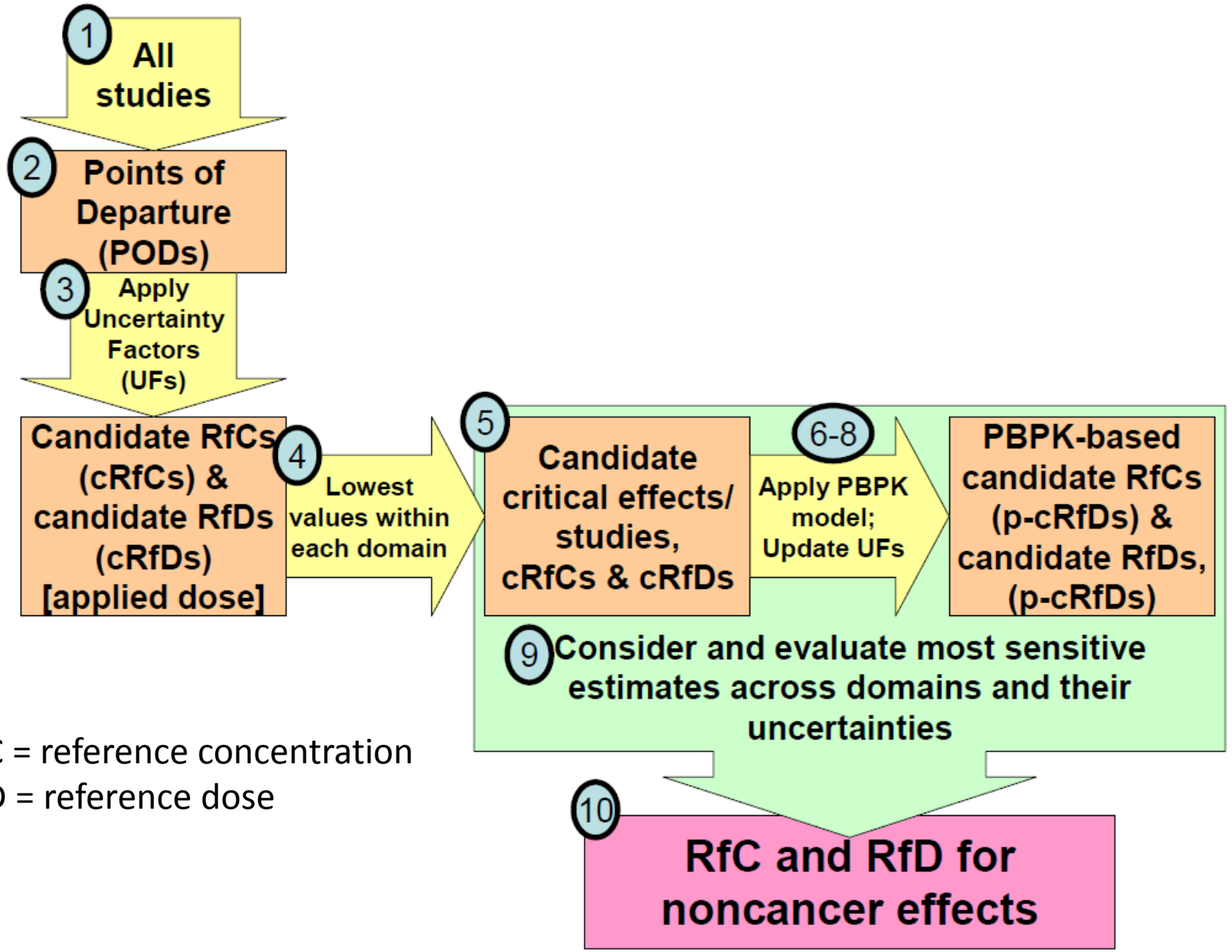
In this diagram, 100 dots are randomly distributed on the grid. By chance, some of the boxes have only one dot, while some have many more. Clustering does occur by chance. Statistical approaches are used to determine the likelihood that a cluster is a real or chance occurrence.



Clusters are Difficult to Investigate

- Clusters of any disease may occur by chance. Investigators may be searching for a cause that doesn’t exist.
- The time between exposure to a harmful substance and the development of disease can be decades.
- People move in and out of counties and states throughout their lives, making it even more difficult to measure a person’s level of exposure.
- Diseases are often caused by a combination of factors not yet fully understood.

Toxicology – Non-carcinogenic effects



RfC = reference concentration
RfD = reference dose

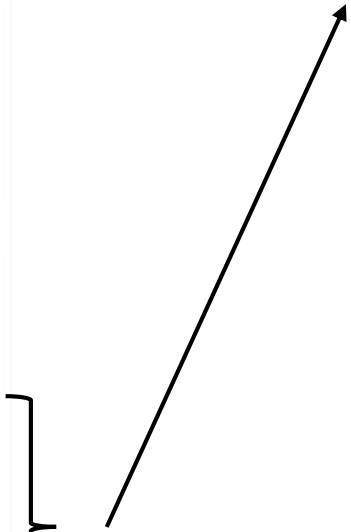
Toxicology – Non-carcinogenic effects

Table 3. Key conclusions for TCE noncancer toxicity.

Tissue or organ system	Key conclusions as to human health hazard
Central nervous system	Strong evidence, based on multiple human and experimental animal studies, that TCE causes • Changes in trigeminal nerve function or morphology • Impairment of vestibular function. Limited evidence, primarily from experimental animal studies, with fewer/more limited human studies, that TCE causes • Delayed motor function, including during neurodevelopment • Changes in auditory, visual, and cognitive function or performance.
Kidney	Strong evidence, based on experimental animal studies, a few human studies, and mechanistic studies, that TCE causes nephrotoxicity, particularly in the form of tubular toxicity. Nephrotoxicity is likely mediated primarily through the TCE GSH conjugation metabolite DCVC.
Liver	Limited evidence in humans and strong evidence from experimental animal studies that TCE causes hepatotoxicity but not necrosis. Mice appear to be more sensitive than other experimental species, and hepatotoxicity is likely mediated through oxidative metabolites including, but not exclusively, TCA.
Immune system	Strong evidence, based on multiple human and experimental animal studies, that TCE exposure causes • Autoimmune disease, including scleroderma • A specific type of generalized hypersensitivity disorder. Limited evidence, primarily from experimental animal studies, with fewer/more limited human studies, that TCE causes immunosuppression.
Respiratory tract	Suggestive evidence, primarily from short-term experimental animal studies, that TCE causes respiratory tract toxicity, primarily in Clara cells.
Reproductive system	Strong evidence, based on multiple human and experimental animal studies, that TCE causes male reproductive toxicity, primarily through effects on the testes, epididymides, sperm, or hormone levels. Suggestive evidence, based on few/limited human and experimental animal studies, that TCE causes female reproductive toxicity.
Development	Strong evidence, based on weakly suggestive epidemiologic studies, limited experimental animal studies, and multiple mechanistic studies, that TCE causes fetal cardiac malformations; limited experimental evidence that oxidative metabolites, such as TCA and/or DCA, cause similar effects. Limited evidence, primarily from experimental animal studies, with weakly suggestive epidemiologic studies, that TCE causes fetal malformations (in addition to cardiac), prenatal losses, decreased growth or birth weight of offspring, and alterations in immune system function.

Abbreviations: DCVC, *S*-dichlorovinyl-L-cysteine. Data from U.S. EPA (2011d).

Most sensitive non-carcinogenic effects are developmental. TCE causes fetal cardiac malformations (strong evidence) and developmental immunotoxicity based on animal studies.



Toxicology – Cardiac malformations

The most sensitive endpoints by far are the increased fetal heart malformations in rats reported by Johnson et al. (2003) and the developmental immunotoxicity in mice reported by Peden-Adams et al. (2006), and these are both considered candidate critical effects.

						Total of Uncertainty Factors				Candidate RfD mg/kg/d	
Johnson et al. (2003)	Rat	BMDL	0.0146	1	10	10	1	1	100		0.00015	Heart malformations (litters); BMR = 10% extra risk (only ~1/10 from each litter affected); highest-dose group (1,000-fold higher than next highest) dropped for model fit.
Johnson et al. (2003)	Rat	BMDL	0.0207	1	10	10	1	1	100		0.00021	Heart malformations (pups); BMR = 1% extra risk; preferred due to accounting for intralitter effects via nested model and pups being the unit of measure; highest-dose group (1,000-fold higher than next highest) dropped for model fit

Cardiac malformations are induced in an early window of development by TCE exposures. There is very strong evidence that TCE causes developmental cardiac defects in avian models (chickens). The evidence in rodents is less consistent with some well-conducted studies (Carney et al., 2006) showing no effects, and other studies (Johnson et al., 2003) showing effects at low levels of exposure. The Johnson results are controversial, but have driven the risk assessment.

Toxicology – Cardiac malformations

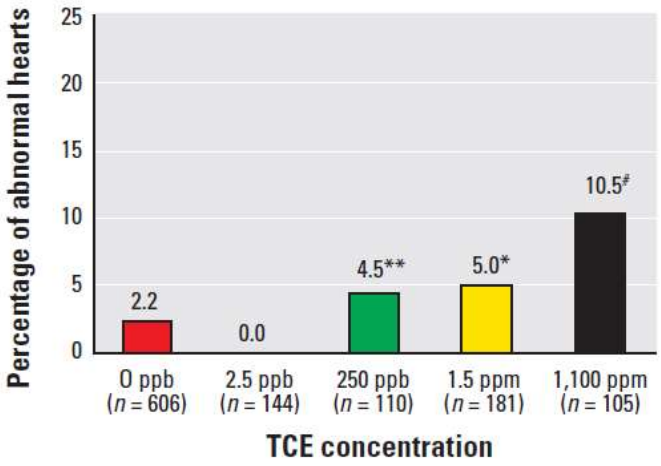


Figure 1. Dose–response pattern for treated and control groups.
*Compared to control, $p = 0.14$; **compared to control, $p = 0.04$; #compared to control, $p < 0.001$.

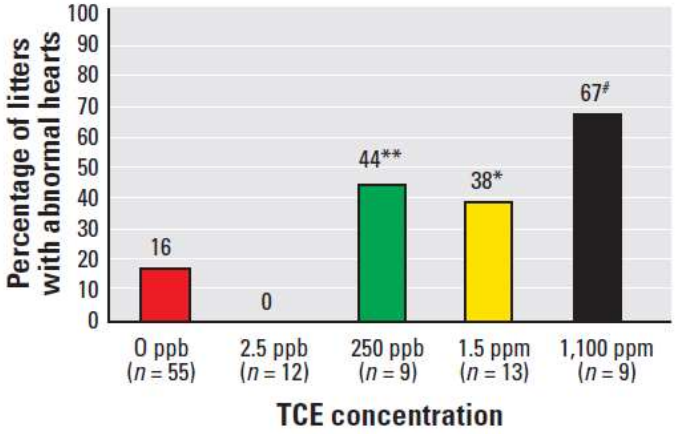


Figure 2. Dose–response pattern for treated and control litters.
*Compared to control, $p = 0.08$; **compared to control, $p = 0.05$; #compared to control, $p < 0.001$.

Johnson Env Health Perspect 111:289 (2003)

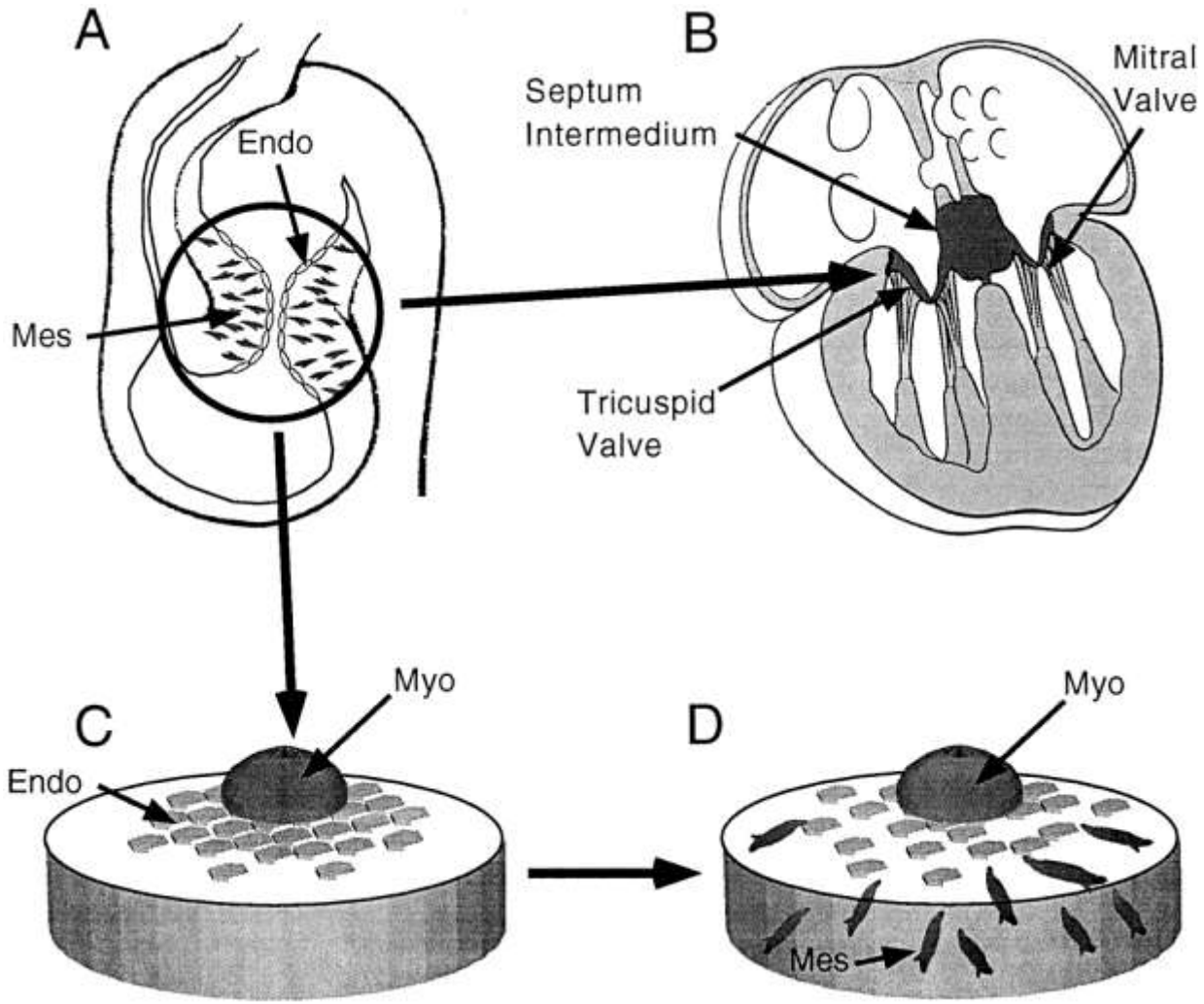
Concerns raised by Hardin (EHP 112: A607-8, 2004):

"Johnson and Dawson, with their collaborators, are alone in reporting that TCE is a "specific" cardiac teratogen……We have always considered those findings suspect, and our comparison of data from the studies of Dawson et al. (1993) and Johnson et al. (2003) serves only to intensify our reservations."

"In sum, while the studies by Dawson et al. (1993, 1990) and Johnson et al. (2005, 2003), have significant limitations, there is insufficient reason to dismiss their findings."

TCE IRIS 2011 4-561

Collagen gel bioassay system.



Angelique S. Boyer et al. Toxicol. Sci. 2000;53:109-117

Toxicology – Developmental immunotoxicity

Total of Uncertainty Factors

Candidate RfD mg/kg/d

Developmental immunotoxicity												
Peden-Adams et al. (2006)	Mouse	LOAEL	0.37	1	10	10	10	1	1,000		0.00037	↓ PFC, ↑ DTH: POD is estimated dam dose (exposure throughout gestation and lactation + to 3 or 8 wks of age); UF LOAEL = 10 since multiple immunotoxicity effects

TCE IRIS 5-43

A LOAEL-to-NOAEL UF of 10 was used for the multiple effects of decreased PFC response and increased delayed-type hypersensitivity at the same dose. While there is uncertainty in this estimate, it is notable that decreased PFC response was also observed in an immunotoxicity study in adult animals (Woolhiser et al., 2006), lending biological plausibility to the effect.

TCE IRIS 5-46

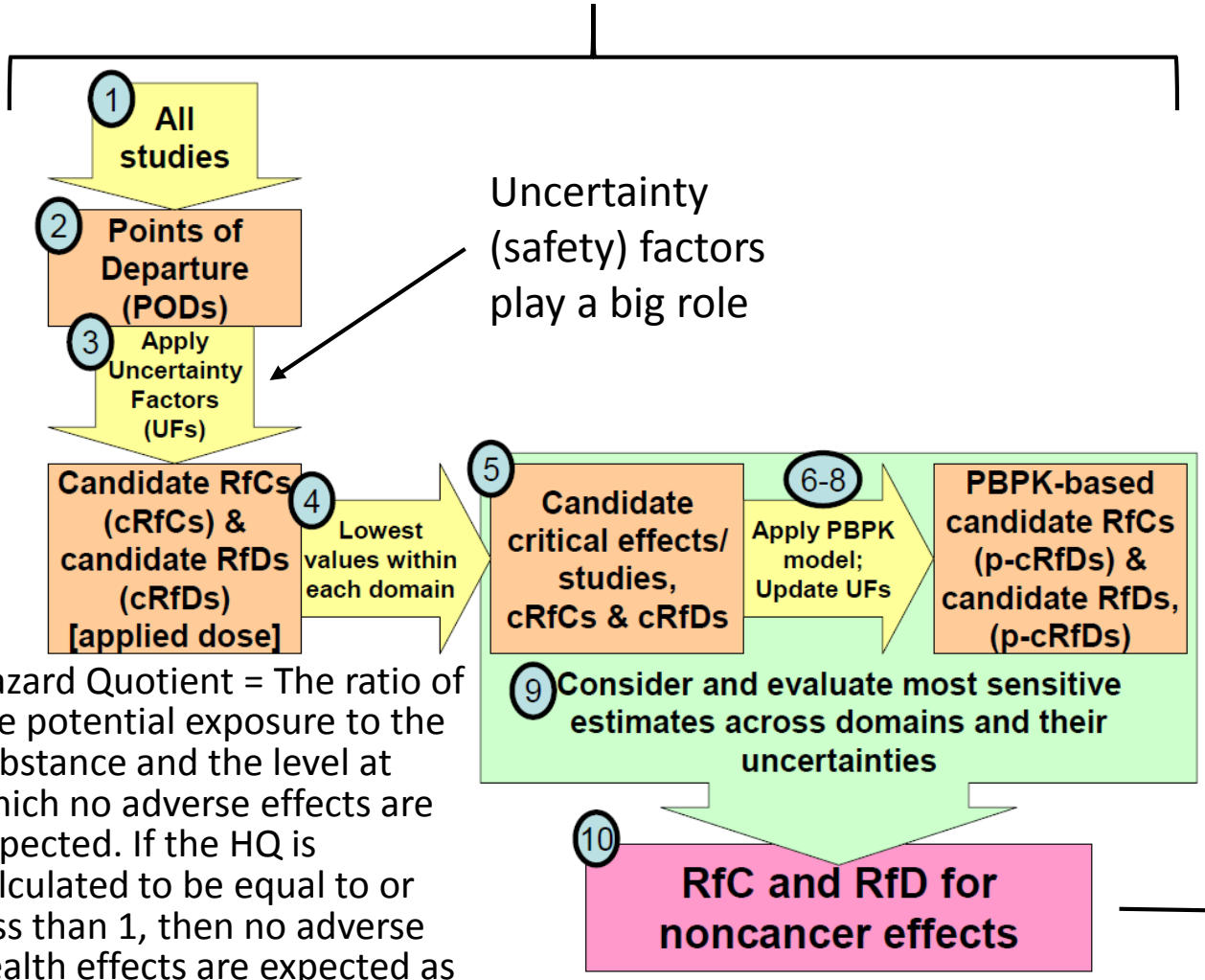
PFC = plaque forming cell; quantitates the number of Sheep Red Blood Cell-specific IgM antibody-forming cells using the hemolytic plaque assay

DHT = delayed type hypersensitivity; an indicator of cell-mediated immune status and is dependent upon both T helper 1(Th1)-driven responses as well as cell recruitment and chemotaxis to a local site

Changes in TCE reference levels over time

MAJOR ISSUE: TCE is not one of the federally mandated priority pollutants

Risk characterization – EPA IRIS (federal) process



Risk management is the responsibility of local states and counties, all of which apply different rules for the calculation of allowable limits of exposure (e.g., cancer at 1 per 10^{-5} or 10^{-6}, toxic hazard quotients ranging from 0.1 to 10)

Hazard Quotient = The ratio of the potential exposure to the substance and the level at which no adverse effects are expected. If the HQ is calculated to be equal to or less than 1, then no adverse health effects are expected as a result of exposure

Hazard index = sum of all hazard quotients

My questions and confusion revealed in interactions with Barbara Morin (RIDEM) and Bob Vanderslice (RIDOH)

1) It seems like the developmental heart defect risk of TCE has driven an immediate action level response for short-term exposure because of an applied Hazard Quotient/Index.....I'd like to understand how this works in the regulatory world, who decides this stuff, and why.

2) It seems like the developmental immunotoxicity effects of TCE have not warranted the same kind of action level response regulations.....why?

3) The process of going from an inhalation unit risk for cancer to an allowable risk for an exposure is a mystery to me, and seems to differ in different states.

4) How does one get from the RfD to an allowable drinking water standard?

5) How much of this regulatory decision making is national, regional, or state-based, and why?

My questions and confusion revealed in interactions with Barbara Morin (RIDEM) and Bob Vanderslice (RIDOH) (cont.)

- Should developmental cardiac defects and developmental immunotoxicity be handled differently?
  - My perusal of various state proposed implementations suggest this is happening regarding the immediate action level response for short-term exposures.
- What is the biologic rationale for this?
  - The human developmental window for susceptibility for cardiac defects is short (hours to days) while that for immunotoxicity is much longer (weeks to months)
  - The severity of the defect is greater with cardiac versus immunotoxicity effects.

Trichloroethylene (TCE) Update
Waste Site Cleanup Advisory Committee Meeting
January 24, 2013

Massachusetts

Trichloroethylene (TCE) Update

Timeline on TCE

- 1989 EPA withdrew TCE values from IRIS
- 2001 EPA released draft TCE Health Assessment
- 2002 EPA SAB reviewed the draft Health Assessment
- 2006 NAS released report and recommendations
- 2009 EPA issued draft Health Assessment for TCE
- 2011: USEPA released its Final Assessment for TCE on IRIS. http://www.epa.gov/iris/subst/0199.htm

Basis for New Values

RfC	**2 µg/m^3 (2 x 10^{-3} mg/m^3)**	• **Immune system effects** • **Fetal heart malformations**
RfD	**0.5 µg/kg/day (5 x 10^{-4} mg/kg-day)**	• **Fetal heart malformations** • **Immune system effects** • **Developmental immune system effects**
Oral Slope Factor	**5.0 x 10^{-2} per mg/kg-day**	• **Kidney cancer** • **Liver cancer** • **non-Hodgkin Lymphoma** **"Carcinogenic to humans via ingestion "**
Unit Risk (Inhalation)	**4.0 x 10^{-6} per µg/m^3**	• **Kidney cancer** • **Liver cancer** • **non-Hodgkin Lymphoma** **"Carcinogenic to humans via inhalation"**

Effects of Toxicity Value Changes on Method 1 and 3

(Residential; Risk Drivers – cancer or noncancer)

	Current (Old Value)	**New IRIS Value**	**Health Endpoint (new IRIS value)**
Method 1 No Significant Risk (Risk Driver)	GW-2 = 30 µg/L (Based on air background of 4.5 µg/m^3) Risk-based indoor air conc. = 1.4 µg/m^3 (Cancer risk of 1 x 10^{-5} from 30 year exposure)	GW-2 = 5 µg/L (Based on air background of 0.8 µg/m^3) Risk-based indoor air conc. = 0.4 µg/m^3 Chronic Exposure Non-cancer Risk (HQ= 0.2)	Fetal heart developmental effects and immune effects for all receptors
Method 3 No Significant Risk (Risk Driver)	14 µg/m^3 (Cancer risk of 1 x 10^{-5} from 30 year exposure)	2 µg/m^3 Chronic Exposure Non-cancer Risk (HQ=1)	Fetal heart developmental effects and immune effects for all receptors

MCP Imminent Hazard

The conditions at the disposal site pose an Imminent Hazard when:

1. ”a Hazard Index equal to 1.0 for OHM that have the potential to cause serious effects (including but not limited to lethal, **developmental,** or neurological effects) following short-term exposures; and
2. a Hazard Index equal to 10 for all other oil or hazardous materials.”

Effect of Toxicity Value Change on Imminent Hazard

Method 3 Short Forms	**Current (Old Value)**	**New IRIS Value for Interim Approach**	**Health Endpoint (new IRIS value)**
Imminent Hazard (Risk Driver)	85 µg/m^3 (Cancer Risk of 1 x 10^{-5} from 5-year exposure)	2 µg/m^3 Sub-chronic exposure Non-cancer Risk (HQ=1) For sensitive groups: pregnant women and women of childbearing age	Fetal (heart) developmental effects for sensitive groups and immune effects for all receptors
		20 µg/m^3 Sub-chronic exposure Non-cancer Risk (HQ=10) For all other people	Immune effects

Other Agencies

Agency	Hazard Index	Comment
US EPA NCEA	Guidance not yet published	Promised last Fall
US EPA OSWER Region X Removal Action Levels (RALs)	HI = 1	Pregnant women/women of childbearing age
US EPA OSWER Region IX (RALs)	HI = 3	Pregnant women/women of childbearing age
ATSDR	HI = 2 (MA case)	Pregnant women/women of childbearing age
New Jersey DEP	HI= 2 (Rapid Action Limits)	Pregnant women/women of childbearing age

Brief Review of Trichloroethylene (TCE) Developmental Risks CT Department of Public Health, Environmental and Occupational Health February 2015

"The Connecticut Department of Public Health is relying upon the USEPA 2011 review of trichloroethylene developmental effects to make a determination that there is an acute risk of cardiac defects and impaired immunity from encountering TCE during pregnancy (USEPA IRIS 2011; USEPA 2011).

……..In summary, CT DPH finds that TCE is a low dose developmental risk such that exposures to pregnant women and women of childbearing age should be avoided or at least mitigated to below targets associated with the RfD (if in drinking water) or RfC (if in indoor or outdoor air)."