Trichloroethylene: Occupational Exposure Level for the DoD

Desmond I. Bannon[1], Tammie R. Covington[2], Mark S. Johnson[1], Glenn J. Leach[1]
[1]Toxicology Directorate U.S. Army Public Health Center
[2]HJF on contract to Airman Systems Directorate U.S. Air Force Research Laboratory

Feb 9, 2022

Trichloroethylene (TCE)

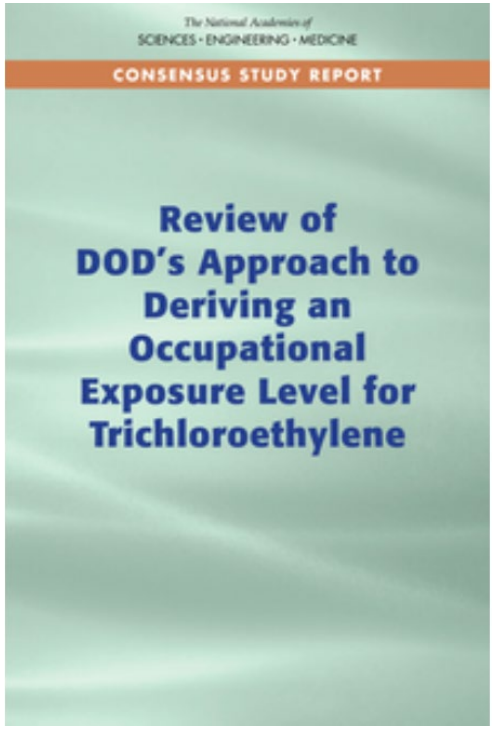
The views expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy of the Department of Defense, Department of the Army, U.S. Army Medical Department, U.S. Air Force or the U.S. Government.

The mention of any non-federal entity and/or its products is not to be construed or interpreted, in any manner, as federal endorsement of that non-federal entity or its products.

Trichloroethylene (TCE)

- TCE is a widely used industrial solvent.
- Thousands of studies demonstrate widespread toxic effects of TCE exposure.
- Inhalation is the primary route of exposure for workers.
- Another exposure concern is from soil vapor intrusion.
- Exposure standards endorsed by various governmental regulatory agencies:
  - 1978 NIOSH Recommended Exposure Limit (25 parts per million (ppm))
  - 1993 OSHA Permissible Exposure Limit (100 ppm)
  - 2007 ACGIH Threshold Limit Values (TLV®) (10 ppm)
  - EPA Regional Screening Levels Composite Worker Air (non-cancer: 0.0016 ppm, $1x10^{-6}$ cancer risk: 0.0006 ppm)
  - 2011 EPA Integrated Risk Information System (IRIS) Reference Concentration (RfC) (0.0004 ppm)
- The goal of this DoD report is to develop an acceptable occupational exposure level (OEL) for inhalation TCE exposure that applies to all workers, including those potentially impacted by vapor intrusion.

Background: 2019 Report



- Agreed with DoD on need for an updated OEL for TCE.
- Agreed with leveraging use of prior reviews (e.g., US EPA, ACGIH, etc.). Agreed with dose-response, use of Physiologically Based Pharmacokinetic Modelling (PBPK), Bayesian approach for uncertainty analysis.
- Suggested implementing provisional TCE OEL (0.9 ppm)
- Did not endorse DoD's systematic approach.
- Recommendations for improvement included:
  - Used narrative approach for cancer and non-cancer studies.
  - Improved transparency of report.
  - Used internal dose metric as Point of Departure (POD).
- A small "Meeting of Experts" under the Committee on Toxicology (COT) provided additional comments (August 2021) as Rev 1.1 was underway.

Report Rev 1.1

- Narrative review of the currently current toxicological data to identify adverse health effects associated with TCE exposure.
- Leverage previous toxicology reports (EPA, ATSDR, etc.).
- Identify evidence supporting causal interpretations of any adverse human health effects due to TCE.
- Utilize methods that maximize scientific robustness and transparency, while balancing timeliness and resources (published approach from Lent et al, 2021).

Approach (Lent et al. 2021)

Original Article

International Journal of Toxicology
2021, Vol. 40(2) 178-195

DOI: 10.1177/1091581820970494
journals.sagepub.com/home/ijt
SAGE

Using Evidence Integration Techniques in the Development of Health-Based Occupational Exposure Levels

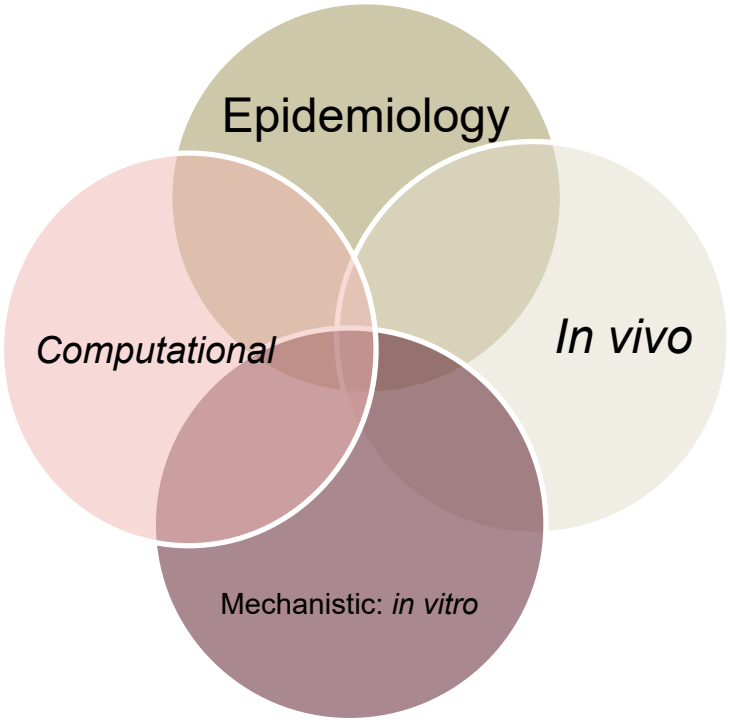
Emily May Lent[1], Thomas E. Sussan[1], Glenn J. Leach[2], and Mark S. Johnson[1]

Abstract

Development of toxicology-based criteria such as occupational exposure levels (OELs) are rarely straightforward. This process requires a rigorous review of the literature, searching for patterns in toxicity, biological plausibility, coherence, and dose–response relationships. Despite the direct applicability, human data are rarely used primarily because of imprecise exposure estimates, unknown influence of assumptions, and confounding factors. As a result, high reliance is often placed on laboratory animal data. Often, data from a single study is typically used to represent an entire database to extrapolate an OEL, even for data-rich compounds. Here we present a holistic framework for evaluating epidemiological, controlled *in vivo*, mechanistic/*in vitro*, and computational evidence that can be useful in deriving OELs. It begins with describing a documented review process of the literature, followed by sorting of data into either controlled laboratory *in vivo*, *in silico*/read-across, mechanistic/*in vitro*, or epidemiological/field data categories. Studies are then evaluated and qualified based on rigor, risk of bias, and applicability for point of departure development. Other data (eg, *in vitro*, *in silico* estimates, read-across data and mechanistic information, and data that failed to meet the former criteria) are used alongside qualified epidemiological exposure estimates to help inform points of departure or human-equivalent concentrations that are based on toxic end points. Bayesian benchmark dose methods are used to estimate points of departure and for estimating uncertainty factors (UFs) to develop preliminary OELs. These are then compared with epidemiological data to support the OEL and the use and magnitude of UFs, when appropriate.

Toxicological Evidence (Lent et al, 2020)

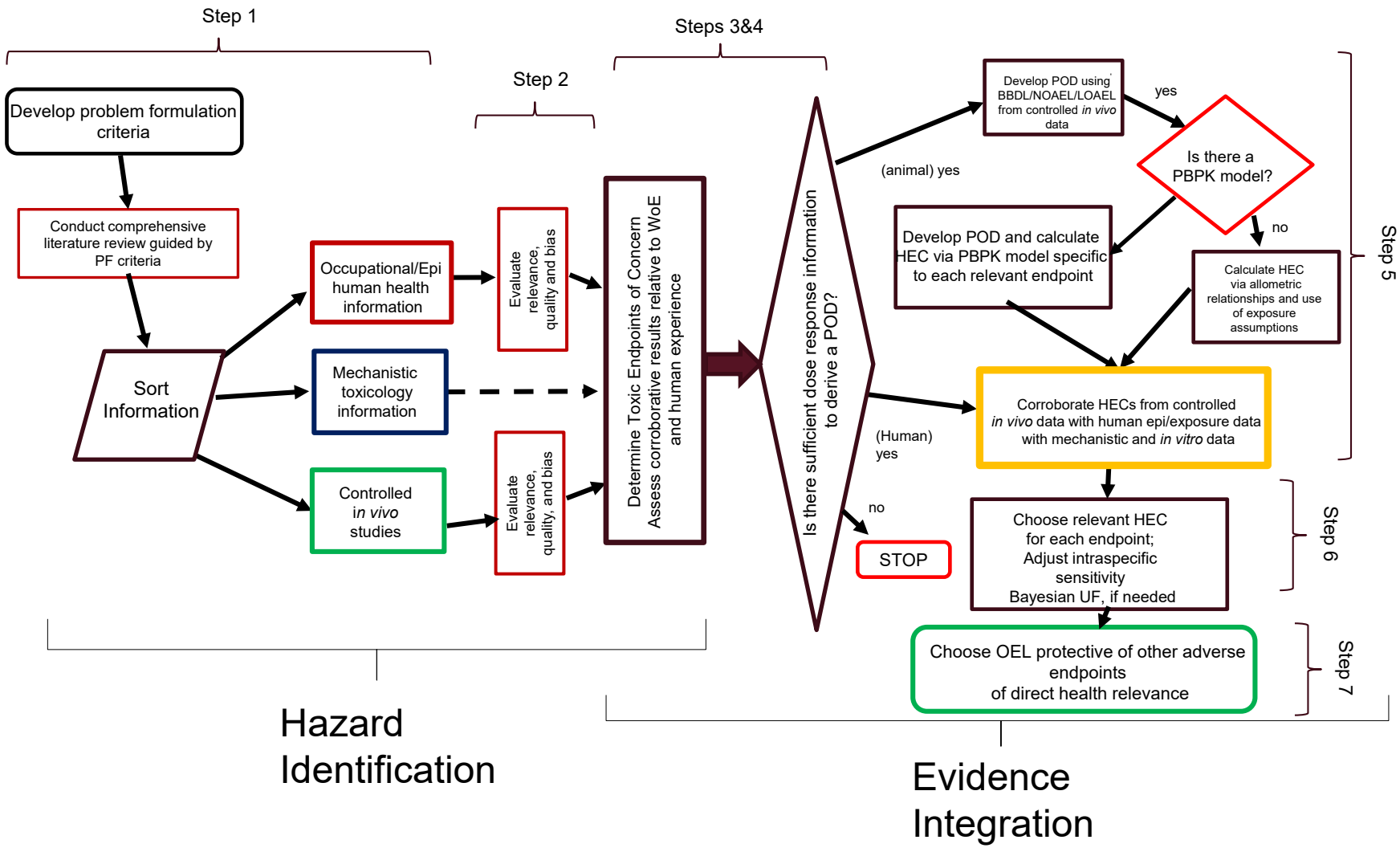
- Epidemiology:
  - Pros: Human data, realistic exposure scenarios
  - Cons: Confounders (mixtures); lack of cause-effect
- *In vivo* animal:
  - Pros: Models include toxicokinetics and dynamics
  - Cons: Animals are different than humans
- *In vitro:*
  - Pros: Can investigate low doses in human cell lines
  - Cons: Missing interconnectivity, kinetics, adaptation
- Computational:
  - Pros: Relatively fast, based on shared molecular moieties/Modes of Action
  - Cons: Models often incorrect



Summary – DoD Response

- Main differences in Rev 1.1:
  - Developed narrative approach (Lent et al, 2021):
    - Began with hazard assessment/identification.
    - Evaluated cancer studies to same extent as non-cancer studies.
    - Evaluated all potential endpoints equally/objectively.
  - Clarified evidence integration:
    - Added Figures 1 and 2 (revised) to clarify/summarize the narrative process.
    - Added evidence integration tables (Tables 2 and 3).
    - Better incorporation of mechanistic evidence (Table 2).
    - Cancer dose-response.
    - Added Figure 9 to compare OEL values to known human exposures.
  - Dose-Response:
    - Dose-response based on (Benchmark Dose Software) BMDS modelling of internal doses (via PBPK).

Lent et al. 2020 (adapted from)

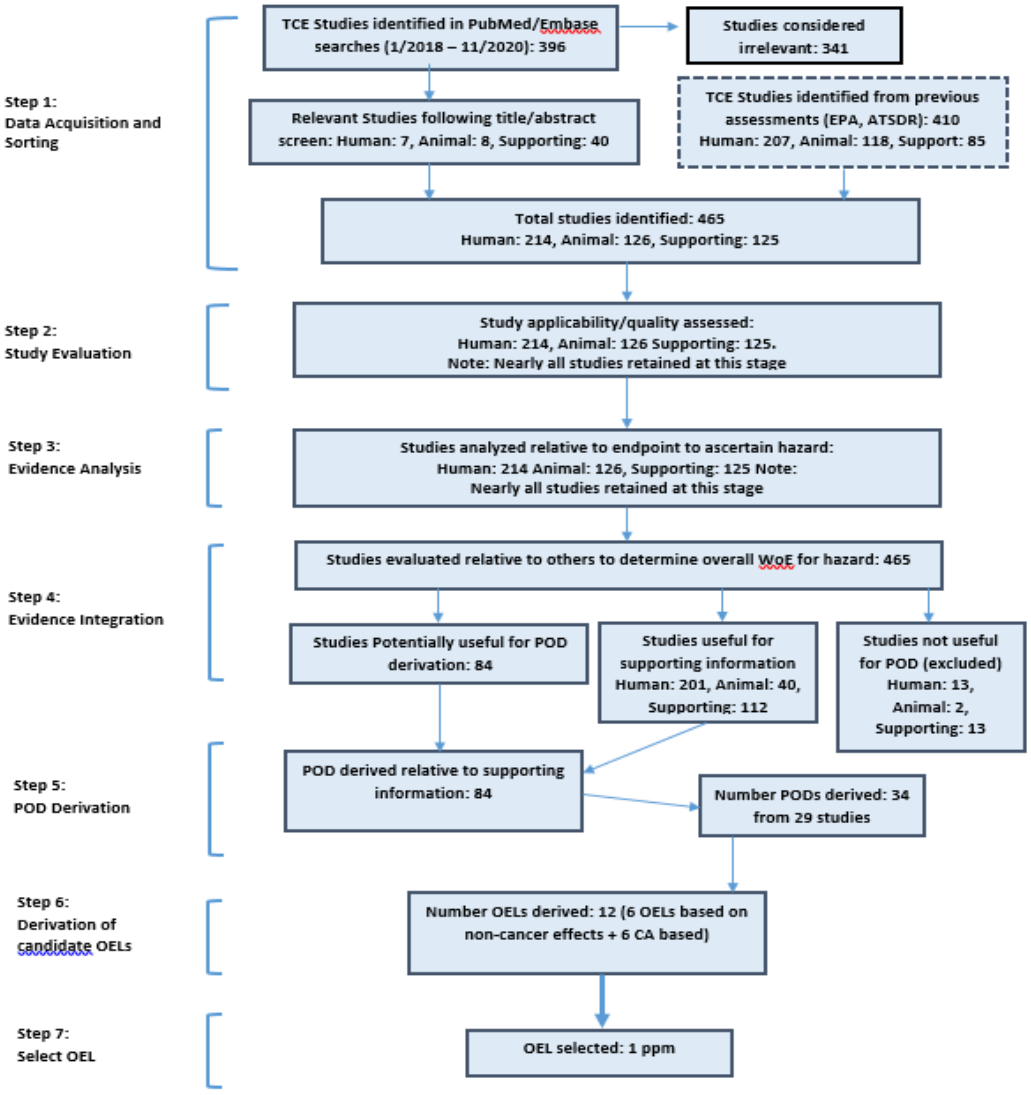


Note: Narrative for Steps 1-7 listed in the report

Literature Search

- Existing reviews (e.g., reports from EPA, NAS, IARC, ATSDR, NIOSH, ACGIH) used as scoping reviews.
- Studies published prior to 2020 were identified via:
  - Summary tables published in EPA and ATSDR reports.
  - Key studies identified in other expert reviews.
- Human and mammalian toxicity studies published from January 2019 – November 2020 were identified via a literature search of PubMed and Embase ("Trichloroethylene OR Trichloroethene").
- Mechanistic evidence was identified via scoping reviews and targeted literature searches.

Summary of Steps



Hazard Identification

- Evidence Analysis
  - Narrative review of relevant studies:
    - Controlled mammalian studies: inhalation (other routes considered when inhalation data lacking), ≥ subchronic duration studies (or appropriate for study type).
    - Human observational studies (occupational and residential).
  - Identify target organs/critical effects:
    - Neurological, kidney, liver, immunological, reproductive, developmental, and cancer.
    - Nearly all information considered for Hazard ID; dose-response data where available for POD derivation.

Hazard Identification – Evidence Integration

- Within Lines of Evidence (LOEs) (Synthesis of Evidence):
  - Narrative synthesis of strengths and weaknesses (e.g., strength of effect, consistency, temporality, dose-response, plausibility, coherence); done in Step 2, presented in Steps 3&4).
  - Qualitative hazard characterization of “sufficient evidence of hazard” or “insufficient evidence of hazard” for each endpoint/effect/target organ.
- Across LOEs (Evidence Integration):
  - “Insufficient” vs. “sufficient” information based on review of all three lines of evidence (animal, human, mechanistic).
  - Integrate evidence within and between LOEs.
  - Informed by MOA/mechanistic evidence.

Table 2. Synthesis of Evidence

Table 2. Summary of evidence integration for target organ systems across categorical data streams

Target Organ System	Human	Animal	Mechanistic*	Comments
Neurological	Sufficient	Sufficient	Suggestive	Historical anesthetic use. Auditory, psychomotor, and visual effects.
Kidney	Sufficient	Sufficient	Suggestive	Biomarkers of kidney injury in animals and humans suggests tubular injury
Hepatic	Sufficient (high exposures)	Sufficient	Suggestive	Weak human evidence
Reproductive	Sufficient (males)	Sufficient (males)	Suggestive (males)	No change in fertility in rodents
Developmental	Insufficient	Sufficient (growth) Insufficient (terrata)	Indeterminate (inhalation) Suggestive (oral)	Perinatal survival and growth at high exposures in animals.
Immune	Sufficient	Sufficient	Suggestive	Autoimmunity
Kidney cancer	Sufficient	Insufficient	Suggestive	High doses.
Non-Hodgkin's Lymphoma	Insufficient	Insufficient	Indeterminate	
Liver cancer	Insufficient	Sufficient	Indeterminate	
Repro. and other cancers	Insufficient	Sufficient	Indeterminate	Testicular/lung in specific animal strains

*Terms "suggestive" and "indeterminate" were used to apply to mode of action/mechanistic qualitative information.

Table 3. Integration of Evidence

Table 3. Summary of evidence integration for target organ systems

Target Organ System	Overall	Comments
Neurological	Sufficient	Evidence across all three data streams; historical use as an anesthetic.
Kidney	Sufficient	Evidence across all three data streams; GSH conjugation to toxic metabolites consistent with proximal tubule effects.
Hepatic	Sufficient	Evidence across all three data streams; weak human evidence.
Reproductive	Sufficient – (males)	Plausible testicular effects from all three data streams; none for females.
Developmental	Sufficient (weak)	Evidence from all three data streams for growth/development, Evidence for terrata considered insufficient (no evidence of terrata from inhalation exposures (human or animal); growth and reductions in offspring observed (oral).
Immune	Sufficient	Autoimmunity, immunosuppression
Kidney cancer	Sufficient	Site of cancer (proximal tubule) and potential carcinogen concordant.
Non-Hodgkin's Lymphoma	Insufficient	Consistency lacking in overall evidence.
Liver cancer	Insufficient	Relevance of animal evidence questionable.
Repro., lung, and other cancers	Insufficient	Variation in metabolism of metabolites in lung of rodents.

Dose-response

- Is there sufficient dose-response information to derive an inhalation POD?
  - Within animal and human LOEs
  - For each effect domain with sufficient evidence of hazard
- Scatter diagrams help support benchmark development:
  - Visualize variation potentially due to study design (species, exposure pathway, specific endpoint)
  - Suitable dose-response (i.e., multiple doses, exclude unbounded no-observed-adverse-effect level (NOAEL)/ lowest-observed-adverse-effect level (LOAEL))
  - Adequacy for Benchmark dose modeling (Frequentist or Bayesian)
  - Identify candidate PODs/key studies
- If inhalation data limited, supporting evidence sought from oral studies:
  - Reproductive
  - Developmental
  - Immune

Scatterplots of Studies (Neurological Effects)

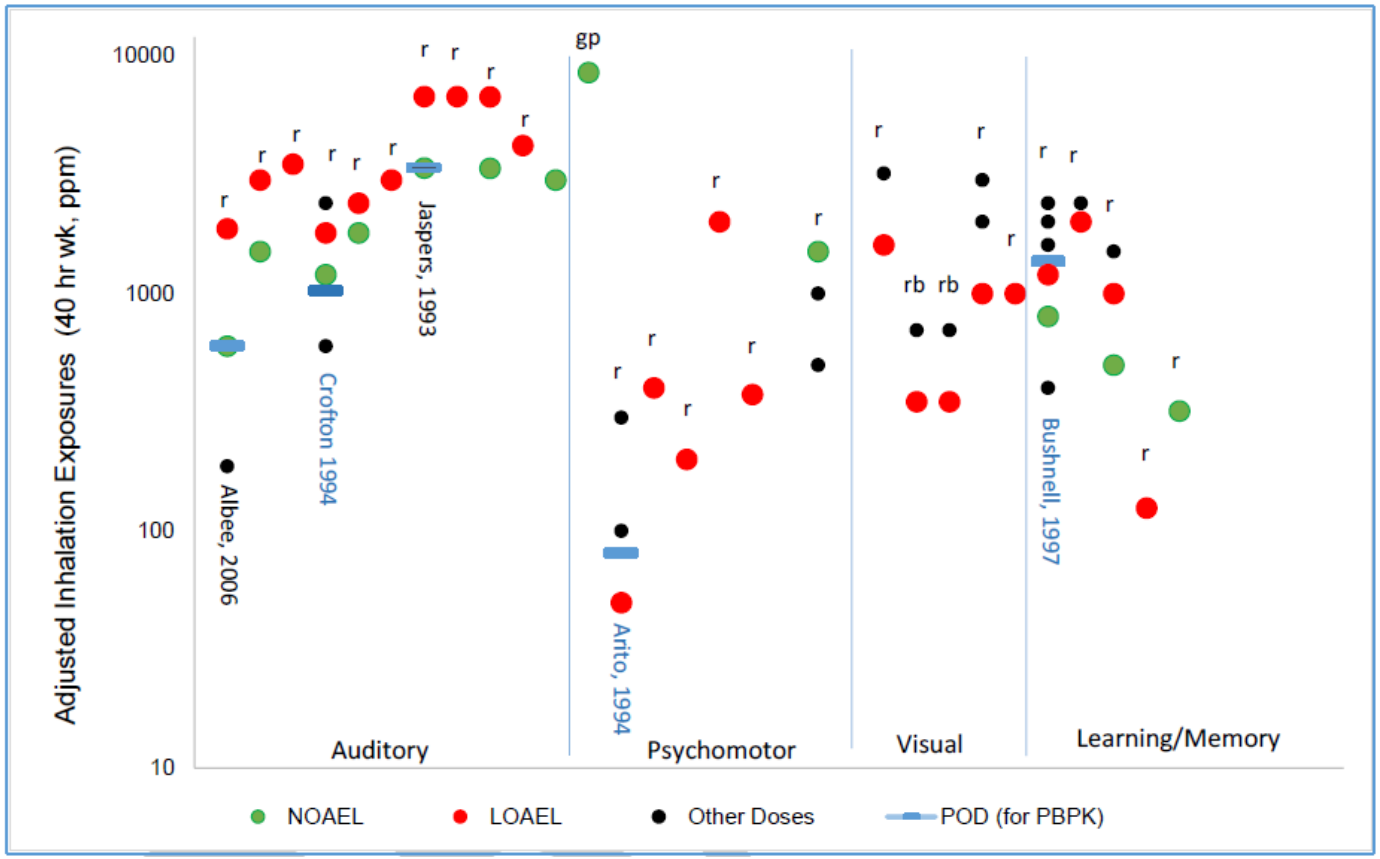


Figure 3. Neurological Effects. Comparison of exposures for neurological effects in a range of rodent inhalation studies with those selected as PODs. Exposure concentrations were time-adjusted for equivalence to a 40 h/wk for auditory and psychomotor effects, with the exception of visual and learning/memory effects which demonstrated greater reliance on exposure concentration rather than duration; therefore, concentrations were not adjusted to 40 h/wk for these effects. NOAEL values are represented with green circles, LOAEL values are red circles, and other exposure concentrations are black dots. All studies carried forward for PBPK analysis (Appendix B) are identified by name, with those suitable for BMD analysis further highlighted with blue text. Annotations within the graph indicate the animal model used (r: rat; gp: guinea pig; rb: rabbit) and type of endpoint measured (auditory, psychomotor, visual, learning/memory, sciatic nerve). See Tables 11 and 12 for HEC values derived from these studies as well as the overall selected OEL value for neurological effects; note that the blue lines identifying exposure derived PODs from selected studies are for comparison only, and these values were not used further for HEC development (see Appendix B).

Scatterplots of Studies (Kidney Effects)

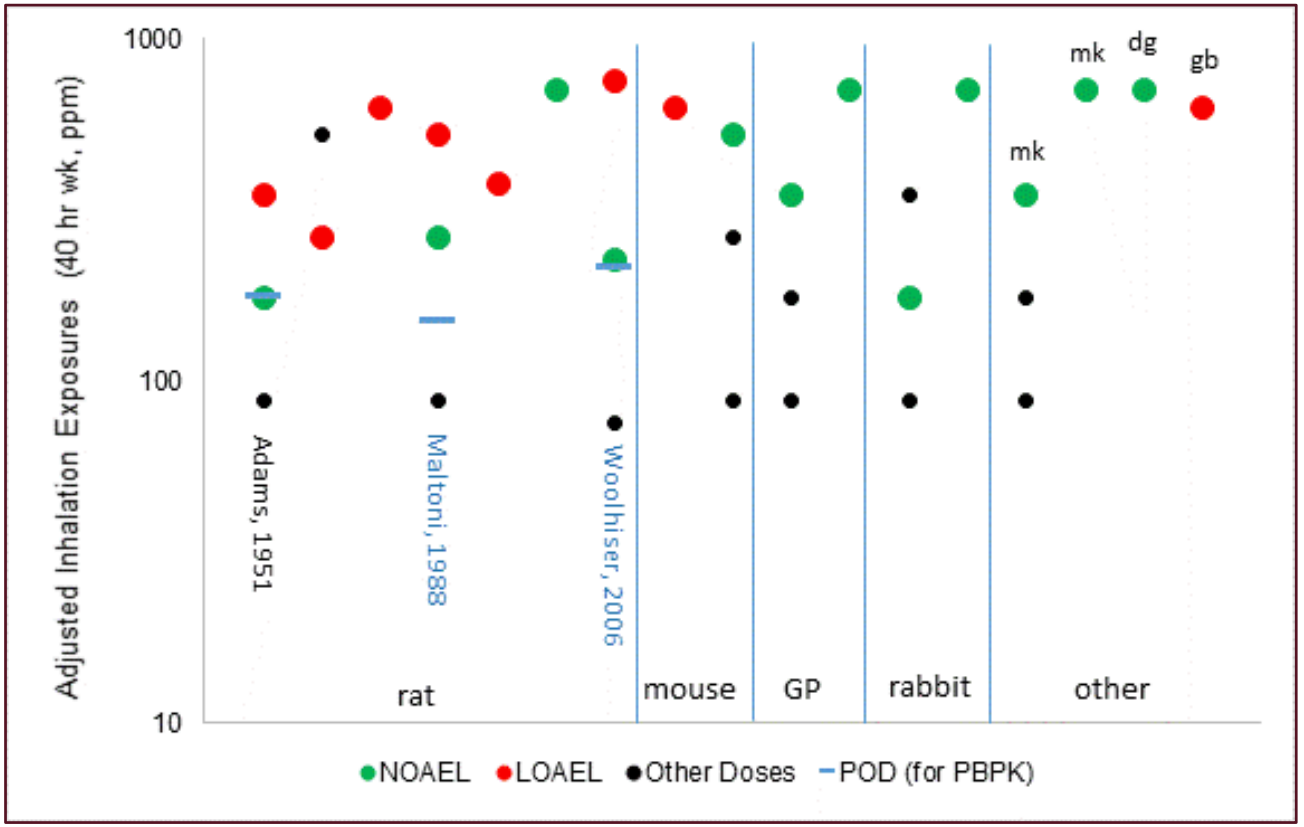


Figure 4. **Kidney Effects**. Comparison of kidney effects in a range of animal models due to inhalation exposures including those selected as PODs. Data from five animal model species shows comparison between exposure(s) and effects. Exposure concentrations were all adjusted to 40 h/wk for comparison purposes. NOAEL (green circles), LOAEL (red circles), other exposure concentrations (black dots). All PODs carried forward for PBPK analysis (Appendix B) are identified by name, with those suitable for BMD analysis further highlighted in blue text. Annotations within the graph indicate the animal model used (rat, mouse, GP: guinea pig, rabbit, other (mk = monkey, dg = dog, and gb=gerbil). See Tables 11 and 12 for HEC values derived from these studies as well as the overall selected OEL value for kidney; note that the blue lines identifying exposure derived PODs from selected studies are for comparison only, and these values were not used further for HEC development (see Appendix B).

Scatterplots of Studies (Reproductive Effects)

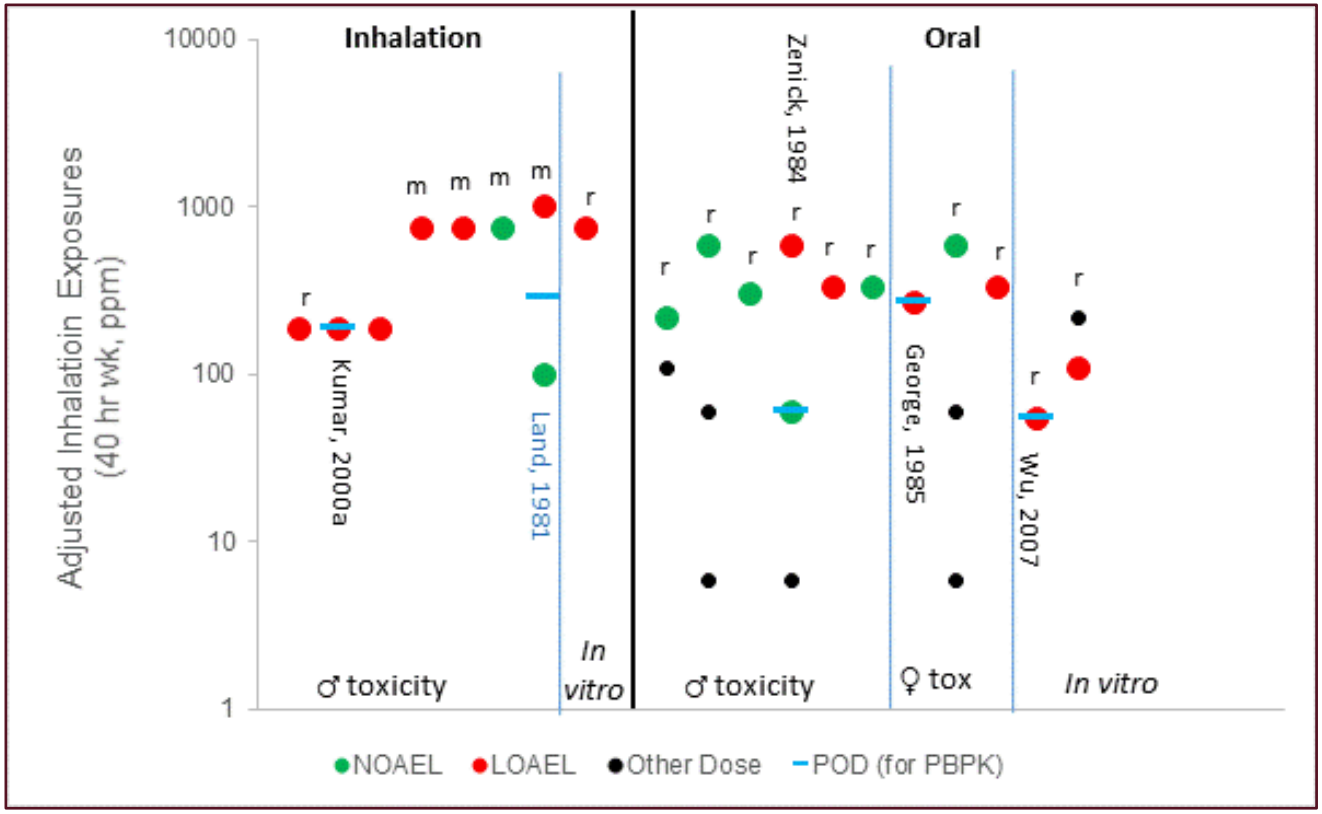


Figure 6. **Reproductive Effects**. Comparison of experimental studies by exposure route and sex. *In vitro* data are included for comparison purposes only. Included in dose-response analysis and derivation of candidate PODs for reproductive effects from both inhalation and oral exposures. Oral values were adjusted according to the methods and assumptions used in Appendix C. Inhalation exposure concentrations were adjusted to 40 h/wk, oral exposures were adjusted to 5 d/wk. NOAEL (green circles), LOAEL (red circles), other exposure concentrations (black dots). All PODs carried forward for PBPK analysis (Appendix B) are identified by name, with those suitable for BMD analysis further highlighted in blue text. Annotations within the graph indicate the animal model used (r: rat; m: mouse) and type of endpoint measured (male toxicity, *in vitro* effects, and female toxicity). See Tables 11 and 12 for HEC values derived from these studies as well as the overall selected OEL value for reproductive effects; note that the blue lines identifying exposure derived PODs from selected studies are for comparison only, and these values were not used further for HEC development (see Appendix B).

PBPK Modelling

- Derived human equivalent concentrations (HECs) for PODs using PBPK model:
  - Modeling support provided by the Air Force Research Laboratory (AFRL).
  - Update of harmonized TCE model developed with EPA.
  - BMD modeling with subsequent Uncertainty Factors (UFs) (Bayesian) performed on internal rodent dose metrics.
  - Initial rodent exposures adjusted to 40-hour week used for comparison purposes only (shown in Tables 11 and Appendix B).

TCE PBPK Model

- The AFRL previously worked with the EPA to develop a harmonized PBPK model for TCE:
  - Updated by EPA for use in their IRIS toxicological review.
  - AFRL noted some issues which were addressed prior to this current assessment.
- Modeling support provided by AFRL for the current assessment included:
  - Add code to the model to ensure mass balance in tissue blood flows and volumes.
  - Modify/edit the code to resolve instability in the model.
  - Regenerate the validation figures and re-run the sensitivity analysis.
  - Use the model to predict dose metrics for relevant endpoints for OEL determination for specific predetermined oral and inhalation studies.
- Updating report produced by AFRL “Translation of a Physiologically-Based Pharmacokinetic (PBPK) Model Used to Develop Health Protective Levels for Trichloroethylene” (AFRL-SA-WP-TR-2019-0006).

Table 9. PBPK Rodent Internal Dosimetry

Table 9. Internal rodent dosimetry of TCE from PBPK modeling of the unadjusted POD.
(Note: numbers in bold were further used in HEC development; green text = NOAEL; red text = LOAEL)

Study Name	Species	Sex	Route	Exposure Duration	Critical Effect	Dose(s) Simulated	Simulation	Peak TCE in Blood (mg/L)	TCE AUC Blood (mg hr/L/day)
Neurological									
Albee 2006	Rat	F	Inhalation	6 h/d, 5 d/w for 13 w	Hearing deficits/loss of cochlear hair cells	800 ppm	6 h/d, 5 d/w for 13 w	**55.8**	223
		M						**50.6**	200
Arito 1994	Rat	M	Inhalation	8 h/d, 5 d/w for 2, 4, or 6 w	Decreased wakefulness	50 ppm	8 h/d, 5 d/w for 6 w	**1.04**	5.95
						100 ppm		**2.24**	12.7
						300 ppm		**11.1**	56.8
						Estimated internal dose BMDL is 0.410 mg/L			
Bushnell 1997	Rat	M	Inhalation	1 h/d, 3 d/w for 2 w	Sensitivity to light stimulus (visual learning)	400 ppm	1 h/d for 1 day	**10.2**	11.4
						800 ppm		**26.6**	31.1
						1200 ppm		**43.7**	54.7
						1600 ppm		**61.0**	80.8
						Estimated internal dose BMDL is 35.6 mg/L			
Crofton 1997	Rat	M	Inhalation	6 h/d, 5 d/w for 1 d, 1 w, 4 w or 13 w	Auditory threshold at 13 wks	800 ppm	6 h/d, 5 d/w for 13 w	**46.1**	181
						1600 ppm		**110**	476
						2400 ppm		**175**	790
						3200 ppm		**240**	1114
						Estimated internal dose BMDL is 70.9 mg/L			
Jaspers 1993	Rat	M	Inhalation	18 h/d, 5 d/w for 3 w	Auditory threshold	1500 ppm	18 h/d, 5d/w for 3 w	**133**	1635
Kidney									
Adams 1951	Rat	F	Inhalation	7 h/d, ~5 d/wk for 6-8 mo	Relative kidney weight	200 ppm	7 h/d, 5 d/w for 6 w (until periodicity)	6.03	28.4
		M						5.36	25.7
Maltoni 1988	Rat	M	Inhalation	7 h/d, 5 d/w for 2 y	Meganucleocytosis (male rat only)	100 ppm	7 h/d, 6 d/w for 6 w (until periodicity)	2.11	10.6
						300 ppm		8.51	40.0
						600 ppm		30.3	134
						Estimated internal dose BMDL is 51.0 mg/kg$^{0.75}$/day			
Woolhiser 2006	Rat	F	Inhalation	6 h/d, 5 d/w for 4 w	Increased relative kidney weight	100 ppm	6 h/d, 5 d/w for 4 w	2.32	9.86
						300 ppm		12.5	47.4
						1000 ppm		72.8	298
						Estimated internal dose BMDL is 41.0 mg/kg$^{0.75}$/day			
Liver									
Adams 1951	Rat	F	Inhalation	7 h/d, ~5 d/wk for 6-8 mo	Relative liver weight	200 ppm	7 h/d, 5 d/w for 6 w (until periodicity)	6.03	28.4
		M						5.36	25.7
Kjellstrand 1983b	Mouse	F	Inhalation	Cont (30 or 120 d) Int (1-16 h/d, 7 d/w for 30 or 120 d)	Relative liver weight in mice (continuous exposure, 30 days)	37 ppm	Continuous for 30 d	0.790	19.0
		M						0.789	18.9
Kumar 2001a	Rat	M	Inhalation	4 h/d, 5 d/w for 12 or 24 w	Enlarged fatty hepatocytes (via histology)	376 ppm	4 h/d, 5 d/w for 7 w (until periodicity)	13.3	34.9
Ramdhan 2010	Mouse	M	Inhalation	8 h/d for 7 d	ALT	1000 ppm	8 h/d, 7d/w for 7 d	54.9	415
						2000 ppm		128	979
						Estimated internal dose BMDL is 106 mg/kg$^{0.75}$/day			
Woolhiser 2006	Rat	F	Inhalation	6 h/d, 5 d/w for 4 w	Increased relative liver weight	100 ppm	6 h/d, 5 d/w for 4 w	2.32	9.86
						300 ppm		12.5	47.4
						1000 ppm		72.8	298
						Estimated internal dose BMDL is 42.5 mg/kg$^{0.75}$/day			

Study Name	Total Metabolized (mg/kg$^{0.75}$/day)	Total Amount Metabolized by Oxidation (mg/kg$^{0.75}$/day)	Peak TCE in Liver (mg/L)	TCE AUC in Liver (mg-h/L/d)	TCE Metabolized in Liver (mg/kg$^{0.75}$/day)	Peak TCE in Kidney (mg/L)	TCE AUC in Kidney (mg-hr/L)	TCE Metabolized in Kidney (mg/kg$^{0.75}$/day)
Neurological								
Albee 2006	95.52	95.07						
	112.9	112.5						
Arito 1994	19.49	19.45						
	36.32	36.27						
	90.34	90.21						
Bushnell 1997	9.72	9.70						
	16.59	16.55						
	22.18	22.12						
	26.90	26.82						
Crofton 1997	127.8	127.4						
	167.9	166.6						
	192.2	190.0						
	209.9	206.8						
Jaspers 1993	241.2	237.7						
Kidney								
Adams 1951	**56.65**	56.59				7.369	34.62	0.04146
	58.92	58.85				6.545	31.41	0.04805
Maltoni 1988	**32.72**	32.66				2.569	12.87	0.05220
	87.03	86.92				10.389	48.76	0.07023
	131.43	131.06				37.003	163.05	0.08818
Woolhiser 2006	**26.76**	26.73				2.83247	12.03	0.031
	64.04	63.94				15.2509	57.83	0.043
	104.72	104.10				88.951	363.38	0.060
Liver								
Adams 1951	56.65	56.59	4.331	17.77	**53.07**			
	58.92	58.85	3.042	12.76	**54.86**			
Kjellstrand 1983b	146.4	146.3	0.3001	7.202	**41.62**			
	146.7	146.6	0.2973	7.134	41.60			
Kumar 2001a	57.29	57.20	13.26	27.56	**53.85**			
Ramdhan 2010	355.1	351.1	94.59	669.2	**285.5**			
	422.8	413.0	252.12	1851.1	**337.9**			
Woolhiser 2006	26.76	26.73	0.85	3.42	**23.98**			
	64.04	63.94	13.50	43.76	**60.44**			
	104.72	104.10	107.24	415.27	**99.00**			
Immunological								
Blossom 2017	**1.306**							
Gilbert 2014	**1.508**							
Griffin 2000	**9.150**	9.142						
	43.501	43.460						
	172.717	172.529						
Kaneko 2000	**135.1**	134.7						
Sanders 1982	**7.868**	7.861						
	8.295	8.288						
Woolhiser 2006	**26.76**	26.73						
	64.04	63.94						
	104.72	104.10						

Table 10. Human Equivalent Concentrations

Table 10. Human equivalent concentration (HEC) exposures modeled at 8 h/d, 5 d/w for 13 w that produce the target internal TCE concentration according to each metric derived in Table 9. (Green text = from NOAEL; red text = from LOAEL; blue text = from BMDS model)

Study Name	Species	Sex	Route	Rodent POD (internal dose)	HEC (ppm) Derived from PBPK Modelling of the POD					
					Peak TCE in Blood		TCE AUC in Blood		Total Metabolized	
					Male	Female	Male	Female	Male	Female
Neurological										
Albee 2006	Rat	F	Inhalation	50.59 mg/L	1625.0	1699.7	1156.7	1157.5	352.6	354.2
		M			**1492.8**	1558.8	1061.5	1061.0	439.9	445.4
Arito 1994	Rat	M	Inhalation	0.410 mg/L	**21.2**					
Bushnell 1997	Rat	M	Inhalation	35.60 mg/L	**1109.0**					
Crofton 1997	Rat	M	Inhalation	70.9 mg/L	**2007.0**					
Jaspers 1993	Rat	M	Inhalation	132.52 mg/L	**3554.2**	3753.4	6553.3	6536.3	1668.8	1616.7
Kidney										
Adams 1951	Rat	F	Inhalation	56.65 mg/kg$^{0.75}$/d	268.3	276.6	214.6	216.9	189.1	**186.5**
		M			242.7	250.9	196.8	199.4	197.8	195.2
Maltoni 1988	Rat	M	Inhalation	51.03 mg/kg$^{0.75}$/d					**168.3**	
Woolhiser 2006	Rat	F	Inhalation	40.97 mg/kg$^{0.75}$/d						**132.4**
Liver										
Adams 1951	Rat	F	Inhalation	53.1 mg/L (F)	268.3	276.6	214.6	216.9	189.1	186.5
		M		54.9 mg/L (M)	242.7	250.9	196.8	199.4	197.8	195.2
Kjellstrand 1983b	Mouse	F	Inhalation	41.62 mg/kg$^{0.75}$/d	40.3	43.4	149.0	152.4	648.8	661.9
		M			40.3	43.3	148.7	152.1	650.9	664.1
Kumar 2001a	Rat	M	Inhalation	53.85 mg/kg$^{0.75}$/d	506.8	517.6	257.2	258.6	191.6	188.9
Ramdhan 2010	Mouse	M	Inhalation	105.8 mg/kg$^{0.75}$/d						
Woolhiser 2006	Rat	F	Inhalation	42.51 mg/kg$^{0.75}$/d						
Immunological										
Blossom 2017	Mouse	F	Water	2.96 mg/kg/d						**3.7**
Gilbert 2014	Mouse	F	Water	3.42 mg/kg/d						**4.3**
Griffin 2000	Mouse	F	Water	8.1 mg/kg$^{0.75}$/d						**23.7**
Kaneko 2000	Mouse	M	Inhalation	135.1 mg/kg$^{0.75}$/d	640.7	656.1	409.6	407.6	**571.1**	582.2
Sanders 1982	Mouse	F	Water	18.4 mg/kg/d	0.7	0.7	2.7	2.8	23.6	**23.0**
		M			0.7	0.7	2.7	2.8	24.9	24.3
Woolhiser 2006	Rat	F	Inhalation	42.7 mg/kg$^{0.75}$/d						**135.6**
Reproductive										
George 1985	Mouse	M	Diet	750 mg/kg/d	154.5	162.2	200.6	203.1	**2696.0**	2546.0
Kumar 2000a	Rat	M	Inhalation	376 ppm	506.8	517.6	257.2	258.6	**191.6**	188.9
Land 1981	Mouse	M	Inhalation	89.2 mg/kg$^{0.75}$/d					**323.5**	
Wu 2007	Rat	F	Water	66 mg/kg/d	4.8	5.2	18.3	19.1	139.1	**136.3**
Zenick 1984	Rat	M	Water	100 mg/kg/d					**46.9**	
Developmental										
Blossom 2017	Mouse	F	Water	2.96 mg/kg/d						**3.7**
Carney 2006	Rat	F	Inhalation	124 mg/kg$^{0.75}$/d	1159.4	1204.0	1074.8	1074.4	502.3	**510.7**
Cosby 1992	Mouse	F	Gavage	240.2 mg/kg/d	540.2	551.9	81.3	84.2	282.9	**282.1**
Fisher 2001	Rat	F	Gavage	500 mg/kg/d	3343.8	3529.5	1271.2	1273.8	840.8	**853.1**
Healy 1982	Rat	F	Inhalation	25.4 mg/kg$^{0.75}$/d	108.9	115.7	72.4	75.1	79.6	**77.7**
Isaacson 1989	Rat	F	Water	11.1 mg/kg$^{0.75}$/d						**32.7**
Manson 1984	Rat	F	Gavage	66.1 mg/kg$^{0.75}$/d	783.0	805.2	157.4	160.7	225.7	**223.6**
Narotsky 1995	Rat	F	Gavage	11.8 mg/kg$^{0.75}$/d						**34.9**
Schwetz 1975	Mouse	F	Inhalation	193.4 mg/kg$^{0.75}$/d	399.2	408.2	449.1	446.3	1068.2	**1069.9**
Schwetz 1975	Rat	F	Inhalation	112.2 mg/kg$^{0.75}$/d	448.8	458.4	465.9	462.8	439.9	**445.4**

Study Name	HEC (ppm) Derived from PBPK Modelling of the POD											
	Total Amount Metabolized by Oxidation		Peak TCE in Liver		TCE AUC in Liver		TCE Metabolized in Liver		Peak TCE in Kidney		TCE AUC in Kidney		TCE Metabolized in Kidney	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Neurological														
Albee 2006	919.4	839.8												
	1314.4	1161.7												
Arito 1994														
Bushnell 1997														
Crofton 1997														
Jaspers 1993	>30,000	>30,000												
Kidney														
Adams 1951	292.5	307.2							214.3	222.5	170.1	173.5	3.9	4.0
	319.9	333.7							193.3	201.5	155.6	159.3	4.6	4.6
Maltoni 1988													5.1	
Woolhiser 2006														2.1
Liver														
Adams 1951	292.5	307.2	231.1	209.6	220.2	195.8	**292.8**	307.0						
	319.9	333.7	201.2	181.6	192.7	170.7	315.4	328.9						
Kjellstrand 1983b	2443.0	2364.9	68.9	61.3	152.1	134.0	**183.6**	189.2						
	2457.1	2386.4	68.5	60.9	151.5	133.4	183.5	189.0						
Kumar 2001a	299.7	314.3	369.8	342.6	263.4	235.6	**302.5**	316.5						
Ramdhan 2010							**1301.0**							
Woolhiser 2006								**196.5**						
Immunological														
Blossom 2017														
Gilbert 2014														
Griffin 2000														
Kaneko 2000	1973.8	1771.7												
Sanders 1982	25.7	25.1												
	27.1	26.5												
Woolhiser 2006														
Reproductive														
George 1985	>30,000	>30,000												
Kumar 2000a	299.7	314.3												
Land 1981														
Wu 2007	172.0	176.4												
Zenick 1984														
Developmental														
Blossom 2017														
Carney 2006	1613.2	1419.6												
Cosby 1992	634.2	607.1												
Fisher 2001	4221.4	>30,000												
Healy 1982	89.0	87.4												
Isaacson 1989														
Manson 1984	416.5	421.7												
Narotsky 1995														
Schwetz 1975	>30,000	>30,000												
Schwetz 1975	1319.5	1165.9												

Table 12. Uncertainty Factor Application

Table 12. Conversion of HECs to candidate occupational exposure levels via application of Bayesian uncertainty factors.

Study	Human Equivalent Concentration	ln(HEC)	Uncertainty Factor (UF)											Composite UF (Standard)	Composite UF (Bayesian)	Notes	ln(OEL)	Occupational Exposure Level
			UF_S	σ_{UFS}	UF_A	σ_{UFA}	UF_H	σ_{UFH}	UF_L	μ_{UFL}	σ_{UFL}	UF_D	σ_{UFD}					
Neurological																		
Albee 2006	1493 ppm	7.309	10	1.4	3	0.668	3	0.668	1	0	0	1	0	100	16.1		4.53	93 ppm
Arito 1994	21.2 ppm	3.052	1	0	3	0.668	3	0.668	1	0	0	1	0	10	4.7	UF_S=1; effect is not time dependent and is reversible with 24h	1.50	**4.5 ppm**
Bushnell 1997	1109 ppm	7.011	10	1.4	3	0.668	3	0.668	1	0	0	1	0	100	16.1		4.23	69 ppm
Crofton 1997	2007 ppm	7.604	10	1.4	3	0.668	3	0.668	1	0	0	1	0	100	16.1		4.83	125 ppm
Jaspers 1993	3554 ppm	8.176	10	1.4	3	0.668	3	0.668	1	0	0	1	0	100	16.1		5.40	221 ppm
Kidney																		
Adams 1951	187 ppm	5.231	1	0	3	0.668	3	0.668	1	0	0	1	0	10	4.7		3.68	40 ppm
Maltoni 1988	168 ppm	5.124	1	0	3	0.668	3	0.668	1	0	0	1	0	10	4.7		3.57	36 ppm
Woolhiser 2006	132 ppm	4.883	1	0	3	0.668	3	0.668	1	0	0	1	0	10	4.7	UF_S=1; see Kjellstrand 1983b	3.33	**28 ppm**
Liver																		
Adams 1951	293 ppm	5.680	1	0	3	0.668	3	0.668	1	0	0	1	0	10	4.7		4.13	62 ppm
Kjellstrand 1983b	184 ppm	5.215	1	0	3	0.668	3	0.668	10	1.504	0.531	1	0	100	26.8	UF_S=1; Rel Liver/Kidney weights at 120d not higher than at 30d.	1.93	**6.9 ppm**
Kumar 2001a	303 ppm	5.714	1	0	3	0.668	3	0.668	10	1.504	0.531	1	0	100	26.8		2.43	11 ppm
Ramdhan 2010	1301 ppm	7.171	10	1.4	3	0.668	3	0.668	1	0	0	1	0	100	16.2		4.39	81 ppm
Woolhiser 2006	197 ppm	5.281	1	0	3	0.668	3	0.668	1	0	0	1	0	10	4.7	UF_S=1; see Kjellstrand 1983b	3.73	42 ppm
Immunological																		
Blossom 2017	*3.73 ppm*	*1.316*	*1*	*0*	*3*	*0.668*	*2*	*0.421*	*1*	*0*	*0*	*1*	*0*	*6*	*3.7*	*UFH=2; autoimmune prone strain*	*0.02*	*1.0 ppm*
Gilbert 2014	*4.3 ppm*	*1.459*	*1*	*0*	*3*	*0.668*	*2*	*0.421*	*1*	*0*	*0*	*1*	*0*	*6*	*3.7*	*UF_H=2; autoimmune prone strain*	*0.16*	*1.2 ppm*
Griffin 2000	*23.7 ppm*	*3.165*	*1*	*0*	*3*	*0.668*	*2*	*0.421*	*1*	*0*	*0*	*1*	*0*	*6*	*3.7*	*UF_H=2; autoimmune prone strain*	*1.87*	*6.5 ppm*
Kaneko 2000	571 ppm	6.347	10	1.4	3	0.668	2	0.421	10	1.504	0.531	10	1.4	6000	166.9	UF_H=2; autoimmune prone strain, UFD=10; only 2 inhalation studies	1.23	**3.4 ppm**
Sanders 1982	*23.0 ppm*	*3.135*	*1*	*0*	*3*	*0.668*	*3*	*0.668*	*10*	*1.504*	*0.531*	*1*	*0*	*100*	*26.8*		*-0.15*	*0.9 ppm*
Woolhiser 2006	136 ppm	4.910	10	1.4	3	0.668	3	0.668	1	0	0	10	1.4	1000	37.0	UFD=10; only 2 inhalation studies	1.30	**3.7 ppm**
Reproductive																		
George 1985	*2696 ppm*	*7.900*	*1*	*0*	*3*	*0.668*	*3*	*0.668*	*10*	*1.504*	*0.531*	*1*	*0*	*100*	*26.8*	*UF_S=1; sperm assessed at the end of the cohabitation period*	*4.61*	*101 ppm*
Kumar 2000a	192 ppm	5.257	1	0	3	0.668	3	0.668	10	1.504	0.531	1	0	100	26.8		1.97	7.2 ppm
Land 1981	324 ppm	5.779	10	1.4	3	0.668	3	0.668	1	0	0	1	0	100	16.1		3.00	20 ppm
Wu 2007	*136 ppm*	*4.913*	*1*	*0*	*3*	*0.668*	*3*	*0.668*	*10*	*1.504*	*0.531*	*1*	*0*	*100*	*26.8*	*UF_S=1; exposed throughout sensitive period of oocyte maturation*	*1.63*	***5.1 ppm***
Zenick 1984	*153 ppm*	*5.030*	*10*	*1.4*	*3*	*0.668*	*3*	*0.668*	*1*	*0*	*0*	*1*	*0*	*100*	*4.9*		*2.25*	*9.5 ppm*
Developmental																		
Blossom 2017	*3.73 ppm*	*1.316*	*1*	*0*	*3*	*0.668*	*3*	*0.668*	*10*	*1.504*	*0.531*	*1*	*0*	*100*	*26.8*		*-1.97*	*0.14 ppm*
Carney 2006	511 ppm	6.236	1	0	3	0.668	3	0.668	1	0	0	1	0	10	4.7		4.68	108 ppm
Cosby 1992	*282 ppm*	*5.642*	*10*	*1.4*	*3*	*0.668*	*3*	*0.668*	*1*	*0*	*0*	*1*	*0*	*100*	*16.1*		*2.86*	*18 ppm*
Healy 1982	77.7 ppm	4.353	1	0	3	0.668	3	0.668	10	1.504	0.531	1	0	100	26.8		1.07	**2.9 ppm**
Isaacson 1989	*32.7 ppm*	*3.487*	*1*	*0*	*3*	*0.668*	*3*	*0.668*	*10*	*1.504*	*0.531*	*1*	*0*	*100*	*26.8*		*0.20*	*1.22 ppm*
Manson 1984	*224 ppm*	*5.412*	*1*	*0*	*3*	*0.668*	*3*	*0.668*	*1*	*0*	*0*	*1*	*0*	*10*	*4.7*		*3.86*	*47 ppm*
Narotsky 1995	*34.9 ppm*	*3.552*	*1*	*0*	*3*	*0.668*	*3*	*0.668*	*1*	*0*	*0*	*1*	*0*	*10*	*4.7*		*2.00*	*7.4 ppm*
Schwetz 1975 (m)	1070 ppm	6.975	1	0	3	0.668	3	0.668	1	0	0	1	0	10	4.7		5.42	226 ppm
Schwetz 1975 (r)	445 ppm	6.098	1	0	3	0.668	3	0.668	1	0	0	1	0	10	4.7		4.54	94 ppm

Flow of Non-Cancer Approach

Table 9. Internal rodent dosimetry of TCE from PBPK modeling of the unadjusted POD.
(Note: numbers in bold were further used in HEC development; green text = NOAEL; red text = LOAEL)

Study Name	Species	Sex	Route	Exposure Duration	Critical Effect	Dose(s) Simulated	Simulation	Peak TCE in Blood (mg/L)	TCE AUC in Blood (mg-h/L/d)
Neurological									
Albee 2006	Rat	F	Inhalation	6 h/d, 5 d/w for 13 w	Hearing deficits/loss of cochlear hair cells	800 ppm	6 h/d, 5 d/w for 13 w	55.80	222.8
		M						**50.59**	200.4
Arito 1994	Rat	M	Inhalation	8 h/d, 5 d/w for 2, 4, or 6 w	Decreased wakefulness	50 ppm	8 h/d, 5 d/w for 6 w	**1.04**	5.95
						100 ppm		**2.23**	12.68
						300 ppm		**11.10**	56.83

Table 10. Human equivalent concentration (HEC) exposures modeled at 8 h/d, 5 d/w for 13 w that produce the target internal TCE concentration according to each metric derived in Table 9. (Green text = from NOAEL; red text = from LOAEL; blue text = from BMDS model)

Study Name	Species	Sex	Route	Rodent POD (internal dose from Table 9)	Adjusted external exposure (for comparison)	HEC (ppm) Derived from PBPK Modelling of the POD					
						Peak TCE in Blood		TCE AUC in Blood		Total Metabolized	
						Male	Female	Male	Female	Male	Female
Neurological											
Albee 2006	Rat	F	Inhalation	50.59 mg/L	600 ppm	1625.0	1699.7	1156.7	1157.5	352.6	354.2
		M				1492.8	1558.8	1061.5	1061.0	439.9	445.4
Arito 1994	Rat	M	Inhalation	0.410 mg/L	80.7 ppm	**21.2**					

BMDL

Table 12. Conversion of HECs to candidate occupational exposure levels via application of Bayesian uncertainty factors.

Study	Human Equivalent Concentration	ln(HEC)	Uncertainty Factor (UF)											Composite UF (Standard)	Composite UF (Bayesian)	Notes	ln(OEL)	Occupational Exposure Level
			UF_S	σ_{UF_S}	UF_A	σ_{UF_A}	UF_H	σ_{UF_H}	UF_L	μ_{UF_L}	σ_{UF_L}	UF_D	σ_{UF_D}					
Neurological																		
Albee 2006	1493 ppm	7.309	10	1.4	3	0.668	3	0.668	1	0	0	1	0	100	16.1		4.53	93 ppm
Arito 1994	21.2 ppm	3.052	1	0	3	0.668	3	0.668	1	0	0	1	0	10	4.7	UF_D=1; effect is not time dependent and is reversible with 24h	1.50	**4.5 ppm**

HEC

OEL (Bold)

Cancer Risk Assessment

- Both human and animal LOEs provide sufficient evidence of association between TCE exposure and **kidney cancer:**
  - Evidence from animal studies is less consistent than human studies.
  - Human kidney cancer demonstrates exposure-response trend.
  - Human LOE used for dose response assessment:
    - One high quality study available (Charbotel et al. 2006).
    - Case-control study, renal carcinoma.
    - Job matrix related to average level of exposure (low/med/high).
- EPA 2011 no-threshold linear regression of Odds Ratio (OR) (est. of Relative Risk (RR) of Renal Cell Carcinoma (RCC) vs. cumulative exposure (ppm x yrs):
  - Slope 0.001205 (95% Upper Confidence Level (UCL) 0.002554).
- Suggestion of threshold effects based on metabolism and high dose effects.

Cancer Risk Assessment

- Lifetable analysis to calculate extra risk from **occupational** exposure:
  - SEER database: age-dependent RCC incidence rates (R_x)
  - Background RCC rate (R_o) = 0.01074
  - Extra risk (R_x-R_o)/(1-R_o) = 7.86E-04; Relative Risk R_x/R_o = 1.0724
- POD determined based on 1% extra risk (assumed risk/ unit risk):
  - Consistent with EPA 2011, Guidelines for Cancer Risk Assessment
  - Effective Concentration for 1% Extra Risk (EC_{01}) = 26.97 ppm
  - Lower Effective Concentration (LEC_{01}) = 12.73 ppm

Cancer Risk Assessment

Table 6. Extra risk calculation for renal cell carcinoma due to occupational exposure to 1 ppm TCE

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
Interval number (i)	Age interval	All cause mortality (x 10^5/yr)	RCC incidence (x 10^5/yr)	All cause hazard rate (h*)	Prob. of surviving interval (q)	Prob. of surviving up to interval (S)	RCC cancer hazard rate (h)	Cond. prob. of RCC incidence in interval (Ro)	Exp. duration mid interval (xtime)	Cum. exp. mid interval (xdose)	Exposed RCC hazard rate (hx)	Exposed all cause hazard rate (h*x)	Exposed prob. of surviving interval (qx)	Exposed prob. Of surviving up to interval (Sx)	Exposed cond. prob. of RCC in interval (Rx)
1	<1	685.2	0	0.0069	0.9932	1.0000	0.000000	0.000000	0	0	0.000000	0.0069	0.9932	1.0000	0.000000
2	1-4	29.9	0	0.0012	0.9988	0.9932	0.000000	0.000000	0	0	0.000000	0.0012	0.9988	0.9932	0.000000
3	5-9	14.7	0	0.0007	0.9993	0.9920	0.000000	0.000000	0	0	0.000000	0.0007	0.9993	0.9920	0.000000
4	10-14	18.7	0.1	0.0009	0.9991	0.9913	0.000005	0.000005	0	0	0.000005	0.0009	0.9991	0.9913	0.000005
5	15-19	66.1	0.1	0.0033	0.9967	0.9903	0.000005	0.000005	0	0	0.000005	0.0033	0.9967	0.9903	0.000005
6	20-24	94	0.2	0.0047	0.9953	0.9871	0.000010	0.000010	0	0	0.000010	0.0047	0.9953	0.9871	0.000010
7	25-29	96	0.7	0.0048	0.9952	0.9824	0.000035	0.000034	2.5	2.5	0.000035	0.0048	0.9952	0.9824	0.000035
8	30-34	107.9	1.6	0.0054	0.9946	0.9777	0.000080	0.000078	7.5	7.5	0.000082	0.0054	0.9946	0.9777	0.000080
9	35-39	151.7	3.2	0.0076	0.9924	0.9725	0.000160	0.000155	12.5	12.5	0.000165	0.0076	0.9924	0.9725	0.000160
10	40-44	231.7	6.3	0.0116	0.9885	0.9651	0.000315	0.000302	17.5	17.5	0.000329	0.0116	0.9885	0.9651	0.000316
11	45-49	352.3	11	0.0176	0.9825	0.9540	0.000550	0.000520	22.5	22.5	0.000582	0.0176	0.9825	0.9540	0.000550
12	50-54	511.7	17.3	0.0256	0.9747	0.9373	0.000865	0.000801	27.5	27.5	0.000926	0.0256	0.9747	0.9373	0.000857
13	55-59	734.8	26.2	0.0367	0.9639	0.9137	0.001310	0.001175	30	30	0.001410	0.0368	0.9638	0.9136	0.001265
14	60-64	1140.1	36.2	0.0570	0.9446	0.8807	0.001810	0.001549	30	30	0.001949	0.0571	0.9445	0.8805	0.001668
15	65-69	1727.4	44.6	0.0864	0.9173	0.8319	0.002230	0.001777	30	30	0.002401	0.0865	0.9171	0.8316	0.001913
16	70-74	2676.4	49	0.1338	0.8747	0.7631	0.002450	0.001750	30	30	0.002638	0.1340	0.8746	0.7627	0.001883
17	75-79	4193.2	51.6	0.2097	0.8109	0.6675	0.002580	0.001554	30	30	0.002778	0.2099	0.8107	0.6670	0.001671
18	80-84	6717.2	44.4	0.3359	0.7147	0.5412	0.002220	0.001021	30	30	0.002390	0.3360	0.7146	0.5408	0.001098
						0.3868	Ro=	0.010735951						Rx=	0.011513282
Extra risk = (Rx-Ro)/(1-Ro) = 7.86E-04															
Relative Risk = Rx/Ro = 1.072404															

Notes: Column A: interval index number (*i*).
Column B: 5-year age interval (except <1 and 1–4) up to age 85.
Column C: all-cause mortality rate for interval *i* (× 10^5/year) (2004 CDC data).
Column D: RCC incidence rate for interval *i* (× 10^5/year) (2001–2005 SEER data).
Column E: all-cause hazard rate for interval *i* (*h*i*) = all-cause mortality rate × number of years in age interval.
Column F: probability of surviving interval *i* without being diagnosed with RCC (*qi*) = e^{-h^*i}.
Column G: probability of surviving up to interval *i* without having been diagnosed with RCC (*Si*) [*S1* = 1; *Si* = *Si*–1 × *qi*–1, for *i* > 1].
Column H: RCC incidence hazard rate for interval *i* (*hi*) = RCC incidence rate × number of years in interval.
Column I: conditional probability of being diagnosed with RCC in interval *i* = (*hi*/*h*i*) × *Si* × (1–*qi*) (i.e., conditional upon surviving up to interval *i* without having been diagnosed with RCC).
Column J: exposure duration (in years) at mid-interval (xtime).
Column K: cumulative exposure mid-interval (xdose) = exposure level (i.e., 1 ppm) × xtime.
Column L: RCC incidence hazard rate in exposed people for interval *i* (*hxi*) = *hi* × (1 + β × xdose), where β = 0.001205 for MLE, and β = 0.002554 for UCL. The analysis presented in Table 7 is of UCL risk; however Table 7 includes both UCL and MLE risk.
Column M: all-cause hazard rate in exposed people for interval *i* (*h*xi*) = *h*i* + (*hxi* – *hi*).
Column N: probability of surviving interval *i* without being diagnosed with RCC for exposed people (*qxi*) = e^{-h^*xi}.
Column O: probability of surviving up to interval *i* without having been diagnosed with RCC for exposed people (*Sxi*) [*Sx1* = 1; *Sxi* = *Sxi*–1 × *qxi*-1, for i > 1].
Column P: conditional probability of being diagnosed with RCC in interval *i* for exposed people = (*hxi*/*h*xi*) × *Sxi* × (1–*qxi*).

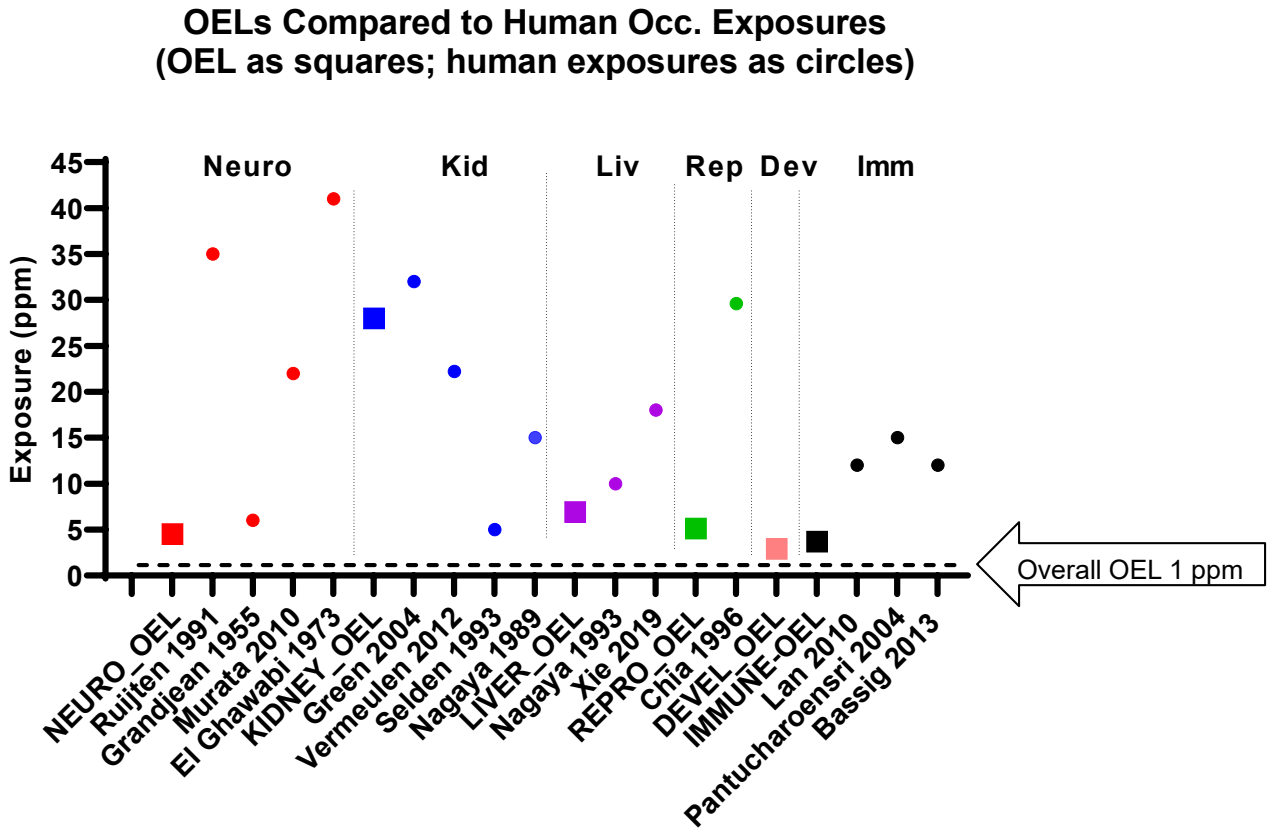
Final OEL Values

Table 14. Occupational Exposure Level for each of the health effects domains

Domain	Rat POD* (ppm)	HEC (ppm)	RSC (OEL; ppm)	RSC (OEL; mg/m^3)	Critical Effect
Neurological	80.7	21.2	4.5	24	wakefulness
Kidney	214	132	28.0	150	kidney weight
Liver	155	184	6.9	37	liver weight
Reproductive	54.5	136	5.1	27	In vitro fertilization of oocytes
Developmental	70	77.7	2.9	16	resorptions, fetal weight
Immunological	193	136	3.3	20	decreased PFC response
Cancer (10^{-2} Risk) 30y			130	700	Kidney
Cancer (10^{-2} Risk) 45y			61	327	Kidney
Cancer (10^{-3} Risk) 30y			13	70	Kidney
Cancer (10^{-3} Risk) 45y			6.1	32.7	Kidney
Cancer (10^{-4} Risk) 30y			1.3	7.0	Kidney
Cancer (10^{-4} Risk) 45y			0.6	3.3	Kidney

*This value is the 40 hr week adjusted rodent exposure (See Table 11) for comparison to the HEC. See Appendix B and Table 9 for actual rodent PODs and HEC derivations.

OEL Values Compared to Human Exposures



"The final OEL value based on kidney cancer (dotted line above) is lower than all the non-cancer derived OELs as well as measures of exposure from human studies."

Final Slide

- **DISCUSSION**