

FINAL STATEMENT OF REASONS
TITLE 27, CALIFORNIA CODE OF REGULATIONS
SECTION 25705(b) SPECIFIC REGULATORY LEVELS
POSING NO SIGNIFICANT RISK

NO SIGNIFICANT RISK LEVEL: *p*-CHLORO- α,α,α -TRIFLUOROTOLUENE

This is the Final Statement of Reasons for the adoption of a No Significant Risk Level (NSRL) for *p*-chloro- α,α,α -trifluorotoluene (*para*-chlorobenzotrifluoride, PCBTF). PCBTF was listed as a chemical known to the state to cause cancer for purposes of Proposition 65¹ on June 28, 2019. On October 18, 2019, the Office of Environmental Health Hazard Assessment (OEHHA) issued a Notice of Proposed Rulemaking to adopt a proposed amendment to Section 25705, Specific Regulatory Levels Posing No Significant Risk, identifying an NSRL of 23 micrograms per day ($\mu\text{g}/\text{day}$) for PCBTF under Title 27, California Code of Regulations, section 25705(b)². The Initial Statement of Reasons (ISOR) sets forth the grounds for the amendment to the regulation. A public comment period was provided from October 18, 2019 to December 2, 2019 and was extended until December 17, 2019. The notice stated that a public hearing would be held upon request. No request for a public hearing was received. OEHHA received written public comments on the proposed rulemaking from the following organization:

- American Coatings Association (ACA).
 - These comments also contained an attachment comprised of the comments previously submitted to OEHHA by the ACA regarding the Notice of Intent to List PCBTF.

UPDATE OF INITIAL STATEMENT OF REASONS

There were no changes from the originally proposed amendments, however, footnote 22 in the ISOR incorrectly refers to footnote 19 for the full citation. This should have referred to footnote 18.

PEER REVIEW

OEHHA also provided the Notice of Proposed Rulemaking and the ISOR for the proposed NSRL for PCBTF to the members of the Carcinogen Identification Committee

¹ The Safe Drinking Water and Toxic Enforcement Act of 1986, codified at Health and Safety Code section 25249.5 *et. seq.*, hereafter referred to as “Proposition 65” or “The Act”.

² All further regulatory references are to sections of Title 27 of the Cal. Code of Regs., unless otherwise indicated.

for their review and comment, as required by Section 25701(e). OEHHA received peer-review comments from committee member Dana Loomis, Ph.D.

SUMMARY AND RESPONSE TO PEER REVIEW COMMENTS RECEIVED

Comment: Dr. Loomis reviewed the materials and indicated that the National Toxicology Program (NTP) studies are of adequate quality and the model is based on the most sensitive species and gender. He concurred with the NSRL calculations.

Response: OEHHA acknowledges the comment. No changes to the proposed regulation were made based on this comment.

SUMMARY AND RESPONSE TO PUBLIC COMMENTS RECEIVED

In developing the NSRL for PCBTF, OEHHA relied on the NTP report, entitled “Toxicology and Carcinogenesis Studies of *p*-Chloro- α,α,α -trifluorotoluene in Sprague Dawley Rats (Hsd:Sprague Dawley SD) and B6C3F1/N Mice (Inhalation Studies)”³. The NTP report summarized the available data from rodent carcinogenicity studies, as well as other information relevant to the carcinogenic activity of PCBTF. The NSRL is based upon the results of the most sensitive scientific study deemed to be of sufficient quality⁴.

OEHHA’s responses to the comments received from the commenter listed above are incorporated within this Final Statement of Reasons (FSOR). Included as an attachment to the commenter’s submission were comments previously submitted on the Notice of Intent to List PCBTF. OEHHA considered these comments during the listing process and a response to these comments was posted on OEHHA’s website⁵ when the chemical was listed. Some of the comments submitted included observations or opinions regarding the benefits of reduced ground level ozone formation due to certain uses of this chemical as an alternative to chemicals that contribute to ground level ozone. Such remarks do not constitute an objection to or recommendation specifically directed at the proposed action or the procedures followed in this rulemaking action. Accordingly, OEHHA is not required under the Administrative Procedure Act to respond to such comments in this FSOR. Because OEHHA is constrained by limitations upon its time and resources and is not obligated by law to respond to irrelevant comments⁶,

³ National Toxicology Program (NTP 2018). Toxicology and Carcinogenesis Studies of *p*-Chloro- α,α,α -trifluorotoluene in Sprague Dawley Rats (Hsd:Sprague Dawley SD) and B6C3F1/N Mice (Inhalation Studies). NTP Technical Report Series No. 594. US Department of Health and Human Services, NTP, Research Triangle Park, NC. Available at https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr594_508.pdf

⁴ Section 25703(a)(4)

⁵ See “Response to Comments Pertaining to the Notice of Intent to List *p*-Chloro- α,α,α -trifluorotoluene” dated June 28, 2019. Available at <https://oehha.ca.gov/proposition-65/crn/chemical-listed-effective-june-28-2019-known-state-california-cause-cancer>

⁶ California Government Code section 11346.9(a)(3)

OEHHA does not provide responses to all of these remarks in this FSOR. However, the absence of responses to such remarks should not be construed to mean that OEHHA in any way agrees with them.

A summary of the public comments received that are relevant to this rulemaking is provided below, along with OEHHA's responses to those comments. As explained in detail in the responses to comments, OEHHA declines to change the proposed NSRL based on the comments.

Comment 1: Limited information on the modeling methods and assumptions was provided. OEHHA did not rely on generally accepted methods for selecting a dose-response model.

"In the Initial Statement of Reasons, documentation of the methods and assumptions that OEHHA used in the estimation of the CSF [cancer slope factor] potency is limited and not fully transparent. This made it difficult for the ACA to conduct a full review of the underlying assumptions and results. For example, no modeling results or data are provided to support the decision that the two-year inhalation studies conducted by NTP (2018) in male and female mice met the criterion in CCR section 25703 as being the most sensitive study of sufficient quality. Further, there are no results to demonstrate that the models applied in the estimation of the CSF adequately fit the data from the NTP (2018) study." (p. 4)

"It could be assumed that the conclusions provided in the Initial Statement of Reasons are based upon modeling approaches and results that were conducted as part of the development of the Inhalation Unit Risk Factor under the Air Toxics Hot Spots Program (OEHHA 2019). However, there is no reference to this document." (p. 4)

"However, if ACA assumes that, when estimating the CSF, OEHHA relied upon the modeling results provided in the IUR [inhalation unit risk] documentation (OEHHA (2019)), then the ACA asserts that OEHHA did not rely on generally accepted methods for selecting a dose-response model. In addition, OEHHA (2019) appears to have failed to adequately assess the goodness-of-fit of the models it applied to the data. These failures may have resulted in the over- or under-estimation of the potential potency of PCBTF and therefore affected the CSF relied upon in the Initial Statement of Reasons." (p. 4)

"Assessing the goodness-of-fit of a model to the data is critical in selecting a benchmark dose and the first item listed in both Standard Operating Procedure for USEPA [US Environmental Protection Agency] subcontractors (USEPA 2014) and USEPA BMDS [Benchmark Dose Software] Guidance (USEPA 2012) is reliance upon the Akaike's Information Criterion (AIC) for comparison across models. The AIC is not reported or relied upon for modeling decisions in the OEHHA (2019) Public Review Draft of the documentation of the IUR for PCBTF. OEHHA (2019) only reported p-values to

characterize goodness-of-fit. However, according to the USEPA (2012) BMDS Guidance, goodness-of-fit values, such as p-values, are not designed to compare results across models. Therefore, the lack of consideration of the AIC indicates that the fit of the models to the data has not been adequately assessed.” (p. 5)

Response 1: OEHHA developed the CSF (cancer slope factor) in accordance with the guidance contained in its Proposition 65 regulations⁷. The methods and assumptions that went into modeling the data are explained on pages 4-5 of the ISOR. Briefly, to derive a measure of the cancer response to PCBTF (per mg/kg-day) for the liver tumor data in the male mouse study (found in Table 1 of the ISOR), the dose associated with a 5% increased risk of developing a tumor was calculated and the lower bound for this dose was estimated using the multistage polynomial model for cancer in the US Environmental Protection Agency (US EPA) Benchmark Dose Software (BMDS)^{8,9,10}. The ratio of the 5% risk level to that lower bound on dose is known as the “animal cancer slope factor (CSF_{animal}),” or the “animal cancer potency.” Model fit is assessed by the ability to meet each of the three goodness-of-fit criteria described in the resources provided by US EPA regarding use of BMDS, such as the BMDS Technical Guidance^{11,12,13} and the Benchmark Dose Training Module on Cancer Models¹⁴. This resulted in a global goodness-of-fit p-value greater than 0.05 for the first and second orders (p = 0.40; 0.57, respectively). Further, the scaled residuals of both orders were less than two in absolute value. Finally, the plot of the curves fitted to the data confirms the numerical measures of goodness-of-fit, showing a clear visual fit. Since none of the parameter estimates was zero, the Akaike’s Information Criterion (AIC) was used to select the appropriate order, which was the 1st order polynomial. For the liver tumor and Harderian gland tumor data in the female mouse study, the appropriate orders of the multistage models were selected for each tumor site using the same fit criteria. A multisite analysis using BMDS (MS_Combio) was then used to estimate the combined risk of treatment-related tumors in female mice.

⁷ Section 25703

⁸ US EPA Benchmark Dose Software (BMDS) Version 2.7.0.4. National Center for Environmental Assessment. Available from: <https://www.epa.gov/bmds>

⁹ US EPA (2014a). Choosing Appropriate Stage of a Multistage Model for Cancer Modeling (BMDS Technical Guidance). Available from <https://cfpub.epa.gov/ncea/bmds/recordisplay.cfm?deid=308382>

¹⁰ US EPA (2014b). Module 5: Benchmark Dose Modeling - Cancer Models [Webinar]. In *Benchmark Dose Software (BMDS) Training Webinars*. Retrieved from: <https://clui.in.adobeconnect.com/a1089459318/p3a32k3l8of/?launcher=false&fcsContent=true&pbMode=normal&archiveOffset=488800>

¹¹ US EPA (2012). Benchmark Dose Technical Guidance. Washington, DC: US EPA. Available from: <https://www.epa.gov/risk/benchmark-dose-technical-guidance>

¹² US EPA (2014a). Full citation provided in footnote 9.

¹³ US EPA (2020). Benchmark Dose Software (BMDS) Version 3.2 User Guide. Document Number EPA/600/R-20/216. Available from: <https://www.epa.gov/bmds/benchmark-dose-software-bmds-32-user-guide-readme>

¹⁴ US EPA (2014b). Full citation provided in footnote 10.

The same long-term carcinogenicity studies of PCBTF in male and female mice and the same cancer dose-response analyses discussed above and in the ISOR also serve as the basis for the PCBTF cancer inhalation unit risk factor (IUR) developed under the Air Toxics Hot Spots program¹⁵. The IUR document underwent peer review by the Scientific Review Panel on Toxic Air Contaminants¹⁶.

Comment 2: OEHHA relied on a draft document for guidance in selecting a model.

“When selecting a dose-response model, OEHHA (2019) [Air Toxics Hot Spots Program. p-Chloro- α,α,α -trifluorotoluene (*p*-Chlorobenzotrifluoride, PCBTF). Cancer Inhalation Unit Risk Factor, Technical Support Document for Cancer Potency Factors, Appendix B. Public Review Draft] appears to have used methods taken from a 2014 draft operating procedure for United States Environmental Protection Agency (USEPA) subcontractors (reference to USEPA 2016 is incorrect in the IUR documentation) that was never finalized. These methods are inconsistent with those found in USEPA’s well-established final BMDS Guidance (2012), as well as the OEHHA (2009) Technical Support Document. As noted previously, for detailed methods on dose-response, OEHHA (2009) defers to USEPA (2005) Guidelines for Carcinogen Risk Assessment.” (p. 4)

Response 2: This is a comment regarding the PCBTF Cancer Inhalation Unit Risk Factor Technical Support Document for Cancer Potency Factors¹⁷ and does not refer directly to the ISOR, which is the basis for the proposed NSRL. However, OEHHA notes that although the 2014 US EPA document¹⁸ referred to in the comment is labeled as “draft”, the US EPA website states, “This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication.”¹⁹ Moreover, the methods presented in the 2014 US EPA document are not inconsistent with the US EPA 2012 BMDS Guidance²⁰. The 2014 US EPA document provides more specific information with respect to choosing an appropriate model for cancer dose response modeling. Simply put, this 2014 US EPA document does not contradict other guidance provided by US EPA.

¹⁵ OEHHA (2020). *p*-Chloro- α,α,α -trifluorotoluene: Cancer Inhalation Unit Risk Factor Technical Support Document for Cancer Potency Factors Appendix B. August 2020. Available at:

<https://oehha.ca.gov/air/crn/notice-adoption-cancer-inhalation-unit-risk-factor-p-chloro-aaa-trifluorotoluene>

¹⁶ <https://oehha.ca.gov/air/crn/p-chloro-aaa-trifluorotoluene-p-chlorobenzotrifluoride-pcbtf-cancer-inhalation-cancer-unit>

¹⁷ OEHHA (2019). *p*-Chloro- α,α,α -trifluorotoluene: Cancer Inhalation Unit Risk Factor Technical Support Document for Cancer Potency Factors Appendix B. Public Review Draft. October 2019.

¹⁸ US EPA (2014a). Full citation provided in footnote 9.

¹⁹ <https://cfpub.epa.gov/ncea/bmds/recordisplay.cfm?deid=308382>

²⁰ US EPA (2012). Full citation provided in footnote 11.

Comment 3: PCBTF is not mutagenic or genotoxic, and OEHHA should not assume a linear low-dose extrapolation.

“In the estimation of both the CSF and NSRL for PCBTF, OEHHA has assumed linear low-dose extrapolation which is based on the mutagenic potential of a chemical. This default assumption is incorrect. The available data show that PCBTF is not mutagenic. The available data also demonstrate that PCBTF and its metabolites are not genotoxic. OEHHA’s approach in the Initial Statement of Reasons is inconsistent with conclusions reached by NTP (2018), which found that PCBTF is neither mutagenic nor more generally genotoxic. In OEHHA (2019), it is stated that ‘All studies of PCBTF mutagenicity have reported negative findings.’ In the absence of data supporting mutagenicity, it is inappropriate for OEHHA to use a linear no-threshold approach to derive a CSF/IUR or NSRL for PCBTF.” (p. 5)

“OEHHA should abandon use of its linear, no-threshold approach and instead derive a CSF/IUR using a threshold model. The available data suggests that there is a threshold below which exposure to PCBTF is without an appreciable increase in the risk of cancer.” (p. 8)

“Further evaluation of the PCBTF database may provide additional support for a non-linear mode of action and allow for the identification of a threshold concentration in animals, below which cancer would not be expected to occur.” (comments received on the NOIL, attachment p. 4)

Response 3: The approach taken in the ISOR is consistent with the conclusions reached by NTP. As described in the ISOR, the mechanisms by which PCBTF induces tumors are not known, and there is limited information available to inform considerations of mechanism, other than findings from genotoxicity assays. PCBTF was positive in assays testing for the induction of micronuclei in mature erythrocytes of male mice following a three-month exposure, sister chromatid exchanges in mouse lymphoma cells, and unscheduled DNA synthesis in human embryonic epithelial cell cultures, and negative in assays testing for bacterial mutagenicity and DNA damage, mutagenicity in yeast and cultured mouse lymphoma cells, chromosomal aberrations in Chinese hamster ovary cells and *in vivo* in rat bone marrow cells, and micronuclei in mature erythrocytes of female mice or rats of either sex^{21,22,23}.

This is consistent with NTP’s discussion regarding the genotoxic action of PCBTF:

“p-Chloro- α,α,α -trifluorotoluene was negative in several bacterial mutagenicity assays (*Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia*

²¹ Hazardous Substances Data Bank (HSDB). <https://pubchem.ncbi.nlm.nih.gov/source/hsdb/4251>

²² NTP (2018). Full citation provided in footnote 3.

²³ Benigni R, Bignami M, Conti L, Crebelli R, Dogliotti E, Falcone E, Carere A. (1982). *In vitro* mutational studies with trifluralin and trifluorotoluene derivatives. Ann Ist Super Sanita 18(1):123-126.

coli strain WP2 *uvrA*/pKM101). A small but statistically significant increase in micronucleated mature erythrocytes was observed in male mice after 3 months of inhalation exposure to the highest concentration of *p*-chloro- α,α,α -trifluorotoluene (2,000 ppm) and was judged to be a positive result. No induction of micronuclei was observed in female mice or male or female rats. Overall these results suggest that while *p*-chloro- α,α,α -trifluorotoluene may be capable of inducing chromosomal damage at high levels of inhalation exposure in male mice, the mode of action for the carcinogenicity of *p*-chloro- α,α,α -trifluorotoluene observed in rats and mice is unlikely to be driven by genotoxicity.” (NTP 2018; p. 77²⁴)

“*p*-Chloro- α,α,α -trifluorotoluene is nongenotoxic (Ames assay negative, chromosomal aberration assay negative) and may not directly cause mutations and initiate carcinogenesis. However, further mechanistic studies are needed to better understand the *p*-chloro- α,α,α -trifluorotoluene-induced hepatocellular carcinogenesis.” (NTP 2018; p. 76²⁵)

For cancer risk assessment, the default approach used by OEHHA^{26,27,28} and US EPA²⁹ is that, in the absence of compelling information indicating the existence of a threshold, the linear extrapolation method will be used. In particular, there is no need to establish a genotoxic mechanism before using the linear extrapolation method. As discussed in the US EPA 2005 Guidelines for Carcinogen Risk Assessment, non-genotoxic mechanisms may also produce a linear dose-response in the low-dose range of interest³⁰. For example, “[a]gents that are generally considered to be linear in this region include:

- agents that are DNA-reactive and have direct mutagenic activity, or
- agents for which human exposures or body burdens are high and near doses associated with key precursor events in the carcinogenic process, so that background exposures to this and other agents operating through a common

²⁴ NTP (2018). Full citation provided in footnote 3.

²⁵ *Ibid.*

²⁶ Initial Statement of Reasons – Amendment to Section 25705: No Significant Risk Level for PCBTF. Available from <https://oehha.ca.gov/media/downloads/cnr/pcbtfisor101719.pdf>

²⁷ Air Toxics Hot Spots Risk Assessment Guidelines Part II: Technical Support Document for Cancer Potency Factors” (May 2009) Office of Environmental Health Hazard Assessment. Available at: http://www.oehha.ca.gov/air/hot_spots/tsd052909.html

²⁸ Final Statement of Reasons – No Significant Risk Levels and No Observable Effect Levels. Available from <https://oehha.ca.gov/proposition-65/cnr/final-statement-reasons-no-significant-risk-levels-and-no-observable-effect>

²⁹ US EPA (2012). Full citation provided in footnote 11.

³⁰ US EPA (2005). US Environmental Protection Agency. Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum. Washington, DC. EPA/630/P-03/001B. March 2005.

mode of action are in the increasing, approximately linear, portion of the dose-response curve.”³¹

The commenter states, “Further evaluation of the PCBTF database may provide additional support for a non-linear mode of action and allow for the identification of a threshold concentration in animals, below which cancer would not be expected to occur.” However, neither a specific database nor additional scientific data were identified that provide the level of evidence necessary to depart from the non-threshold assumption specified in Section 25703 (see also response to comment 4, below).

In conclusion, the information the commenters provided does not include substantial evidence that leads OEHHA to find that a departure from the default approach is scientifically more appropriate. The approach used in the calculation of the NSRL – a non-threshold assumption using the multistage cancer model – is consistent with Section 25703, current quantitative assessment practices for carcinogens by OEHHA, and current US EPA practices³².

No change to the proposed regulation was made based on this comment.

Comment 4: The mode of action of liver tumors in rodents is not relevant to human health.

“In the Initial Statement of Reasons, OEHHA states that the mechanisms by which PCBTF causes tumors are not known. However, for the mouse liver tumors -- the endpoint upon which the recommended CSF is based – OEHHA gave no consideration to the mode of action proposed by NTP (2018), the very authoritative body upon which OEHHA has relied for the Proposition 65 listing and the derivation of the CSF, IUR, and NSRL. Moreover, it appears that OEHHA made no attempt to evaluate the publicly available mode of action data. Had OEHHA undertaken such a review, it would have discovered that the mode of action proposed by NTP (2018) for liver tumors in rodents is not relevant to human health. As such, the mouse liver tumor data should not be used to derive the CSF or NSRL.” (p. 9)

“Based on NTP’s conclusion that the increased incidence of hepatocellular carcinomas reported in male and female mice following inhalation exposure to PCBTF could occur through a potential CAR [constitutive androstane receptor]-mechanism of action (MOA), Ramboll scientists conducted a review of the available results from toxicity studies for PCBTF. NTP (2018) suggested a CAR mode of action for the observed mouse liver tumors based on: (1) the observation of key events for the CAR-MOA including reported increases in CYP2B [cytochrome P450] activity in rats following oral exposure to PCBTF (Pelosi et al. 1998), (2) concentration-related increased liver weights in mice

³¹ *Ibid.*

³² US EPA (2005). Full citation provided in footnote 30.

exposed to PCBTF via inhalation for 3 months (NTP 2018), and (3) the consistent evidence from standard *in vitro* assays that PCBTF is not genotoxic (NTP 2018). The key events focused on by NTP (2018) are also consistent with an adverse outcome pathway (AOP) for CAR activation available on the AOP Wiki (Figure 1).” (pp. 9, 15)

“The results from Ramboll’s review of the toxicity data for PCBTF provide evidence of dose-response relationships (both oral and inhalation) between PCBTF and multiple key events and associative events in an established adverse outcome pathway for CAR-MOA (Figure 1) for the induction of hepatocellular adenomas and carcinomas in rodents (Peffer et al. 2016). These key events and associative events are also consistent with the proposed AOP for CAR (Peffer et a. 2016) and those associated with phenobarbital-induced liver tumors in rodents (Holsapple et al. 2006; Elcombe et al. 2014; Yamamoto et al. 2004; Numazawa et al. 2005; Yoshinari et al. 2001; Waxman and Azaroff 1992), all of which are not relevant to human health.” (p. 10)

“As such, OEHHA should either abandon use of the mouse liver tumor data when developing the CSF and NSRL or conduct a thorough analysis of the available data to evaluate the CAR mode of action and the relevance of the mouse liver tumor data to human health. OEHHA should not proceed any further with the proposed NSRL without making these changes.” (p. 10)

Response 4: A similar comment from ACA was addressed in the response to comments pertaining to the Notice of Intent to List³³. As explained in that document, the information submitted by the commenter does not provide substantial evidence supporting the hypothesis that PCBTF induces liver tumors via the commenter’s proposed mode of action involving activation of the constitutive androstane receptor (CAR). No additional studies or data were provided in the comments submitted on the NSRL that support this proposed mechanism of liver tumor induction. As stated in the ISOR, the mechanisms by which PCBTF induces tumors (including mouse liver tumors) remain unknown.

Although the NTP report discusses the increases in liver weights and nonneoplastic lesions observed in the 3-month and 2-year mouse studies of PCBTF as “consistent with a potential CAR-mechanism of action,” the report does not draw conclusions regarding this potential mechanism of action. Importantly, the report also notes that the potential for PCBTF “to activate CAR was evaluated in the Tox21 screening program but the results were inconclusive” (NTP 2018; p. 77).

Regarding the comments on an adverse outcome pathway (AOP) for CAR activation, it is important to note that this is a proposed pathway – not an established pathway – by which CAR activation has been hypothesized to lead to liver tumor induction. The

³³ <https://oehha.ca.gov/media/downloads/cnr/responsecomments062819.pdf>

commenter cites as support for PCBTF operating through this proposed AOP observations in rats of increases in the liver enzyme CYP2B, and observations in the NTP mouse studies of increases in liver weight. However, as noted in Figure 1 on page 15 of the ACA comments, increases in liver CYP2B levels and liver weights are considered 'associative events' rather than 'key events' in this proposed AOP, and are thus not considered to be on the causal path to liver tumor formation.

Moreover, it has not been scientifically established that CAR activation does not contribute to liver tumors in humans. Thus, there is no reason to dismiss the relevance to humans of the mouse liver tumors induced by PCBTF.

No changes to the proposed regulation were made based on this comment.

Comment 5: No tumors were observed in a study in workers.

"Results from available worker studies provide evidence of exposures for which higher than expected rates of the types of cancers observed in animals following exposure to PCBTF were not observed in the workers (Occidental Chemical Corporation 1992). This resulted despite PCBTF exposure having occurred in combination with more than 80 other chemicals and workers potentially having elevated levels of exposure compared to traditional consumers." (p. 3, footnote 3)

Response 5: The NTP Technical Report discusses the 1992 report referred to by the commenter from the Occidental Chemical Corporation (OCC). NTP states that "higher than expected rates of respiratory system and stomach cancers" were observed in workers in this OCC report. The NTP goes on to state, "However, it is likely that this cohort of individuals was exposed to a large mixture of chemicals, with more than 80 CAS numbers listed as keywords on the submission report."³⁴ Thus, the OCC report provides little information on the carcinogenic potential of PCBTF in humans, since workers were exposed to many chemicals.

With regard to ACA's statement that the tumor types observed in animals in the NTP studies were not observed in workers, OEHHA notes that tumor site concordance between humans and animals is neither expected nor required for risk assessment.

No change to the proposed regulation was made based on this comment.

Comment 6: Doses administered to mice were orders of magnitude higher than human exposures.

"The exposures administered to mice in the NTP (2018) study, as well as the exposures at which tumors were observed, are concentrations orders of magnitude higher than human exposures (100 ppm in mice, compared to 1.15 ppm occupational exposure) (Lee 2015). Therefore, the dosing in the NTP (2018) study does not resemble the

³⁴ NTP (2018). Full citation provided in footnote 3.

expected manner of human exposure, calling into question its use for the derivation of the NSRL. Accordingly, the use of these data in the conduct of a quantitative risk assessment appears inconsistent with the guidance in CCR section 25703.” (p. 8)

Response 6: The accepted paradigm in toxicity testing is to use the maximally tolerated dose (MTD) as the highest dose. It is common for doses used in animal cancer bioassays to be higher than anticipated human exposure levels, sometimes markedly so. The purpose of including high doses is not to model expected human exposure levels, but to maximize the power of the study to detect a carcinogenic effect definitively^{35,36}. As explained by US EPA, “Animal studies are conducted at high doses in order to provide statistical power, the highest dose being one that is minimally toxic (maximum tolerated dose or MTD).”³⁷

The BMD method can then be employed to characterize the dose-response relationship by fitting the multistage cancer model to the bioassay data, allowing for estimation of risk in the low dose region. Thus, OEHHA’s use of the NTP male and female B6C3F1/N mouse studies in the derivation of the NSRL is consistent with the Proposition 65 regulations, as these studies are the most sensitive scientific studies of sufficient quality.

The commenter has not correctly interpreted Section 25703(a)(1), which states, “Animal bioassay studies for quantitative risk assessment shall meet generally accepted scientific principles, including ... the degree to which dosing resembles the expected manner of human exposure...”. This statement is clarified on page 19 of the FSOR of the regulations³⁸, which states,

“In adopting this ‘safe harbor’ methodology the Agency intends that ‘prudent risk assessment policy’ be observed. Where local administration of a chemical does not result in systemic exposure, it may be scientifically more appropriate to depart from this assumption, and the regulation permits such departure. However, it should be noted that, in the selection of data conducting the risk assessment, one consideration is the degree to which dosing resembles the expected manner of human exposure. Thus, if human exposure is anticipated to be oral, and the available data are from dermal administration which does not result in systemic exposure, the study may not provide an adequate basis for the risk assessment.”

³⁵ US EPA (2005). Full citation provided in footnote 30.

³⁶ NTP (2015). Handbook for Preparing Report on Carcinogens Monographs. July 20, 2015. Office of the Report on Carcinogens, Division of the National Toxicology Program, National Institute of Environmental Health Sciences, US Department of Health and Human Services.

³⁷ US EPA (2005). Full citation provided in footnote 30.

³⁸ Final Statement of Reasons – No Significant Risk Levels and No Observable Effect Levels. Full citation provided in footnote 28.

Therefore, the “degree to which dosing resembles the expected manner of human exposure” refers to route of exposure, not the dose levels.

Alternatives Determination

In accordance with Government Code section 11346.9(a)(4), OEHHA has, throughout the adoption process of this regulation, considered available alternatives to determine whether any alternative would be more cost effective in carrying out the purpose for which the regulation was proposed, or would be as cost effective and less burdensome to affected private persons than the proposed action. No alternatives have been suggested. OEHHA has determined that no reasonable alternative would either be more effective in carrying out the purpose for which the action is proposed, or would be as effective and less burdensome to affected private persons, or would be more cost-effective to affected private persons and equally effective in implementing the statutory policy or other provision of law than the proposed regulation.

For chemicals listed under the Act as known to cause cancer, the Act exempts discharges to sources of drinking water and exposures of people without provision of a warning if the exposure poses “no significant risk” of cancer (Health and Safety Code, section 25249.10(c)). The Act does not specify numerical levels of exposure that represent no significant risk of cancer.

The purpose of this regulation is to establish a No Significant Risk Level for PCBTF. At or below this level, the Act does not require a warning or prohibit discharges of the chemical to sources of drinking water. Thus, adopting this level will allow businesses subject to the Act to determine whether a given discharge to sources of drinking water or a given exposure to this chemical is subject to the warning requirement or discharge prohibition provisions of the Act (Health and Safety Code, section 25249.5 and 25349.6).

Although Section 25703 describes principles and assumptions for conducting risk assessments to derive No Significant Risk Levels, some businesses subject to the Act do not have the resources to perform these assessments. Yet each business with ten or more employees must determine whether its activities or products are subject to the discharge prohibition or warning requirements of the Act. Adopting an NSRL for this chemical provides an efficient way of determining if a business is in compliance with the Act.

Local Mandate Determination

OEHHA has determined this regulatory action will not pose a mandate on local agencies or school districts, nor does it require reimbursement by the State pursuant to

Part 7 (commencing with Section 17500) of Division 4 of the Government Code. OEHHA has also determined that no nondiscretionary costs or savings to local agencies or school districts will result from this regulatory action. Proposition 65 provides an express exemption from the warning requirement and discharge prohibition for all state and local agencies. Thus, these regulations do not impose any mandate on local agencies or school districts.