Air Toxics Hot Spots Program

Inhalation Cancer Unit Risk Factor (IUR)

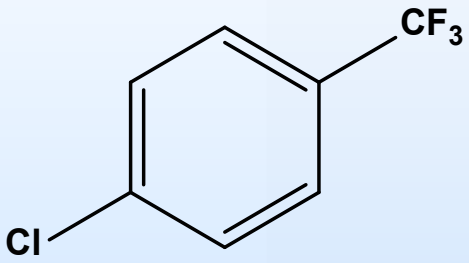
para-Chloro-α,α,α-trifluorotoluene (*para*-Chlorobenzotrifluoride, PCBTF)

Office of Environmental Health Hazard Assessment

February 27, 2020 SRP Review

PCBTF

Selected physical/chemical properties of PCBTF



Molecular weight	180.55 g/mole
Boiling point	139.3 deg C
Melting point	-33 deg C
Vapor pressure	7.63 mm Hg (25 deg C)
Log octanol-water partition coefficient	3.60 (25 deg C) (estimated)
Water solubility	29 mg/L (25 deg C)
Air concentration conversion	1 ppm = 7.38 mg/m^3

PCBTF: Uses and Exposure Potential

- Used in the preparation of dyes, pharmaceuticals, pesticides, and as a solvent in paints, inks, and high-solids coatings; also for metal cleaning
- Production in and import into the US was 5,000 to 25,000 tons-per-year from 2012 through 2015 (US EPA)
- Little information is available regarding air emissions of PCBTF in California
- Exposure could occur from the use of products that contain PCBTF, from contact with contaminated groundwater or soil, or from consumption of food products containing PCBTF residues

PCBTF: Toxicokinetics

- **Limited information from rat studies indicates that PCBTF is:**
  - **Readily absorbed orally and by inhalation**
    - **100% absorption in rats exposed to 10, 50, or 400 mg/kg by oral gavage (NTP, 1992)**
    - **Rat blood-air partition coefficient of 43.7 - ratio of concentration in blood vs. exposure concentration, at equilibrium (Knaak, et al., 1997)**

PCBTF: Toxicokinetics

- **Widely distributed throughout the body, with a tendency to concentrate in fatty tissues**

PCBTF Tissue concentrations in female rats exposed by inhalation to 390 mg/m^3 for 6 hours (umol/L)	
Fat	999
Lung	99.3
Brain	52.7
Kidney	45.9
Liver	36.3
Blood	33.1
Muscle	19.9

(Newton et al., 1998)

PCBTF: Toxicokinetics

- In rats, PCBTF is mainly excreted unchanged via exhalation
  - ~ 60% to 80% (Quistad and Mulholland, 1983)
  - ~ 80% to 90% (Knaak, et al., 1998)
- Secondarily metabolized via aromatic hydroxylation, and excreted as conjugated phenolic compounds
  - ~ 8% (Knaak, et al., 1998)
- Converted in small amounts to mercapturic acid metabolites (Quistad and Mulholland, 1983)

PCBTF: Toxicokinetics

Physiologically-Based Pharmacokinetic (PBPK) Model

- A PBPK model for PCBTF inhalation exposure to rats and humans was developed by Knaak, *et al.* (1995; 1998)
- Included compartments for liver, brain, fat, kidney, and slowly and rapidly perfused organs
- Metabolism represented by model components for:
  - CYP450 oxidation in the liver
  - Glucuronide conjugation of phenolic metabolites
  - Glutathione conjugates

PCBTF: Toxicokinetics

Physiologically-Based Pharmacokinetic (PBPK) Model

OEHHA judged the model to be incomplete:

- **Inadequate model validation - The only *in vivo* data available to verify the model was from a single 50 ppm exposure concentration in female rats**
- **The blood and tissue concentrations of PCBTF predicted by the rat model deviated from the experimental data during post-exposure periods**
- **Human model was not based on experimentally derived metabolic constants, nor was it tested against experimental data**
- **No mouse model**

PCBTF: Carcinogenicity

- The cancer hazard and dose-response evaluation of PCBTF is based on recent animal cancer studies by the National Toxicology Program (NTP, 2018)
- NTP exposed both sexes of B6C3F1 mice and Hsd:Sprague Dawley SD rats (groups of 50) by inhalation for 6.2 hours/day, 5 days/week, 104-to-105 weeks
- Mice were exposed to 100, 200, or 400 ppm and rats to 100, 300, or 1000 ppm
- Animals were necropsied and histopathologic examination of all relevant tissues (more than 40 sites) was performed

PCBTF: Carcinogenicity

Tumor incidence in mice (NTP, 2018) [a,b]				
	PCBTF Concentration			
ppm	0	100	200	400
mg/m^3	0	740	1500	3000
Female				
Harderian Gland: Adenoma or Adenocarcinoma	2/50*	6/50	9/50*	8/50*
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma	18/50**	18/50	29/50**	46/50**
Male				
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma	31/50**	37/50	40/50*	48/50**

(a) The numerator represents the number of tumor-bearing animals; the denominator represents animals examined microscopically (for liver), or the number of animals necropsied (for Harderian gland).

(b) * = $p<0.05$, ** = $p<0.01$; p-value indicators are from pairwise comparisons with controls using Fisher exact tests performed by OEHHA; indicators in the control column are for a Cochran-Armitage trend test performed by OEHHA.

PCBTF: Carcinogenicity

Tumor incidence in rats (NTP, 2018) [a,b]				
	PCBTF Concentration			
ppm	0	100	300	1000
mg/m^3	0	738	2214	7380
Female				
Adrenal Medulla: Benign or Malignant Pheochromocytoma	0/49	4/50	4/50	6/50*
Thyroid Gland (C-cell): Adenoma or Carcinoma	2/50**	10/50*	8/50*	15/50**
Uterus: Stromal Polyp or Stromal Sarcoma	7/50	9/50	17/50*	12/50
Uterus: Adenocarcinoma	1/50**	1/50	0/50	5/50
Male				
Lung: Alveolar/bronchiolar Adenoma or Carcinoma (equivocal)	0/50	2/50	0/50	3/50
Thyroid Gland (C-cell): Adenoma or Carcinoma	3/50**	5/49	4/49	13/50**

(a) The numerator represents the number of tumor-bearing animals; the denominator represents animals examined microscopically (for adrenal gland, lung, and thyroid gland), or the number of animals necropsied (for uterus).

(b) * = $p<0.05$, ** = $p<0.01$; p-value indicators are from pairwise comparisons with controls using Fisher exact tests performed by OEHHA; indicators in the control column are for a Cochran-Armitage trend test performed by OEHHA.

PCBTF: Carcinogenicity

No studies of increased cancer incidence in humans resulting from PCBTF exposure were identified in the literature.

PCBTF: Genotoxicity

Genotoxicity data come from several published studies and unpublished industry reports:

Test Type	**Number of Studies** (# with positive results)
DNA damage and repair	3 (1)
Gene mutation	8 (0)
Chromosomal damage	7 (2)

PCBTF: Genotoxicity

- **Negative results for:**
  - **DNA damage and gene mutation assays in bacteria and yeast**
  - **Chromosomal damage assays in yeast**
  - **Gene mutations in mouse lymphoma cells**

PCBTF: Genotoxicity

- **Positive results for:**
  - **Unscheduled DNA synthesis (UDS) in human embryonic epithelial cells**
  - **Sister chromatid exchanges (SCE) in mouse lymphoma cells**
- **Mixed results for:**
  - ***In vivo* mature erythrocyte micronucleus formation: male and female rat (-), female mouse (-), male mouse (+)**

PCBTF: Cancer Hazard Summary

- **The NTP (2018) studies were well-designed and implemented lifetime studies, carried out in both sexes of B6C3F1/N mice and Hsd:Sprague Dawley SD rats**
- **The studies found that lifetime exposure of rats and mice to PCBTF by inhalation can produce an elevated incidence of tumors in the following tissues:**

Mouse	**Female**	**Harderian gland and liver**
	Male	**Liver**
Rat	**Female**	**Adrenal gland, thyroid gland and uterus**
	Male	**Thyroid gland**

PCBTF: Cancer Hazard Summary

- PCBTF is readily absorbed in rats and is subject to oxidative metabolism, which could result in the production of potentially genotoxic metabolites.
- The metabolism of PCBTF in humans is likely to be qualitatively similar to that observed in the rat
- The available genotoxicity test data provides limited evidence that PCBTF is a genotoxic substance
- The carcinogenic mode(s) of action of PCBTF are not known
- OEHHA recently listed PCBTF as a substance “known to the state to cause cancer” under Proposition 65 (OEHHA, 2019)

PCBTF: Unit Risk Derivation

OEHHA's Standard Approach:

- **Cancer risk factors calculated for tumors with significant tumor incidence and/or positive dose-response trend**
- **Risk factors estimated for incidence of one or more related tumors at each tumor site:**
  - **"Tumor types considered to represent different stages of progression following initiation of a common original normal cell type are combined..." (OEHHA 2009 guidelines)**

PCBTF: Unit Risk Derivation

OEHHA's Standard Approach (cont'd):

- **Crude incidence rates adjusted to correct for differential early-mortality amongst dose groups**
- **Data modeled using US EPA Benchmark Dose Software (BMDS 2.7)**
- **Multistage Cancer Model chosen for modeling (OEHHA default for typical cancer data sets)**
- **Benchmark Response (BMR) of 5% (extra risk) used to calculate the Benchmark Dose (BMD)**

PCBTF: Unit Risk Derivation

OEHHA's Standard Approach (cont'd):

- **The 95% lower confidence bound on the BMD (the BMDL) used to calculate cancer potency**
- **Multi-site BMDL calculated when tumors occur at more than one site in a species (OEHHA uses the BMDS multisite tumor model, "MS-Combo")**
- **Cancer Slope Factor (CSF) = BMR (0.05) / BMDL**
- **Cancer inhalation unit risk (IUR) then calculated from CSF**

PCBTF: Unit Risk Derivation

- **Differential early-mortality adjustment**
  - **Avoids underestimation of risk due to high early mortality.**
- **OEHHA adjustment methods:**
  - **“Effective tumor incidence”: Used for mouse data, where mortality differences of less than 15% were observed at week 85 of study**
  - **“Poly-3 adjustment”: Used for rat data, where larger mortality differences (~15-30%) were seen at week 85**

PCBTF: Unit Risk Derivation

- **Effective tumor incidence:**
  - **The number of tumor-bearing animals divided by the number of animals alive at time of first occurrence of the tumor**
- **Poly-3 adjustment:**
  - **For each animal dying early without the tumor of interest, a fractional amount is added to the denominator according to the following equation:**

$$\text{Contribution to denominator} = \left(\frac{\text{Time in study}}{2 \text{ years}}\right)^3$$

PCBTF: Unit Risk Derivation

Adjusted tumor incidence in mice [(a)]				
	Concentration			
ppm	0	100	200	400
mg/m^3	0	740	1500	3000
Female Mice				
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma	18/47	18/48	29/46	46/47
Harderian Gland: Adenoma or Adenocarcinoma	2/49	6/49	9/49	8/48
Male Mice				
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma	31/50	37/50	40/49	48/49

(a) Incidence ratio after adjusting for intercurrent mortality using the effective number adjustment method.

PCBTF: Unit Risk Derivation

Adjusted tumor incidence in rats [(a)]				
	Concentration			
ppm	0	100	300	1000
mg/m^3	0	740	2200	7400
Female rats				
Adrenal Medulla: Benign or Malignant Pheochromocytoma	0.0%	10.7%	9.9%	13.5%
Thyroid Gland (C-cell): Adenoma or Carcinoma	5.5%	25.5%	20.2%	33.6%
Uterus: Stromal Polyp or Stromal Sarcoma	19.6%	23.8%	41.8%	27.2%
Uterus: Adenocarcinoma	2.9%	2.7%	0.0%	11.3%
Male rats				
Lung: Alveolar/bronchiolar Adenoma or Carcinoma	0.0%	5.3%	0.0%	9.3%
Thyroid Gland (C-cell): Adenoma or Carcinoma	7.6%	13.4%	10.6%	39.2%

(a) Percent tumor incidence after adjusting the number of animals at risk using the poly-3 adjustment method. Values are as reported by NTP (2018).

PCBTF: Unit Risk Derivation

- **The lifetime average daily dose (LADD) was calculated for each of the exposed groups:**

LADD (mg/kg BW-day) = IR × C / BW

Where:

C = time-adjusted exposure concentration, mg/m^3

(6.2 hr / 24 hr) × (5 days / 7 days)

BW = body weight, kg (average over 2-year exposures)

IR = inhalation rate, m^3/day (based on BW of animal)

IR calculation:

mice: IR (m^3/day) = 0.0345 m^3/day × (BW / 0.025 kg)$^{2/3}$

rats: IR (m^3/day) = 0.702 × (BW)$^{2/3}$

PCBTF: Unit Risk Derivation

BMDS Modeling Results					
Sex	**Tumor Types**	**Poly-nomial Degree**	**BMD** (mg/kg-day)	**BMDL** (mg/kg-day)	**Animal CSF** (mg/kg-day)$^{-1}$
Mice					
M	Liver: hepatocellular adenoma, carcinoma, or hepatoblastoma	1	15.04	10.52	4.75E-03
F	Liver: hepatocellular adenoma, carcinoma, or hepatoblastoma	2	84.36	43.55	1.15E-03
F	Harderian gland: adenoma or adenocarcinoma	1	179.86	99.19	5.04E-04
F	Multi-site female mouse tumor risk	2	66.86	35.65	1.40E-03

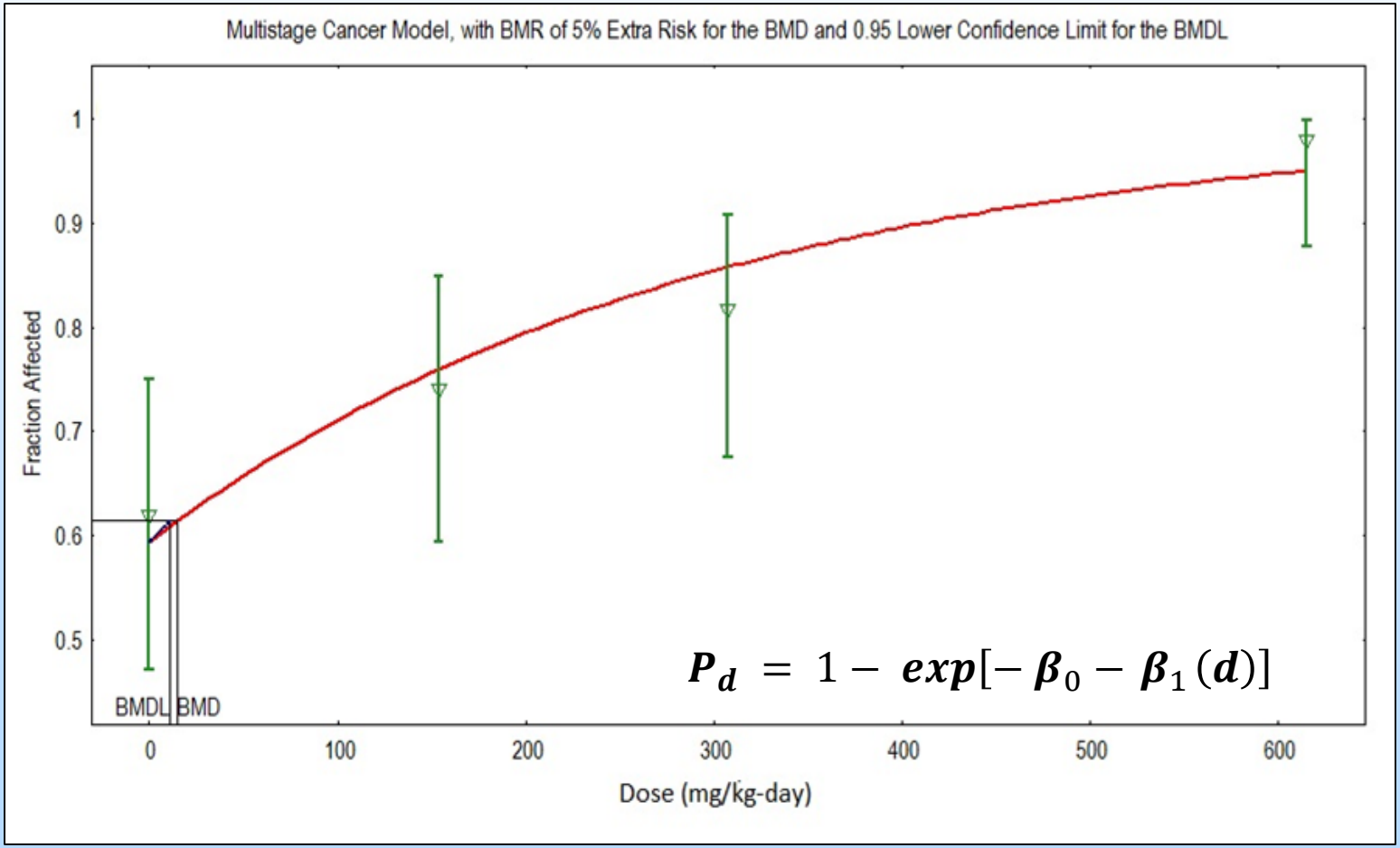
PCBTF: Unit Risk Derivation

BMDS Modeling Results					
Sex	**Tumor Types**	**Poly-nomial Degree**	**BMD** (mg/kg-day)	**BMDL** (mg/kg-day)	**Animal CSF** (mg/kg-day)$^{-1}$
Rats					
M	Lung: alveolar/bronchiolar adenoma or carcinoma	1	816.06	329.09	1.52E-04
M	Thyroid gland (C-cell): adenoma or carcinoma	1	167.62	102.72	4.87E-04
M	Multi-site male rat tumor risk	1	139.06	84.19	5.94E-04
F	Adrenal medulla: benign or malignant pheochromocytoma	1	498.0	236.29	2.12E-04
F	Thyroid gland (C-cell): adenoma or carcinoma	1	246.63	136.89	3.65E-04
F	Uterus: stromal polyp or sarcoma [(a)]	1	68.48	37.86	1.32E-03
F	Uterus: adenocarcinoma	1	988.42	458.09	1.09E-04
F	Multi-site female rat tumor risk	1	46.13	24.56	2.04E-03

[(a)] In this instance, the data from the highest dose group was dropped in order to obtain an acceptable fit.

PCBTF: Unit Risk Derivation

BMDS Multistage Cancer Model plot fit for liver tumors in male mice exposed to PCBTF



PCBTF: Unit Risk Derivation

- **Converting the animal CSF values to human equivalent CSFs using body-weight scaling:**

$$\mathbf{CSF}_{(\text{human})} = \mathbf{CSF}_{(\text{animal})} \times \left(\frac{\mathbf{BW}_{(\text{human})}}{\mathbf{BW}_{(\text{animal})}} \right)^{1/4}$$

- **Interspecies weight-scaling adjusts for pharmacokinetic differences (*e.g.*, breathing rate, metabolism), and for pharmacodynamic considerations (*i.e.*, tissue responses to chemical exposure)**

PCBTF: Unit Risk Derivation

Cancer slope factors					
Species	**Sex**	**Tumor Sites**	**Animal BMDL** (mg/kg-day)	**Animal CSF** (mg/kg-day)$^{-1}$	**Human CSF** (mg/kg-day)$^{-1}$
Mouse	M	Liver	10.52	4.75E-03	3.0E-02
	F	Liver + Harderian gland	35.65	1.40E-03	8.8E-03
Rat	M	Thyroid + Lung	84.19	5.94E-04	2.0E-03
	F	Thyroid + Adrenal gland + Uterus	24.56	2.04E-03	7.9E-03

PCBTF: Inhalation Unit Risk (IUR)

$$IUR = \left(\frac{CSF \times BR}{BW \times CV}\right)$$

- Human breathing rate (BR) of 20 m^3/day
- Average human body weight (BW) of 70 kg
- mg to µg conversion (CV) of 1000

$$IUR = 8.6 \times 10^{-6}\ (\mu g/m^3)^{-1}$$

(Continuous lifetime exposure to 1 µg/m^3 PCBTF is estimated to cause 8.6 additional cancers per million people exposed)

Questions?


OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT
CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY

Comments and Responses

During the public comment period, OEHHA received comments from:

- The American Coatings Association (ACA)

Comments and Responses

Comment #1

- OEHHA incorrectly assumed the mutagenicity of PCBTF and employed this assumption to incorrectly support the use of a low-dose linear risk model.
- OEHHA used a technical approach that is inconsistent with US EPA's 2005 guidelines.

Response to Comment #1

- OEHHA's decision to use the low-dose linear assumption for dose-response modeling was not based upon an assumption that PCBTF is genotoxic or mutagenic, but instead upon the lack of information indicating that a nonlinear threshold modeling approach should be used. In these situations, OEHHA uses a health-protective approach that includes assuming low-dose linearity in the dose-response model.

Comments and Responses

Response to Comment #1 (Continued)

- Contrary to ACA's assertion, OEHHA's use of the low-dose linear risk model is consistent with US EPA's 2005 guidelines on page 3-21, which state:

  "When the weight of evidence evaluation of all available data are insufficient to establish the mode of action for a tumor site and when scientifically plausible based on the available data, linear extrapolation is used as a default approach, because linear extrapolation generally is considered to be a health-protective approach. Nonlinear approaches generally should not be used in cases where the mode of action has not been ascertained."

Comments and Responses

Comment #2

- ACA challenges OEHHA's assessment of the available genotoxicity data as providing "some evidence" that PCBTF is a genotoxic substance. In particular, ACA criticizes use of genotoxicity results obtained for unscheduled DNA synthesis (UDS) by Benigni et al. (1982), for sister chromatid exchanges (SCE) by Litton Bionetics (1979) and for micronucleus formation by NTP (2018).

Comments and Responses

Response to Comment #2

- In Benigni, et al. (1982), a monotonic dose-response for UDS was observed for concentrations between 0 and 2 µl/ml. A positive, but relatively decreased response at the highest dose (10 µl/ml) may be due to cytotoxicity.

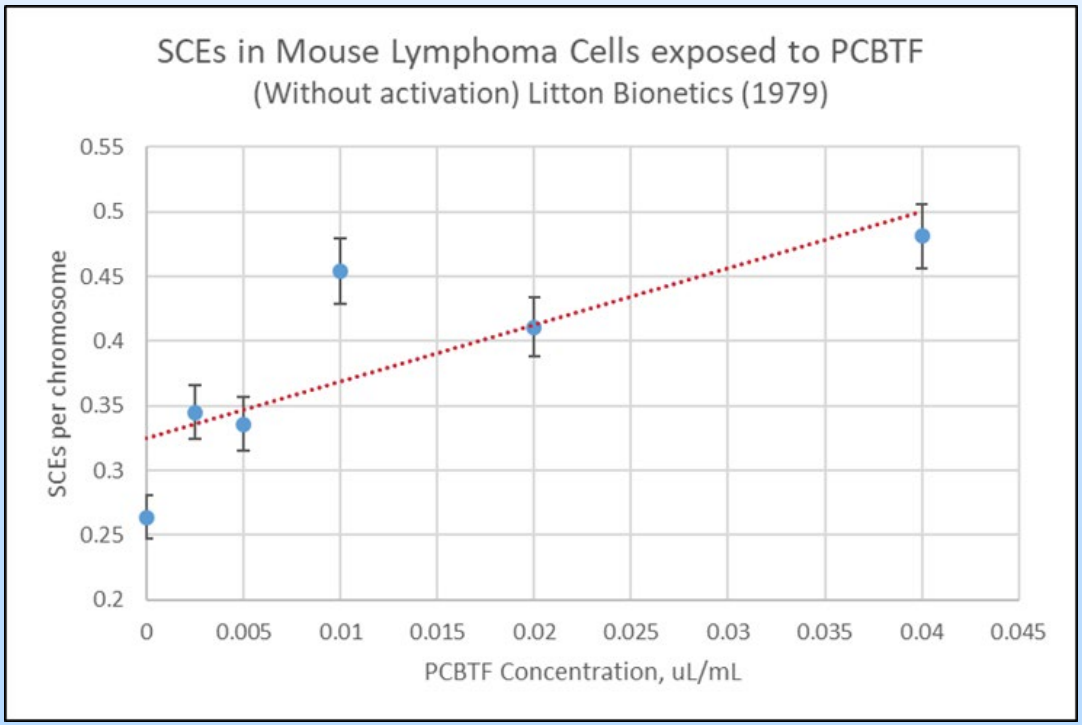
UDS Results for PCBTF (Benigni, et al., 1982)		
Concentration (µl/ml)	**Mean net grains per nucleus**	**Standard error of replicates**
0	1.78	0.53
0.2	3.08	1.7
1	10.02 *	2.21
2	19.82 *	2.18
10	11.94 *	1.33

* Significant at p=0.01 by t-test.

Comments and Responses

Response to Comment #2 (Continued)

- In Litton Bionetics (1979), SCEs per chromosome in the non-activated test were significantly increased compared to controls at all tested concentrations of PCBTF (t-test p-values < 0.01); and 3 of 5 tested concentrations with activation displayed elevated SCEs. The data from the non-activated SCE tests indicated a clear dose-response trend.



Comments and Responses

Response to Comment #2 (Continued)

- In NTP (2018), significantly increased micronuclei were observed in male mice. The NTP report states:

  > "In mice from the 3-month study, small but statistically significant increases in micronucleated mature erythrocytes were seen at the highest exposure concentration (2,000 ppm) […] For male mice, the observed response was outside the historical control range for the laboratory and was therefore judged to be positive."

- Based on ACA's comment, OEHHA revised the wording of its conclusion from "some evidence," to "limited evidence" that PCBFT is genotoxic.

Comments and Responses

Comment #3

- ACA states that OEHHA hypothesized, “the generation of a reactive and genotoxic metabolic intermediate that could potentially be of concern in determining the mutagenic potential of PCBTF. However, the potential for a mutagenic metabolite is not supported by the available evidence provided in Table 4 of OEHHA (2019)…”

Response to Comment #3

- Although the mutagenicity data for PCBTF reported in Table 4 of the IUR document (including tests with metabolic activation) were uniformly negative, this does not invalidate the hypothesis that the metabolism of PCBTF to phenolic compounds involves enzymatic oxidation of PCBTF’s aryl ring, with a potential to form reactive, electrophilic intermediates such as aryl oxides and quinones. These intermediates may covalently bind to cellular macromolecules including DNA.

Comments and Responses

Comment #4

- ACA states that OEHHA did not conduct a proper assessment of the Constitutive Androstane Receptor (CAR) mode of action for mouse liver tumors, and that,

  > "[t]he available science for PCBTF is consistent with a mode of action (CAR activation) proposed by the NTP (2018) for male mice liver tumors (the endpoint relied upon for the OEHHA recommended IUR). Further, tumors occurring by this mode of action in rodents are not relevant to human health."

Response to Comment #4

- ACA is incorrect to say that NTP (2018) "proposed" a CAR-based mode of action (MOA). NTP only discussed some of the evidence indicating that PCBTF may be a CAR activator in rats and mice. In the same report section, NTP also concluded that, "further mechanistic studies are needed to better understand [PCBTF-induced] hepatocellular carcinogenesis."

Comments and Responses

Response to Comment #4 (Continued)

- It has not been adequately demonstrated that rodent liver tumor data from chemicals fitting the putative CAR adverse outcome pathway (AOP) are irrelevant to human cancer risk. Several recent studies with CAR/PXR humanized or transgenic mice indicate that induction of mouse and human CAR/PXR can produce similar responses leading to liver tumors.
- The evidence supporting the CAR MOA for PCBTF liver tumor formation in mice is incomplete. The main elements of the CAR AOP are:
  - Activation of CAR
  - Altered expression of hepatic, CAR-dependent genes related to cell cycle control (with CYP2B and CYP3A induction, increased liver weight, and hepatocellular hypertrophy)
  - Increased mitogenic cell proliferation of hepatocytes
  - Increased pre-neoplastic liver foci
  - Increased hepatocellular adenomas or carcinomas

Comments and Responses

Response to Comment #4 (Continued)

- Although increased liver weight, hepatocellular hypertrophy, and liver foci were observed in the NTP (2018 and 1992) mouse studies, OEHHA has not identified any published studies demonstrating that PCBTF activates CAR in mice, or that PCBTF causes CAR-related, altered gene expression, CYP2B enzyme induction, or hepatocellular proliferation in mice. CAR-knockout mouse studies should be completed to show that CAR activation is a required event for the induction of liver tumors in male mice exposed to PCBTF.

Comments and Responses

Comment #5

- ACA cites an unpublished 1992 epidemiological report of Occidental Chemical Corporation workers as providing evidence that PCBTF exposure in humans does not produce an increased rate of the tumor types observed in animals following exposure to PCBTF.

Response to Comment #5

- The workers in this study were exposed to ~ 80 chemicals in addition to PCBTF, including known or suspected carcinogens such as benzene, trichloroacetic acid, trichloroethylene, perchloroethylene, lindane, mirex, and asbestos.
- Statistically significant increases in respiratory system and stomach cancers were found in the study cohort. Individual chemical risks could not be identified in the study due to the lack of chemical-specific, worker or workstation exposure data.

Comments and Responses

Response to Comment #5 (Continued)

- Had the workers in this study been exposed to PCBTF alone, the observed elevated rates of respiratory and stomach cancer would provide qualitative evidence of PCBTF's carcinogenic potential.
- The fact that the elevated tumor types observed in humans were different than the types found in rodents exposed to PCBTF is not relevant, since strict tumor concordance is not generally observed across different species, nor is it required for cancer risk assessment.
- Given that plant workers were actually exposed to unknown concentrations of multiple potential carcinogens (including PCBTF), this study provides no useful information with which to assess PCBTF's carcinogenicity.

Comments and Responses

Comment #6

- ACA says that, “OEHHA did not use generally accepted modeling approaches.” Specifically, OEHHA relied upon draft (2014) BMDS guidance instead of US EPA’s prior final BMDS guidelines (US EPA 2012)
- OEHHA only reported p-values to characterize goodness-of-fit and did not consider Akaike’s Information Criterion (AIC) values. Thus the fit of the models to the data has not been adequately assessed.

Response to Comment #6

- OEHHA generally follows US EPA guidance on the proper use of its BMD software. This includes the 2012 BMDS guidelines and the 2014 guideline addendum. According to US EPA, the 2014 guideline, “has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication.” OEHHA contacted US EPA staff about the status of the 2014 guidance, and they verified that it has been officially recommended by the Agency Statistical Workgroup (AGS) for use in US EPA risk assessments.

Comments and Responses

Response to Comment #6 (Continued)

- ACA is incorrect that we only used Chi-squared measures of fit (i.e., p-values) to judge the fit of the multistage models to the data. We also used: (i) the scaled residual for the dose nearest the benchmark dose, (ii) visual inspection of the overall curve fit, and (iii) AIC comparison, when recommended by the 2014 BMDS addendum.
- OEHHA also notes that using the 2014 BMDS guideline for male mouse liver tumors, upon which the proposed IUR is based, produces the same BMDL value as is obtained by using only the 2012 BMDS guideline.
- OEHHA added a column to Table 8 of the IUR document, indicating cases in which the AIC or an alternative method was used to choose the model for each tumor site. We also provided text to the Model Calculations section of the Document describing the reasons for those choices.

Comments and Responses

Comment #7

- ACA states that, “The method OEHHA (2019) used to adjust for differential early mortality or significant differences in survival is a crude approach and is not recommended in either the USEPA (2005) Guidelines for Carcinogen Risk Assessment or the OEHHA (2009) Technical Support Document. Rather, the application of time-to-tumor models are noted in both Guidance documents to account for significant decreases in survival. And therefore, currently accepted scientific approaches were not relied upon to adjust for survival.”

Response to Comment #7

- OEHHA used two standard methods to adjust the tumor-incidence data for differential early mortality in the animal studies. The “effective number” method was used for mice and the “poly-3” method was used for rats. These methods, which are described in more detail in the IUR document, have been used regularly by OEHHA, US EPA and researchers in the field.

Comments and Responses

Response to Comment #7 (Continued)

- ACA stated that the effective-number and poly-3 methods are “not recommended” in either US EPA (2005) or OEHHA’s TSD. More precisely, these methods are not directly addressed in the guidelines.
- Both OEHHA and US EPA guidelines present time-to-tumor analysis as an option (not a requirement) that may be used when survival is poor in some dose groups, and when the appropriate information to run the model is available.

Comments and Responses

Comment #8

- ACA notes: “PCBTF was developed as a substitute for use in ACA member products precisely because it assists in reducing the public health effects of ground level ozone. Currently, there are no viable alternatives available to replace PCBTF where it is used as an exempt solvent […] Over-regulating this chemical to avoid an uncertain hazard (i.e., potential health effects in humans) will only bring about the near-certain public health impacts of increased ground level ozone.”

Response to Comment #8

- ACA’s comment is relevant to the risk management of chemicals subject to the Hot Spots regulations. OEHHA is responsible for developing risk assessment guidelines (including IURs) for Hot Spots facility health risk assessments, but is not generally responsible for risk management activities resulting from Hot Spots risk assessments. Such responsibilities are the purview of the California Air Resources Board and the regional air quality management districts.