Air Toxics Hot Spots Program

Inhalation Cancer Unit Risk Factor for Perchloroethylene (PCE; Tetrachloroethylene)

Office of Environmental Health Hazard Assessment (OEHHA)

Scientific Review Panel Presentation
June 24, 2016

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PCE Cancer Unit Risk Factor Update

- **Update based on new scientific information**
- **OEHHA (2009) Methodology:**

  Air Toxics Hot Spots Program Risk Assessment Guidelines: Part II, Technical Support Document for Cancer Potency Factors; **"Cancer TSD"**

- **Added to appendix B of the Cancer TSD**

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PCE Cancer Unit Risk Factor Update

Risk Assessment Process
Hazard Identification
Dose-Response Analysis*
Exposure Assessment
Risk Characterization

*** Scope of Unit Risk Factor Update document**

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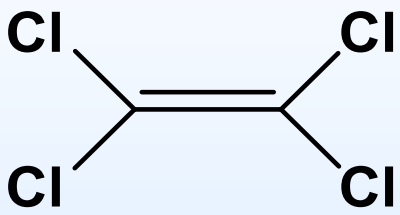
Perchloroethylene (PCE)



- Chemical intermediate, solvent, & cleaning agent
- Volatile: vapor pressure = 18.47 mm Hg @ 25^{o}C
- 2010 Air Emissions in California estimated by Air Resources Board at 3,832 tons per year

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Previous OEHHA Evaluation

- Listed as a Toxic Air Contaminant (TAC) in 1991
- OEHHA cancer potency analysis in 1992
- National Toxicology Program (NTP) 1986 inhalation study (mouse liver tumors)
- Simple pharmacokinetic model used to estimate metabolized doses
- 1992 URF = 5.9×10^{-6} $(\mu g/m^3)^{-1}$

Epidemiology

- **Numerous studies, but none suitable for quantitative assessment**
- **Epidemiologic studies suggest that PCE exposure increases three types of cancer in humans:**
  - Bladder cancer
  - Non-Hodgkin's lymphoma
  - Multiple myeloma

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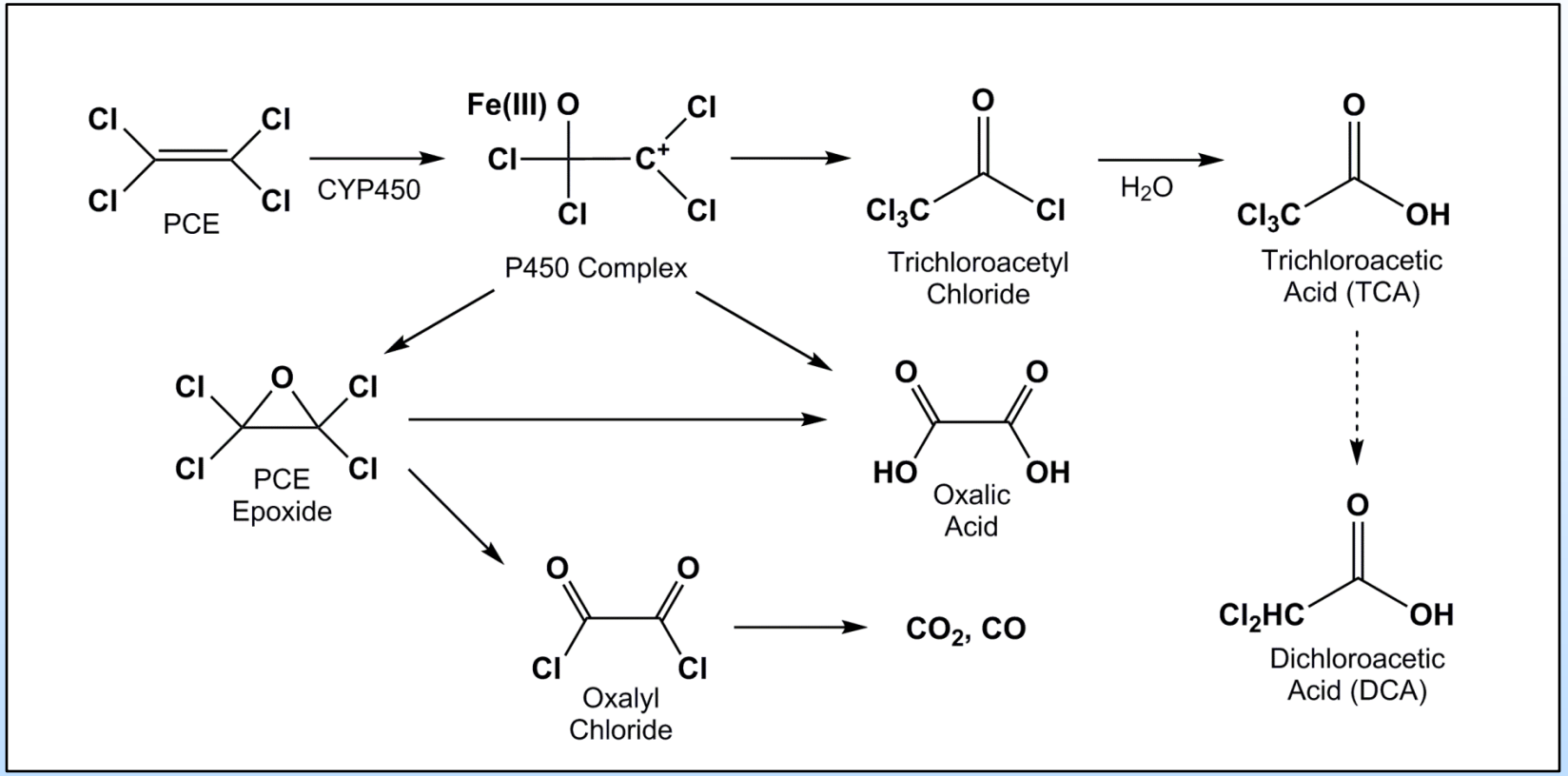
PCE Metabolism: Oxidation



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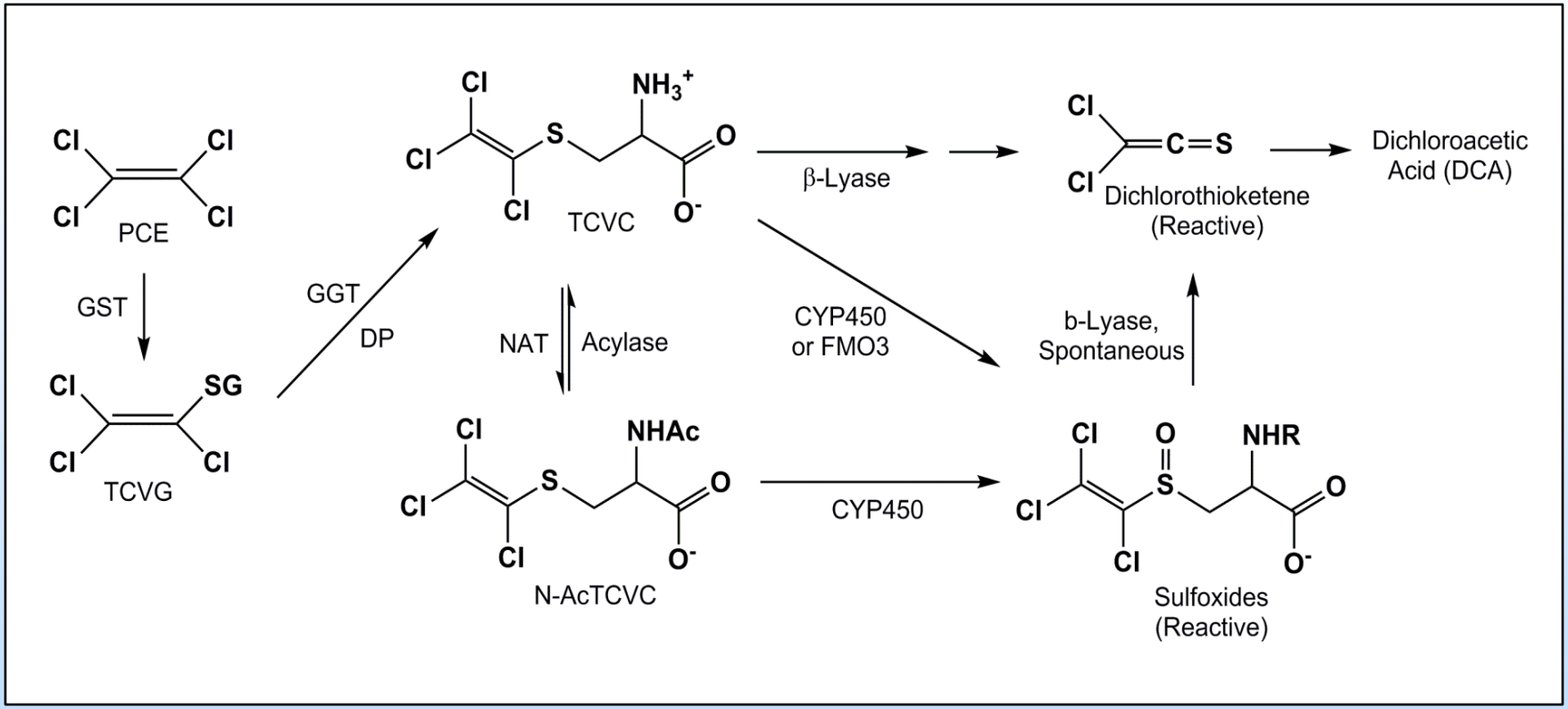
PCE Metabolism: GSH Conjugation



DP:	Dipeptidase	GST:	Glutathione-S-transferase
FMO3:	Flavin mono-oxygenase 3	R:	Acyl group or hydrogen
N-AcTCVC:	N-Acetyl trichlorovinyl cysteine	SG:	Glutathione
NAT:	N-Acetyl transferase	TCVG:	Trichlorovinyl glutathione
GGT:	γ-Glutamyl transferase	TCVC:	Trichlorovinyl cysteine

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Reactive and Genotoxic or Tumorigenic Metabolites

Oxidative Pathway	GSH Conjugation Pathway
PCE epoxide	Dichlorothioketene
Trichloroacetyl chloride	Dichloroacetic acid
Oxalyl chloride	α,β-Unsaturated sulfoxides of TCVC and N-AcTCVC
Trichloroacetic acid	

New Studies Used in Update

Japan Industrial Safety & Health Association study (JISHA, 1993):

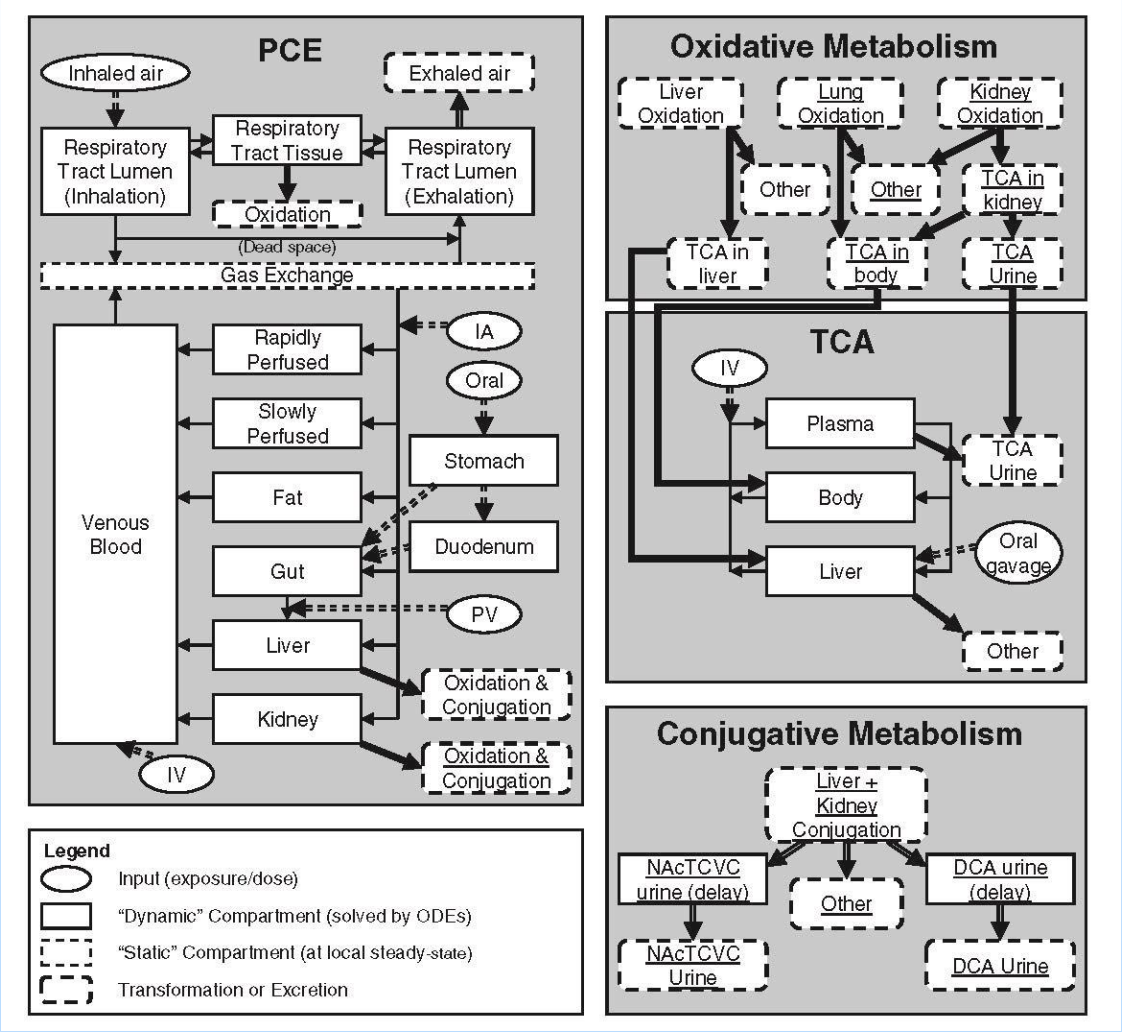
- Lifetime inhalation exposure to mice and rats
  Similar to NTP (1986) in procedures and reporting
- Used additional low-dose groups
- Japanese F344 rats have a lower background rate of mononuclear cell leukemia (MCL)

New Studies Used in Update

Chiu and Ginsberg PBPK model (2011):

- Used Bayesian Markov Chain Monte Carlo (MCMC) method
- Most likely values (posterior modes) for key metabolic parameters
- Calibrated / evaluated using wide range of data from rodent and human studies
- Included a separate GSH-conjugation pathway
- Incorporated trichloroacetic acid toxicokinetics

Chiu and Ginsberg PBPK Model

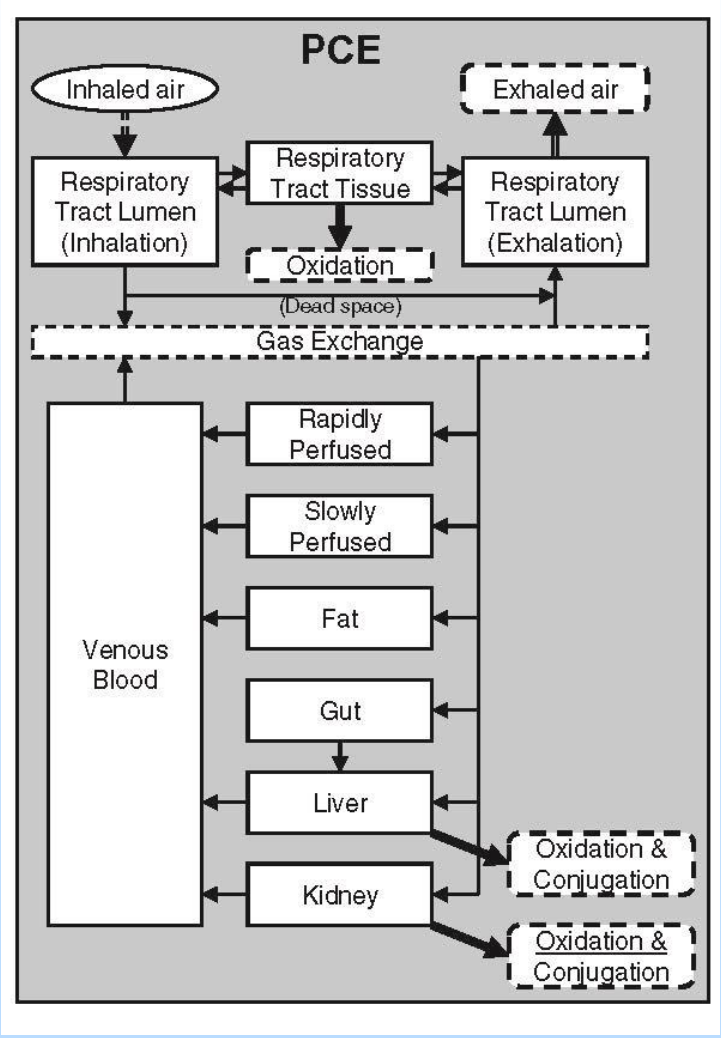


(From: Chiu and Ginsberg, 2011)

Bayesian Analysis with PBPK Model

- **Statistical method to determine the most probable values for important PBPK parameters (rate constants)**
- **Calibration using *in vivo* data on PCE & metabolites**
- **Several routes of exposure and elimination (e.g., inhalation, oral, intra-venous, exhalation, urinary, etc.)**
- **Most likely values then used in PBPK model to predict internal doses ("traditional" PBPK)**
- **Can use Bayesian results to estimate inhalation-only doses**

Inhalation-Only Extract of the Chiu and Ginsberg (2011) Model



- Same blood/air flow compartments as Chiu and Ginsberg
- Includes wash-in / wash-out
- Oxidation: liver, kidney, lung
- GSH conjugation: liver, kidney
- Uses posterior modes and other parameters from Chiu and Ginsberg
- Reproduces Chiu and Ginsberg inhalation results

PCE Internal Dose Metrics

Chiu and Ginsberg (2011) PBPK Model Results

Inhalation Dose (posterior mode estimates)

Dose metric	Exposure Concentration (ppm)				Prediction Range (at 1 ppm)
	0.01	***1***	***10***	***100***	
PCE AUC Blood	*(mg-hr)/(L-d) per ppm* [a]				
Mouse	2.1	2.2	2.4	2.6	2.2-2.4
Rat	2.25	2.25	2.25	2.25	2.25-2.27
Human	2.0	2.0	2.0	2.0	2.0-2.4
PCE Oxidation	*Percent of intake that is oxidized* [a]				
Mouse	18.8	17.4	11.8	7.3	11.5-17.9
Rat	4.2	4.2	4.1	3.3	3.9-4.2
Human	0.98	0.98	0.98	0.98	0.69-1.0
PCE Conjugation	*Percent of intake that is conjugated* [a]				
Mouse	0.015	0.016	0.021	0.025	0.0068-0.43
Rat	0.31	0.31	0.31	0.32	0.20-0.50
Human	9.4	9.4	9.4	9.4	0.003-10.0 (bimodal)[b]

(a) Values are also obtained using OEHHA's model extract at the presented significance level. Data from Chiu and Ginsberg (2011), Tables S-6 through S-8.
(b) Values are presented for higher probability, upper mode.

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NTP 1986 Dose-Response Data

Mice (B6C3F1)				
Tumor Type	Sex	Adjusted Rates[(a)(b)]		
		0	100	200
Hepatocellular adenoma or carcinoma	M	17/49**	31/47**	41/50**
	F	4/44**	17/42**	38/47**

Rats (F344/N)				
Tumor Type	Sex	Adjusted Rates[(a)(b)]		
		0	200	400
Mononuclear cell leukemia (MCL)	M	28/50*	37/48*	37/50*
	F	18/49*	30/50*	29/50*
Renal tubule adenoma or carcinoma	M	1/47[(c)]	3/42	4/40
Brain glioma	M	1/44[(c)]	0/37	4/35
Testicular interstitial cell	M	35/49[(c)]	39/46	41/50

(a) Tumor-incidence denominator adjusted by excluding animals dying before the first corresponding tumor type observed in each study.

(b) Statistical test indicators: (*) P-value < 0.05; (**) P-value < 0.005. Fischer exact test results are as reported by NTP. The control group column indicates the results of trend tests. Both the Cochran-Armitage trend test (reported by NTP) and the exact trend test calculated by OEHHA gave the same indications of significance.

(c) Although testicular tumors and brain glioma did not appear to be significantly increased by the Fischer exact and trend tests, life table tests conducted by NTP did show a significant increase with trends of <0.001, and 0.039 respectively. The life table trend test for kidney was nearly significant at 0.054.

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JISHA 1993 Dose-Response Data

Mice (Crj:BDFr)					
Tumor Type	Sex	Adjusted Rates[(a)(b)]			
		0	10	50	250
Hepatocellular adenoma or carcinoma	M	13/46**	21/47	19/47	40/49**
	F	3/44**	3/41	7/40	33/46**
Hemangioma or hemangiosarcoma (All site)	M	4/46*	2/47	7/47	9/49*
Harderian gland adenoma	M	2/41**	2/45	2/37	8/39

Rats (F344/DuCrj)					
Tumor Type	Sex	Adjusted Rates[(a)(b)]			
		0	50	200	600
Mononuclear cell leukemia (MCL)	M	11/50**	14/48	22/50	27/49*
	F	10/50[(c)]	17/50	16/50	19/50

(a) Tumor-incidence denominator adjusted by excluding animals dying before the first corresponding tumor type observed in each study.

(b) Statistical test indicators: (*) P-value < 0.05; (**) P-value < 0.005. Fischer exact test results are as reported by JISHA, except that mouse, all-site hemangioma/hemangiosarcoma values were calculated by OEHHA. The control group column indicates the results of trend tests. Both the Cochran-Armitage trend test (reported by JISHA) and the exact trend test calculated by OEHHA gave the same indications of significance.

(c) A significant trend was found in a life-table test reported by JISHA, P-value = 0.049.

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Cancer Modeling Approach

- **Assume that PCE acts primarily through its genotoxic metabolites**
- **Use data from NTP (1986) and JISHA (1993)**
- **Use Chiu and Ginsberg PBPK model extract**
  - Estimate rodent internal doses
  - Calculate Human Equivalent Concentrations (HECs)
- **Dose metric = PCE oxidation + GSH conjugation**
- **Calculate single and multi-tumor risks**
- **Consider uncertainty in choosing "best estimate"**

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Dose-Response Analysis

- US EPA Benchmark Dose Software (BMDS)
- Multi-stage cancer model; low-dose linearity
- Benchmark risk (BMR) = 5 percent
- BMDL: lower 95%-ile of benchmark dose
- Use BMDS multi-tumor summation
- Cross-species adjustment of BMDL based on ¾-power body-weight scaling

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Multi-Stage Cancer Model Results

Study	Sex	Tumor Type	BW-Scaled BMDL (mg/kg-day)	HEC based on PBPK Model (ppm)	Unit Risk Factor (URF) per ug/m^3
Results from Mouse Studies					
JISHA	M	Hepatocellular adenoma or carcinoma	0.350	2.14	3.5E-06
		Harderian gland	1.997	12.20	6.0E-07
		Hemangioma or Hemangiosarcoma	2.100	12.83	5.7E-07
		Combined site	0.300	1.83	4.0E-06
	F	Hepatocellular adenoma or carcinoma	0.574	3.51	2.1E-06
NTP	M	Hepatocellular adenoma or carcinoma	0.272	1.66	4.4E-06
	F	Hepatocellular adenoma or carcinoma	0.432	2.64	2.8E-06
Results from Rat Studies					
JISHA	M	Mononuclear cell leukemia	0.251	1.53	4.8E-06
	F	Mononuclear cell leukemia	0.472	2.88	2.6E-06
NTP	M	Mononuclear cell leukemia	0.144	0.88	8.4E-06
		Testicular interstitial cell	0.136	0.83	8.9E-06
		Renal adenoma or carcinoma	0.913	5.57	1.3E-06
		Brain glioma	1.426	8.71	8.5E-07
		Combined site	0.078	0.47	1.6E-05
	F	Mononuclear cell leukemia	0.188	1.15	6.4E-06

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Multi-Stage Cancer Model Results

Combined-site male mouse risk mainly due to liver tumors

Male Mouse (JISHA)	URF
Hepatocellular adenoma or carcinoma	3.5E-06
Harderian gland	6.0E-07
Hemangioma or hemangiosarcoma	5.7E-07
Combined site	4.0E-06

Highest URF: Combined-site risk in male rats in NTP study

(Mostly due to MCL and testicular tumor risks)

Male Rat (NTP)	URF
Mononuclear cell leukemia	8.4E-06
Testicular interstitial cell	8.9E-06
Renal adenoma or carcinoma	1.3E-06
Brain glioma	8.5E-07
Combined site	1.6E-05

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Multi-Stage Cancer Model Results

JISHA – NTP Comparison

Study	Sex	Unit Risk Factor (URF) per ug/m^3
Mouse: Hepatocellular adenoma or carcinoma		
JISHA	M	3.5E-06
NTP	M	4.4E-06
JISHA	F	2.1E-06
NTP	F	2.8E-06
Rat: Mononuclear cell leukemia (MCL)		
JISHA	M	4.8E-06
NTP	M	8.4E-06
JISHA	F	2.6E-06
NTP	F	6.4E-06

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Considerations in Choosing the URF

Mouse liver tumors and rat MCL

- Qualitative and quantitative agreement in the primary studies
- Mouse liver tumors also found in the NCI (1977) oral study
- Judged to be more certain

Other rat tumors in NTP study

- Important to consider but less certain
- Testicular tumors: high background rate (control group = 71%)

Considerations in Choosing the URF

Male rodents more sensitive than females

- **URFs clustered in a narrow range: 4.0×10^{-6} to 1.6×10^{-5} $(\mu g/m^3)^{-1}$**

Use geometric mean of the male mouse and rat URFs from both studies

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Proposed Perchloroethylene Cancer Unit Risk Factor and Potency Factor

Species	Study	URF
Male Mouse	JISHA (Multiple site)	4.02E-06
	NTP (Liver)	4.44E-06
Male Rat	JISHA (MCL)	4.81E-06
	NTP (Multiple site)	1.57E-05
	Geometric Mean	6.06E-06

- **Therefore: URF = 6.1 x 10^{-6} ($\mu g/m^3$)$^{-1}$**
  (when rounded to two significant figures)
- **Cancer potency factor = 2.1 x 10^{-2} (mg/kg-day)$^{-1}$**
  (assumes a 70 kg person breathing 20 m^3/day of air)

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Proposed Perchloroethylene Cancer Unit Risk Factor and Potency Factor

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Response to Public Comments

Public comment was received from:

- Center for Public Environmental Oversight (CPEO)
- U.S. Department of Defense (DoD)
- California Chamber of Commerce (CalChamber)
- Halogenated Solvents Industry Alliance (HSIA)

Total of 44 individual and compound comments and were addressed in OEHHA's written response

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Response to Public Comments

- **Several criticisms were shared by the commenters**
- **For presentation, the major issues and OEHHA responses were grouped:**
  1. Not following US EPA methods
  2. PBPK inhalation model
  3. Use of the NTP study data
  4. Use of rat MCL data

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Response to Public Comments

- **Major issues, continued:**

5. Use of total metabolized dose
6. Use of multiple tumor types
7. Use of geometric mean for final URF
8. Need for more uncertainty analysis

Response to Public Comments

Issue #1: Did not follow US EPA guidelines; should adopt US EPA (2012) PCE potency value

Response: OEHHA has independent responsibility under California law to develop cancer potency values for protecting the health of Californians. Our PCE potency update is based on our 2009 Cancer TSD methodology. The Cancer TSD was reviewed and approved by the Scientific Review Panel on Toxic Air Contaminants.

Response to Public Comments

Issue #1, Continued:

OEHHA agrees with some of US EPA's methods, Thus portions of the Cancer TSD are consistent with US EPA guidance. However, OEHHA's methodology is not exactly the same as US EPA's, and where it differs, it tends to be more health-protective.

OEHHA used the currently available scientific information on PCE, and developed a potency estimate that is consistent with our guidelines, considered uncertainties in the data, and is health-protective.

Response to Public Comments

Issue #2: PBPK model not validated; unclear that it reproduces Chiu and Ginsberg model results

Response: OEHHA's model extract uses the relevant inhalation equations and modeling parameter values from Chiu and Ginsberg (2011), including the posterior modes for key model parameters, determined via the MCMC simulation. Chiu and Ginsberg's equations, input parameters, and model results were peer-reviewed and validated. Our use of the inhalation-only components of the Chiu and Ginsberg model is not a reanalysis of the data.

Response to Public Comments

Issue #2, Continued:

Table 1 of the draft presents dose-metric estimates that were reported by Chiu and Ginsberg (2011) and were also obtained by OEHHA using its inhalation-only model, at the level of significance presented in the table. Based on the concordance of the estimates, the inhalation-only model adequately reproduces the original model results.

Response to Public Comments

Issue #3: OEHHA should not use the NTP (1986) data

Response: Different strains and substrains of rats and mice used in carcinogenicity testing programs display genetic and phenotypic variation as a result of mechanisms such as genetic drift.

The two rodent cancer studies (JISHA & NTP) showed variability with respect to types of tumor elevated, and strength of the dose-response relationships. It is unknown whether the differences are due to genetic variation, but this observation suggests that data from each study provides non-redundant information for the analysis.

Response to Public Comments

Issue #4: Should justify / not use Rat MCL data:

- **Not a relevant tumor type in humans, F344 rats have a high background rate**

Response: OEHHA does not require tumor concordance between rodents and humans to use rodent data in dose-response analysis, per our 2009 Cancer TSD.

The draft discussed evidence that rat MCL corresponds to at least one form of human leukemia: Large Granular Lyphocyte Leukemia. It may arise from a lymphocyte or monocyte lineage; the cell of origin appears to reside or undergo transformation in the spleen.

Response to Public Comments

Issue #4 Continued:

US EPA and NRC also noted (during the 2010 peer review of the US EPA's PCE analysis):

> *"discounting a rodent neoplasm simply because it has no human counterpart is not a scientifically defensible position. Strict site concordance is not a requirement for relevance in extrapolation of hazard potential."*

The JISHA (1993) study had a relatively low control group rate for MCL (20-22%). This was at the high end of historical laboratory background (6-22%) for the rat substrain, so a false positive result is unlikely.

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Response to Public Comments

Issue #5: Justify chosen dose metric; Should not use GSH conjugation because of large uncertainty

Response: The precise mechanisms by which PCE causes increased tumor formation are unknown. However, oxidation and conjugation of PCE in rodents and humans produce several potentially genotoxic and/or tumorigenic metabolites. Some of these are stable enough to circulate widely throughout the organism. Also, PCE metabolism showed saturation effects in the rodent studies. Thus, the metabolized dose is a reasonable choice for the dose metric.

Response to Public Comments

Issue #5 Continued:

Dose metrics used by US EPA (oxidation pathway in liver and PCE AUC for other tissues) avoid use of the GSH-conjugation pathway but may be less accurate and are less health-protective than using total metabolism.

The PBPK results for GSH conjugation could be due to biological variation within the population (as opposed to modeling uncertainty). Some humans are devoid of one or more GST isoforms, which may contribute to a large range of PCE-conjugation levels. Also, there is some evidence that long-term PCE exposure may induce GST metabolism.

Response to Public Comments

Issue #5 Continued:

There is still substantial uncertainty regarding the formation of reactive α,β-unsaturated sulfoxides in the GSH-conjugation pathway, which may be more important in humans than in rodents.

Including the GST-pathway in the total dose-metric, vs. using an oxidation-only dose increases the PCE cancer potency factor approximately 11-fold.

Population variability and toxicokinetic uncertainty is properly addressed by making appropriate health-protective assumptions in the cancer potency assessment.

Response to Public Comments

Issue #5 Continued:

OEHHA has included additional discussion in the document on the uncertainty/variation in the human PBPK model, and on the choice of a total metabolism dose-metric over other alternatives.

Response to Public Comments

Issue #6: Should not use tumor types other than liver tumors in mice

Response: The use of data from multiple tumors in the mouse and rat is based on the 2009 Cancer TSD:

> "...for chemicals that induce tumors at multiple sites, the single-site approach may underestimate the true carcinogenic potential. For example, the overall assessment of cancer risk from cigarette smoking […] is estimated from all the sites at which agent induced tumors are observed (lung, bladder, leukemia, etc), combined."

Response to Public Comments

Issue #6 Continued:

In addition, the draft includes sections justifying the use of rat MCL and renal tumors (α2u-globulin discussion).

OEHHA does not require interspecies tumor concordance and generally uses all tumor types that appear to be statistically elevated in the exposed groups.

Response to Public Comments

Issue #7: Should justify / not use the geometric mean of multiple potency estimates; instead choose a value from a single tumor type

Response: The cancer TSD suggests, as a default option, identifying a single study that represents the best estimate of potency, but does not prohibit using alternative methods (e.g. geometric mean) for deriving potency factors.

Response to Public Comments

Issue #7 Continued:

Both the JISHA (1993) and the NTP (1986) studies provided acceptable and non-redundant dose-response information suitable for a quantitative estimate of cancer potency. Because some of the higher potency estimates are more uncertain, OEHHA chose a mid-range potency from the available values (i.e., the geometric mean) as a best estimate for PCE's cancer potency, a value that the Office also judged to be adequate to protect public health.

Response to Public Comments

Issue #8: No uncertainty analysis in document; need a comprehensive uncertainty analysis

Response: OEHHA discussed various uncertainties in the first draft and we have added to this in the revised document, covering several of the more important aspects effecting the potency factor derivation.

Chiu and Ginsberg (2011) provided a detailed quantitative uncertainty analysis for their PBPK model. US EPA explored the range of PCE potency estimates obtained using various dose metrics. OEHHA considered and referenced all of this information in deriving the PCE potency update.

Response to Public Comments

Issue #8 Continued:

It is neither necessary nor desirable to carry out a comprehensive uncertainty analysis. The National Academy of Sciences (*Science and Decisions, Advancing Risk Assessment*, 2009) states that:

> "If an uncertainty analysis will not substantially influence outcomes of importance to the decision maker, resources should not be expended on a detailed uncertainty analysis..."