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The Role of Trichloroethene in Congenital Heart Defects: Updated Weight of Evidence Shifts Risk Management

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2024 Chlorinated Conference
Denver, Colorado

Summary

- In addition to long-term cancer risks, regulators have been managing TCE exposures/risks based on developmental health effects associated with short-term exposures
- The science supporting developmental health effects is not robust and has been widely criticized
- New evidence has emerged further questioning the significance of developmental health effects
- In consideration of this new evidence, EPA (TSCA) has elected to use other health effects to support risk management
- This could have implications for managing TCE exposures/risks in the future

Agenda

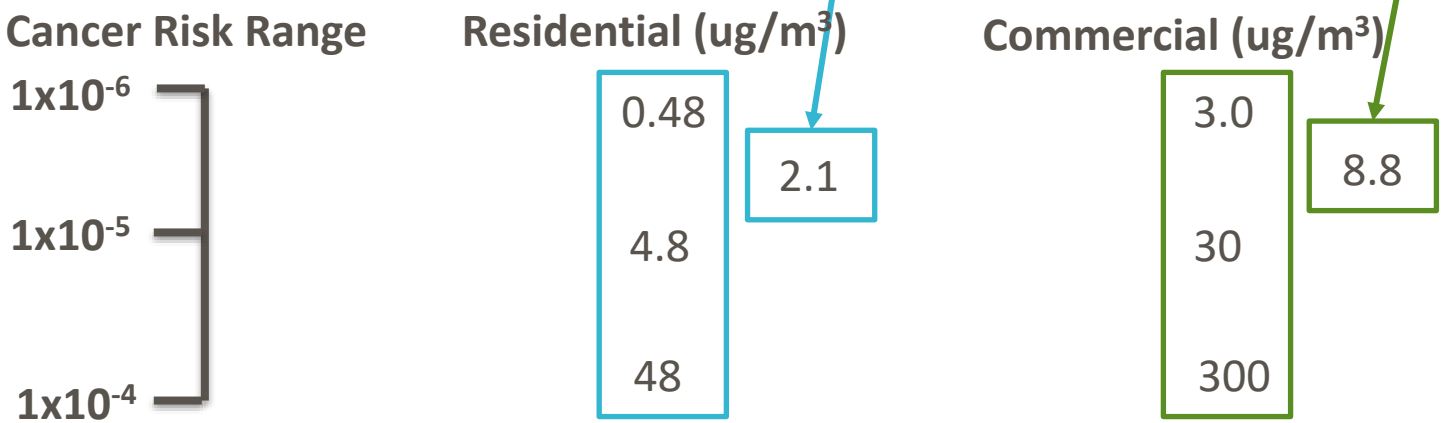
1. Health effects endpoints
2. Current state
3. Weight of evidence for developmental effects (specifically, congenital heart defects [CHDs])
4. Implications for new information and EPA's position
5. Implications for risk management of TCE at vapor intrusion sites

Current State – TCE toxicity endpoints and air concentrations

- Three non-cancer endpoints = essentially same indoor air screening levels

TCE Toxicity endpoint (EPA, 2011)	Associated Indoor Air Concentration (ug/m³) Residential	Commercial
Immune system (HI = 1)	2.1	8.8
Developmental (HI = 1)	2.1	8.8
Kidney (HI = 1)	3.0	12

- Non-cancer screening levels correspond to relatively low cancer risks (less than $5x10^{-6}$); as a result, TCE risk decisions are typically made using non-cancer endpoints



Current State – Application of toxicity endpoints

TCE Toxicity endpoint (EPA, 2011)		Associated Indoor Air Concentration (ug/m^3)	
		Residential	Commercial
Immune system (HI = 1)	Chronic	2.1	8.8
Developmental (HI = 1)	Acute	2.1	8.8
Kidney (HI = 1)	Chronic	3.0	12

- EPA/TSCA (Draft, 2012; Final, 2014) applied developmental toxicity as an acute exposure endpoint in assessment of consumer risks for TCE exposure
  - RfC basis: developmental toxicity [congenital heart defects (CHDs)] in rats exposed entire gestational period via drinking water (Johnson, et al., 2003)
  - Identified women of child-bearing age as receptor at risk from short-term exposure to TCE; increased risk of CHDs in fetuses of women exposed during first trimester
  - Specific type of malformations can only occur during a 5-week period of heart development (in humans)
  - Interpreted by EPA as a 'severe and irreversible effect'

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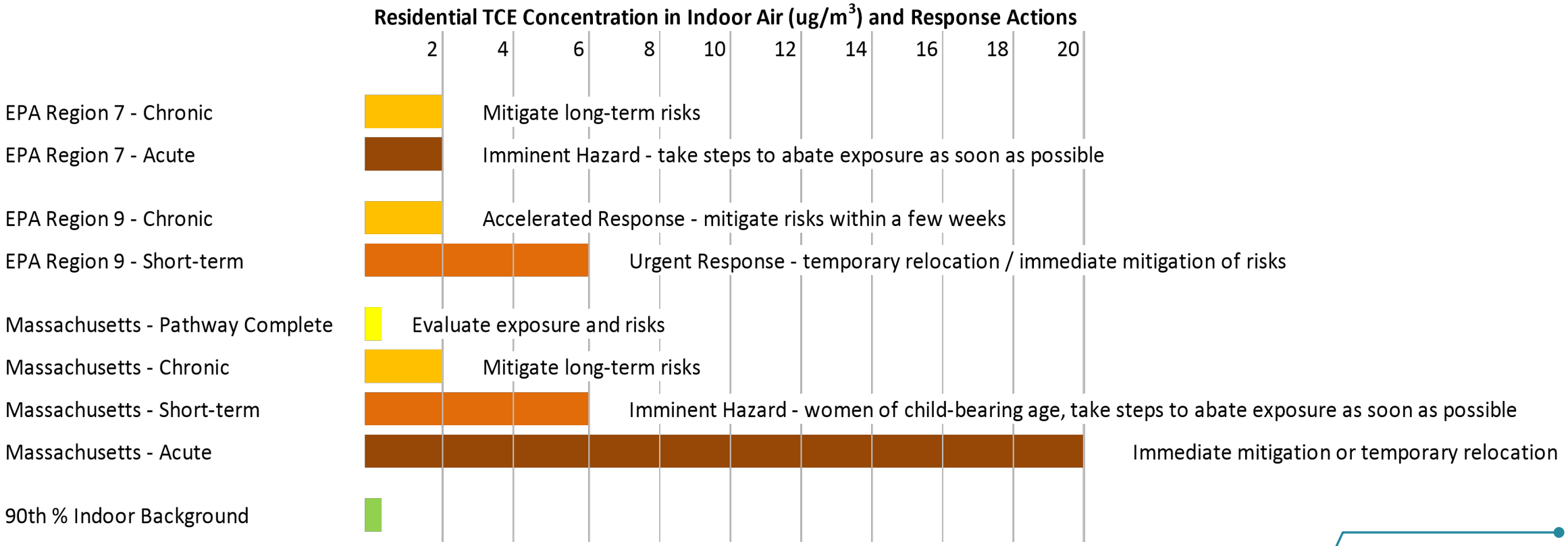
Current State – Multiple Approaches to risk management

- Position advanced by TSCA was adopted by EPA and state agencies



What is the weight of evidence for CHDs?

1. Epidemiology studies
   - Only 2 studies show positive association with TCE; many show no association or equivocal evidence
   - None of the studies measured TCE exposure
   - None of the studies recorded location relative to exposure during first trimester
2. Animal studies
   - 11 are negative, including all 7 inhalation studies
   - 2 are positive (both by Johnson) – drinking water studies
3. Mechanistic information
   - Support a role for TCE in developmental toxicity, but only at doses that exceed solubility of TCE in water / not environmentally relevant

How strong is the evidence for CHDs? Limitations of the Johnson Study

- Pooling of nonconcurrent control data (which may have exaggerated the statistical significance of the critical effect)
- Lack of analytical results for TCE in the drinking water to confirm the administered dose levels
- Use of a non-standardized dissection method whereupon identification of CHDs was determined by consensus among the investigators
- Lack of a positive control by which to evaluate the sensitivity of the dissection / identification method
- Lack of a clear, meaningful dose-response relationship for the CHDs
- Results could not be duplicated

Summary of CHDs by Quantity Observed in Each Group Reported by Johnson *et al.* (2003)

TCE (ppm)	*No. dams/ No. fetuses*	*Atrial septal defect (ASD)*	*Ventricular septal defect (VSD)*	*Malformed valves*	*Other heart defects*	*Total*	*Percent Incidence (anomalies / total fetuses)*
0	55 / 606	7	4	0	3	13	2.1%
0.025	12/ 144	0	0	0	0	0	0%
0.25	10 / 110	1	0	3	1	5*	4.5%
1.5	13 / 181	4	3	0	2	9	5.0%
1,100	9 / 105	7	5	2	0	11*	10.5%

* Statistically significant compared to control ($p < 0.05$)

EPA (2011) Toxicological Review (in support of IRIS): Weight of Evidence Review

Table 4-103. Summary of studies that identified cardiac malformations associated with TCE exposures

Finding	Species	References
Cardiac defects	Human	ATSDR (2008b, 2006a); Yauck et al. (2004)
	Rat	Dawson et al. (1993, 1990); Johnson et al. (2003); Johnson et al. (2005); Johnson et al. (1998b; 1998a)[a]; Smith et al. (1989), (1992)[a]; Epstein et al. (1992)[a]
	Chicken	Bross et al. (1983); Boyer et al. (2000); Loeber et al. (1988); Drake et al. (2006a; 2006b); Mishima et al. (2006); Rufer et al. (2010; 2008)
Altered heart rate	Human	Jasinka (1965, translation)

[a]Metabolites of TCE.

Same study cohort

Significant limitations

All from the same research group

Metabolite (not relevant to environmental exposures)

Not relevant to human environmental exposures and risk

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Makris (2016): Weight of Evidence Review

Overall, the WOE supported the conclusion that TCE exposure at sufficient doses during prenatal development has the potential to cause cardiac defects in humans. In Johnson et al. [51], the lowest dose to rats that resulted in these outcomes was 0.048 mg/kg-day TCE in drinking water.

This conclusion is based upon multiples lines of evidence:

- Epidemiological studies that identified a clear association between cardiac defects and maternal TCE exposures via vapor intrusion [29] and limited evidence for an association of TCE, or TCE in combination with other solvents, in drinking water (Bove [8]/Bove et al. [9]).
- Toxicology studies with TCE from one laboratory [51,20] that identified treatment and dose-related defects in cardiac development in rats following maternal drinking water exposures, although study design and reporting deficiencies were noted, and other laboratories were unable to replicate the findings using different routes of exposure [15,28].
- Toxicology studies with metabolites of TCE from two laboratories that observed defects in cardiac development in rats after maternal high-dose gavage or drinking water exposure to DCA [79,27] or TCA [78,49].
- In ovo studies from two laboratories [72,23,24,57] that found defects in cardiac structure or function in chicken embryos resulting from low-dose TCE exposures that disrupted valvulo-septal development (a process highly conserved across species, including humans)
- In vitro assays (whole embryo culture studies) from two laboratories that identified alterations in cardiac development with high doses of TCE [60] or its metabolites DCA and TCA [44] exposures to chicken or mouse embryos, respectively.
- Mechanistic data, including a putative AOP construct, that is consistent with the potential for TCE to cause cardiac defects and supports the biological plausibility of an effect on cardiac development with exposure to TCE.

The evidence was characterized as "Sufficient Experimental Animal Evidence" and "Limited Human Evidence" in accordance with *Guidelines for Developmental Toxicity Risk Assessment* [85].

Cited Endicott (statement in paper *"epidemiological studies are not sufficient to establish a causal link..")*

No association between TCE and CHD

All from the same research group

Metabolite (not relevant to environmental exposures)

Avian not relevant to human environmental exposures and risk

Doses 1000'sX higher than environmentally relevant exposures

Possible mode of action; not proven

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ATSDR Toxicological Profile (2019): Weight of Evidence Review

Cites other EPA documents as lines of evidence

- "… in the absence of convincing information to the contrary, the report of trichloroethylene-induced cardiac malformations in rat fetuses is considered valid and relevant to humans, based on available epidemiological and animal data, as well as mechanistic information (EPA 2011e)."

EPA (2011) Toxicological Review (in support of IRIS)

- "EPA concluded that "while the Johnson et al. studies have limitations, there is insufficient reason to dismiss their findings, especially when the findings are analyzed in combination with the remaining body of human, animal and mechanistic evidence "

EPA (2014) TSCA Risk Evaluation

- "An EPA executive panel (EPA 2016) reviewed EPA's position regarding the weight-of-evidence for trichloroethylene-induced fetal cardiac malformations in rats and concluded that the information presented in the Toxicological Review of Trichloroethylene (EPA 2011e) is "consistent with EPA's IQG [Information Quality Guideline] standards of objectivity and utility.""

EPA (2016) Review Panel (subsequently published as Makris et al., 2016)

* Tox profile was published prior to publication of DeSesso et al. study

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Summary of EPA's position on CHDs related to TCE

- Since 2011, EPA has used the results of the Johnson (2003) study as the basis for the developmental toxicity endpoint
  - Largely downplayed the negative evidence of CHDs
- Despite wide-spread criticism of the Johnson study, EPA's position has been:
  - "…in the absence of convincing information to the contrary, the report of trichloroethylene-induced cardiac malformations in rat fetuses is considered valid and relevant to humans, based on available epidemiological and animal data, as well as mechanistic information…"
  - "while the Johnson et al. studies have limitations, there is insufficient reason to dismiss their findings, especially when the findings are analyzed in combination with the remaining body of human, animal and mechanistic evidence"
- *i.e., 'we are sticking with this until compelling information arises that contradicts these findings'*

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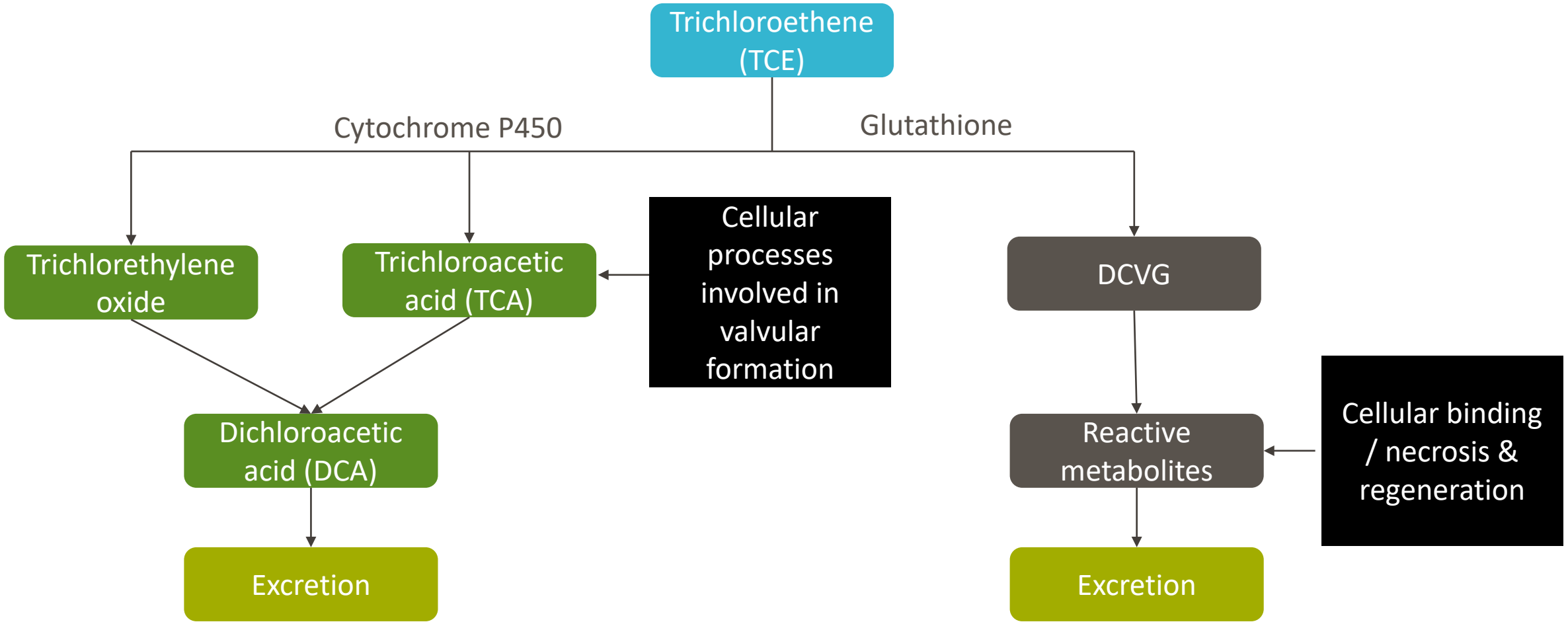
Weight of Evidence: New toxicity study (DeSesso, 2019)

- DeSesso, et al. (2019) replicated Johnson study, but corrected deficiencies: ***negative findings for CHD***

Deficiencies in Johnson Study	Corrections in DeSesso Study
Pooling of nonconcurrent control data	Balanced numbers of animals
Lack of analytical results for TCE in the drinking water	Chemicals were from the same lots / measured throughout study
Use of a non-standardized dissection method	Followed standard EPA-approved method for evaluating fetal hearts
Lack of a positive control	Included a positive control group
Lack of a clear, meaningful dose-response relationship for the CHDs	Obtained contemporaneous steady state blood level data supporting lack of dose-response relationship
Results could not be duplicated	Duplicated Johnson study methods; negative findings

Metabolism of TCE



Mechanistic information

- Maternal blood TCA only detected at highest dose levels via drinking water
- Maternal blood TCA levels lower via drinking water exposure vs. other exposure routes
- No CHDs in inhalation and gavage exposure routes
- Not possible for 0.25 and 1.5 ppm doses in Johnson study to cause CHDs

	Peak (AUC) concentration (µg/mL or mg·hr/L)					
	TCE					TCA
Exposure Route	Drinking water[a]	Drinking water[b]	Inhalation[b]	Gavage[b]	Gavage[c]	Gavage[c]
TCE/TCA	0.25–1,000 ppm	350 ppm	600 ppm, 4 hr	2.3 mg/kg	591 mg/kg	98 mg/kg
TCE blood	ND	ND	24 (1,864)	0.26 (0.72)	33	—
TCA plasma	1.1–1.2	2.7 (585)	13 (5,201)	0.70 (106)	25	201

Abbreviations: AUC, area under the curve; TCA, trichloroacetic acid; TCE, trichloroethylene.

[a]Current study, ND = Below LOD (50 ng/mL); TCA detected only 500 and 1,000 ppm, not at 0.25 and 1.5 ppm.

[b]Fisher et al. (1989); TCE and TCA measured in pregnant GD21 SD rats following dosing at 5 days/week for 3 weeks.

[c]Larson and Bull (1992); TCE and TCA measured after single dose to adult male rats; TCE C_{max} estimated from graphical data.

Source: DeSesso et al., 2019

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Implications of new information: EPA/TSCA consideration in weight of evidence

- EPA/TSCA (2020) considered DeSesso study in developing weight of evidence for TCE-induced cardiac defects
- For use in evaluating risks for TCE exposure, EPA/TSCA did not select developmental toxicity to inform risk management decisions
  - "… EPA make decisions consistent with the "best available science"…. the "extent of independent verification" and "weight of the scientific evidence"…"
  - "… EPA believes that public health is best served when EPA relies upon the highest quality information for which EPA has the greatest confidence…"
- Internal EPA/TSCA review of Draft TSCA report concluded that Johnson study and CHDs should not form basis of risk management decisions

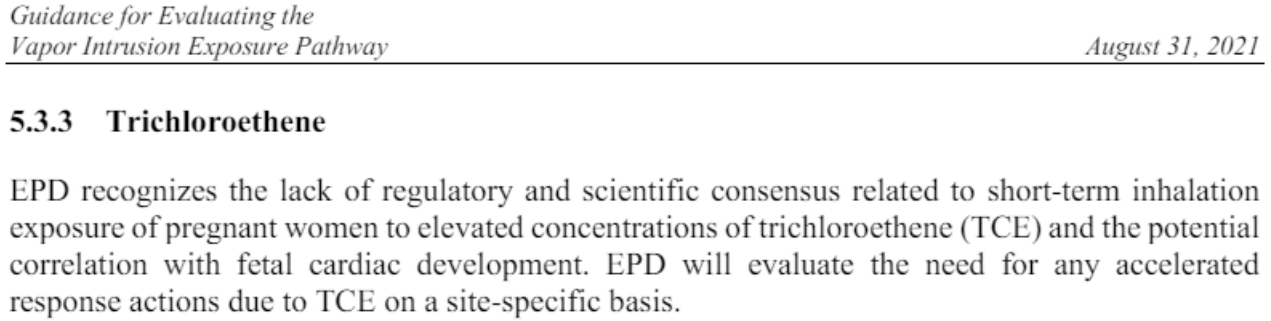
Implications for new information: EPA/TSCA position

- Does the EPA/TSCA (2020) position and the DeSesso (2019) provide the information needed to respond to EPA's (2011) position?
  - "…in the absence of convincing information to the contrary, the report of trichloroethylene-induced cardiac malformations in rat fetuses is considered valid and relevant to humans, based on available epidemiological and animal data, as well as mechanistic information…"
  - "while the Johnson et al. studies have limitations, there is insufficient reason to dismiss their findings, especially when the findings are analyzed in combination with the remaining body of human, animal and mechanistic evidence"
- This should provide the 'additional studies' needed to re-consider the developmental toxicity of TCE

"the NAS recommended further low dose studies to replicate the effects observed in the critical (Johnson et al. [2003]) study. Until such studies are conducted, ORS concurs with US EPA that the current available weight of the scientific evidence on TCE-induced congenital cardiac toxicity is sufficient to warrant concern and the critical study is a reasonable basis for developing toxicity numbers."

Implications for risk management of TCE at vapor intrusion sites – other states

- Prior to publication of DeSesso (2019) study and TSCA Risk Evaluation (2020), two states had moved away from managing TCE risks based on short-term effects
  - Indiana Department of Environmental Management concluded that "an accelerated response [for TCE] is not scientifically supportable based upon current information" and noted that application of accelerated response levels for TCE have been controversial and problematic as a policy (IDEM, 2016)
  - The Missouri Department of Natural Resources indicated that its revisions to Missouri Risk Based Corrective Action screening tables would base values for TCE solely on chronic exposure because the agency believes that scientific support is lacking for the short-term exposure levels related to the Johnson et al. (2003) study (MDNR, 2019)
- 2021 Georgia VI Guidance:



Guidance for Evaluating the Vapor Intrusion Exposure Pathway *August 31, 2021*

5.3.3 Trichloroethene

EPD recognizes the lack of regulatory and scientific consensus related to short-term inhalation exposure of pregnant women to elevated concentrations of trichloroethene (TCE) and the potential correlation with fetal cardiac development. EPD will evaluate the need for any accelerated response actions due to TCE on a site-specific basis.

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Implications for risk management of TCE at vapor intrusion sites

- If developmental toxicity is removed as an endpoint:
  - **Threshold levels at HI = 1 are still 2.1 ug/m^3 (residential) and 8.8 ug/m^3 (commercial/industrial) based on current USEPA (2011) assessment**
  - However, risk management is based on:
    - Air concentrations (exposure point concentrations) evaluated as long-term averages, not single sampling events with concentrations above a bright line value
    - No more immediate response actions for short-term exposures due to concerns about CHD

TCE Toxicity endpoint (EPA, 2011)	Associated Indoor Air Concentration (ug/m^3) Residential	Commercial
Immune system (HI = 1)	2.1	8.8
~~Developmental (HI = 1)~~	~~2.1~~	~~8.8~~
Kidney (HI = 1)	3.0	12

Conclusions

- Strength of the underlying science does not support use cardiac heart defects (CHDs) as a key metric in risk management for TCE
  - TSCA (2020) concurs with this and used chronic endpoints as basis for risk management decisions to support regulation of TCE
  - Other states concur
- Although toxicity values for TCE would remain unchanged, removing CHDs as a risk management endpoint would eliminate concerns over short-term exposures to low TCE concentrations
- Risk communication
  - Would eliminate emotional stress to women of child-bearing age
  - At the very least, messaging to women of child-bearing age “concerns about developmental effects reflect a very conservative interpretation of scientific evidence”

Thank you!

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