INITIAL STATEMENT OF REASONS
TITLE 27, CALIFORNIA CODE OF REGULATIONS

PROPOSED AMENDMENT TO:
SECTION 25705(b) SPECIFIC REGULATORY LEVELS POSING NO SIGNIFICANT RISK

p-CHLORO-α, α, α-TRIFLUOROTOLUENE

SAFE DRINKING WATER AND TOXIC ENFORCEMENT ACT OF 1986
PROPOSITION 65

PURPOSE AND BACKGROUND OF PROPOSED AMENDMENTS

This proposed regulatory amendment would adopt a No Significant Risk Level (NSRL) for *p*-chloro-α,α,α-trifluorotoluene (*para*-chlorobenzotrifluoride, PCBTF, CAS No. 98-56-6) under Proposition 65[1] in Title 27, California Code of Regulations, section 25705(b)[2]. The proposed NSRL of 23 micrograms per day (µg/day) for PCBTF is based on a carcinogenicity study in rodents and was derived using the methods described in Section 25703.

Proposition 65 was enacted as a ballot initiative on November 4, 1986. The Office of Environmental Health Hazard Assessment (OEHHA) within the California Environmental Protection Agency is the lead state entity responsible for the implementation of Proposition 65[3]. OEHHA has the authority to adopt and amend regulations to implement and further the purposes of the Act[4].

The Act requires businesses to provide a warning when they cause an exposure to a chemical listed as known to the state to cause cancer or reproductive toxicity. The Act also prohibits the discharge of listed chemicals into sources of drinking water. Warnings are not required and the discharge prohibition does not apply when exposures are insignificant. The NSRL provides guidance for determining when this is the case for exposures to chemicals listed as causing cancer.

[1] The Safe Drinking Water and Toxic Enforcement Act of 1986, codified at Health and Safety Code section 25249.5 et. seq., commonly known as Proposition 65, 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.
[3] Section 25102(o)
[4] Health and Safety Code, section 25249.12(a).

OEHHA has proposed to list PCBTF as known to the state to cause cancer under Proposition 65 via the authoritative bodies mechanism. The proposed listing is based on the National Toxicology Program (NTP) report entitled "Toxicology and Carcinogenesis Studies of *p*-Chloro-α,α,α-trifluorotoluene in Sprague Dawley Rats (Hsd:Sprague Dawley SD) and B6C3F$_1$/N Mice (Inhalation Studies)"[5]. The NTP is a body recognized as authoritative for the listing of chemicals as known to cause cancer under Proposition 65 (Section 25306(m)). In the event the chemical is not listed, this rulemaking will be withdrawn.

DEVELOPMENT OF PROPOSED NSRL

To develop the proposed NSRL for PCBTF, OEHHA relied on the National Toxicology Program (NTP) report entitled "Toxicology and Carcinogenesis Studies of *p*-Chloro-α,α,α-trifluorotoluene in Sprague Dawley Rats (Hsd:Sprague Dawley SD) and B6C3F$_1$/N Mice (Inhalation Studies)"[6]. 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 for PCBTF is based upon the results of the most sensitive scientific study deemed to be of sufficient quality[7].

Selection of Studies Used to Determine Cancer Potency

OEHHA reviewed the available data from the rodent carcinogenicity studies of PCBTF discussed by NTP (2018)[8] and determined that the two-year inhalation studies conducted by NTP in male and female B6C3F$_1$/N mice met the criterion in Section 25703 as being sensitive studies of sufficient quality.

In the NTP studies[9], groups of 50 mice of both sexes were exposed to PCBTF by inhalation at concentrations of 0, 100, 200, 400 parts per million (ppm), 6 hours plus 12 minutes per day, 5 days per week for 104 weeks. The lifetime average daily doses of PCBTF administered in the studies were calculated to be 0, 153.8, 307.7 and 615.4 milligrams per kilogram of body weight per day (mg/kg-day) in male mice, and to be 0, 155.3, 310.6 and 621.1 mg/kg-day in female mice. Survival of the male mice was not affected by treatment with PCBTF until near the end of the study (after 90 weeks), when the survival of the male mice exposed to 400 ppm was significantly less than that of the

[5] 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 B6C3F$_1$/N Mice (Inhalation Studies). 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

[6] *Ibid.*

[7] Section 25703(a)(4).

[8] NTP (2018). Full citation provided in footnote 5.

[9] *Ibid.*

control group. Survival of female mice was not affected by treatment with PCBTF at any dose.

In male mice, statistically significant increases in incidences of hepatocellular carcinoma, hepatoblastoma, and hepatocellular adenoma, carcinoma, and hepatoblastoma (combined) were observed, with statistically significant positive trends. The tumor incidence data used to estimate cancer potency are presented in Table 1.

Table 1. Tumor incidence[a] of treatment-related tumors in male B6C3F$_1$/N mice administered PCBTF by inhalation (NTP 2018)[10]

Organ	Tumor Type	Administered Concentrations (ppm)				Trend test *p*-value[b]
		0	100	200	400	
Liver	Hepatocellular adenoma, carcinoma, or hepatoblastoma[c] (first occurrence of tumor: day 424)	31/50	37/50	40/49*	48/49***	$p < 0.001$

[a] The numerator represents the number of tumor-bearing animals and the denominator represents the number of animals alive at the time of first occurrence of tumor.
[b] *p*-values for exact trend test conducted by OEHHA.
[c] Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (performed by OEHHA): * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

In female mice, statistically significant increases in incidences of hepatocellular adenoma, carcinoma, hepatoblastoma, and hepatocellular adenoma, carcinoma, and hepatoblastoma (combined) were observed, with statistically significant positive trends. Statistically significant increases in the incidence of Harderian gland adenoma and adenoma or adenocarcinoma (combined) were observed, with statistically significant positive trends. The tumor incidence data used to estimate cancer potency are presented in Table 2.

[10] NTP (2018). Full citation provided in footnote 5.

Table 2. Tumor incidence[a] of treatment-related tumors in female B6C3F$_1$/N mice administered PCBTF by inhalation (NTP 2018)[11]

Organ	Tumor Type	Administered Concentrations (ppm)				Trend test *p*-value[b]
		0	100	200	400	
Liver	Hepatocellular adenoma, carcinoma, or hepatoblastoma[c] (first occurrence of tumor: day 530)	18/47	18/48	29/46*	46/47***	$p < 0.001$
Harderian gland	Adenoma or adenocarcinoma[c] (first occurrence of tumor: day 480)	2/49	6/49	9/49*	8/48*	$p < 0.05$

[a] The numerator represents the number of tumor-bearing animals and the denominator represents the number of animals alive at the time of first occurrence of tumor.
[b] *p*-values for exact trend test conducted by OEHHA.
[c] Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (performed by OEHHA): * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Estimation of Cancer Potency Using the Multistage Model and Multisite Analysis

The mechanisms by which PCBTF induces tumors are not known. As discussed in the NTP report[12], there is limited information available to inform considerations of mechanism, other than mostly negative findings from genotoxicity assays. Specifically, PCBTF was positive in assays testing for the induction of sister chromatid exchanges in mouse lymphoma cells and micronuclei in mature erythrocytes of male mice following a three-month exposure, 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[13,14].

Based on consideration of the available mechanistic information, a multistage model is applied to derive a cancer potency estimate, following the guidance in Section 25703. There are no principles or assumptions scientifically more appropriate, based on the available data, than this approach.

The lifetime probability of a tumor at a specific site given exposure to the chemical at dose d is modeled using the multistage polynomial model:

[11] NTP (2018). Full citation provided in footnote 5.
[12] *Ibid.*
[13] *Ibid*.
[14] Hazardous Substances Data Bank (HSDB) https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+4251

$$p(d) = \beta_0 + (1 - \beta_0)\left(1 - \exp\left[-\left(\beta_1 d + \beta_2 d^2 + \cdots + \beta_j d^j\right)\right]\right)$$

where the background probability of tumor, β_0, is between 0 and 1 and the coefficients β_i, i = 1…j, are positive. The β_i are parameters of the model, which are taken to be constants and are estimated from the data. The parameter β_0 provides the basis for estimating the background lifetime probability of the tumor.

To derive a measure of the cancer response to PCBTF (per mg/kg-day) in studies where increases in treatment-related tumors were observed at a single site, 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 US Environmental Protection Agency's (US EPA) Benchmark Dose Software (BMDS)[15]. 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." The animal cancer potency was estimated using this approach for the male mouse study described in Table 1.

For carcinogens that induce tumors at multiple sites and/or in different cell types at the same site in a particular species and sex, BMDS (MS_Combo) can be used to derive maximum likelihood estimates (MLEs) for the parameters of the multisite carcinogenicity model by summing the MLEs for the individual multistage models for the different sites and/or cell types. This multisite model provides a basis for estimating the cumulative risk of carcinogen treatment-related tumors. The animal cancer potency was estimated using this approach for the female mouse inhalation study described in Table 2.

Calculation of Average Daily Doses

The lifetime average dose in units of mg/kg-day of PCBTF was calculated for each of the relevant dose groups, based on the dose level, duration, exposure regimen, and animal body weights reported by NTP[16]. The average body weights for male and female mice were calculated to be 0.0455 kg and 0.0442 kg, respectively, from the data reported by NTP[17] for control animals.

[15] US EPA Benchmark Dose Software (BMDS) Version 2.7.0.4. National Center for Environmental Assessment. Available from: https://www.epa.gov/bmds. BMDS version 3.1 produced the same cancer potency. In BMDS version 2.7 and earlier versions, the multistage polynomial model for cancer is referred to as the "multistage cancer" model. In order to use the equivalent model in BMDS version 3.1, users must select the 'Frequentist Restricted" option on the multistage model, which restricts the parameter estimates to be positive.
[16] NTP (2018). Full citation provided in footnote 5.
[17] *Ibid.*

The inhalation rate (IR) for male and female mice, in m^3/day, was calculated using the equation of Anderson et al. (1983)[18], which was derived using experimental data on animal breathing rates (m^3/day) and corresponding body weights (kg):

$$IR_{mice} = 0.0345 \times (bw_{mice}/0.025)^{2/3}$$

In this equation, the constant 0.0345 is in m^3/day, and the constant 0.025 is in kg.

The calculated inhalation rates were 0.0514 m^3/day for male mice and 0.0504 m^3/day for female mice. The lifetime average doses (D_{avg}) cited on pages 2 and 3 were determined by multiplying the chamber air concentration (C_{air}) of PCBTF in units of mg/m^3 by the following factors: the inhalation rate divided by the body weight; 6.2/24 to account for the six hours and 12 minutes per day exposure; 5/7 to account for a five day per week dosing. The equation for the lifetime average dose (mg/kg-day) calculation is:

$$D_{avg} = C_{air} \times \frac{IR_{mice}}{bw_{mice}} \times \frac{6.2}{24} \times \frac{5}{7}$$

Estimation of Human Cancer Potency

Human cancer potency is estimated by an interspecies scaling procedure. According to Section 25703(a)(6), dose in units of mg per kg body weight scaled to the three-quarters power is assumed to produce the same degree of effect in different species in the absence of information indicating otherwise. Thus, for each of the studies described above, scaling to the estimated human potency (CSF_{human}) is achieved by multiplying the animal potency (CSF_{animal}) by the ratio of human to animal body weights (bw_{human}/bw_{animal}) raised to the one-fourth power when CSF_{animal} is expressed in units $(mg/kg\text{-}day)^{-1}$:

$$CSF_{human} = CSF_{animal} \times (bw_{human} / bw_{animal})^{1/4}$$

The default human body weight is 70 kg. As noted above, the average body weights for male and female mice were calculated to be 0.0455 kg and 0.0442 kg, respectively, based on the data reported by NTP (2018) for control animals. The derivations of the human cancer slope factors using these body weights are summarized below in Table 3.

[18] Anderson EL and the Carcinogen Assessment Group of the US EPA (1983), Quantitative approaches in use to assess cancer risk. *Risk Analysis.***3**:277-295.

Table 3. Derivation of CSF_{human} using mean animal body weights for the studies and data presented in Tables 1 and 2

Sex/Strain/ Species	Type of Neoplasm	Body Weight (kg)	CSF_{animal} $(mg/kg\text{-}day)^{-1}$	CSF_{human} $(mg/kg\text{-}day)^{-1}$
Male $B6C3F_1$/N mice	Hepatocellular adenoma, carcinoma or hepatoblastoma	0.0455	0.00475	**0.030**
Female $B6C3F_1$/N mice	Hepatocellular adenoma, carcinoma or hepatoblastoma	0.0442	0.00115	
	Harderian gland adenoma or adenocarcinoma		0.000503	
	Multisite: Hepatocellular adenoma, carcinoma or hepatoblastoma; Harderian gland adenoma or adenocarcinoma		0.00140	0.0088

As shown in Table 3, male mice were the most sensitive to the carcinogenic effects of PCBTF and thus the NSRL will be based on the human cancer slope factor of 0.030 $(mg/kg\text{-}day)^{-1}$, derived from the study in male mice.

Calculation of No Significant Risk Level (NSRL)

The NSRL can be calculated from the cancer slope factor as follows. The Proposition 65 no-significant-risk value is one excess case of cancer per 100,000 people exposed, expressed as 10^{-5}. This value is divided by the slope factor, expressed in units of one divided by milligram per kilogram body weight per day. The result of the calculation is a dose level associated with a 10^{-5} risk in units of mg/kg-day. This dose then can be converted to an intake amount in units of mg per day by multiplying by the body weight for humans. When the calculation is for the general population, the body weight is assumed to be 70 kg[19]. The intake can be converted to a µg per day amount by multiplying by 1000. This sequence of calculations can be expressed mathematically as:

$$\text{NSRL} = \frac{10^{-5} \times 70\ \text{kg}}{\text{CSF}_{\text{human}}} \times 1000\ \mu\text{g/mg}$$

As indicated previously, the human cancer slope factor for PCBTF derived from the male mouse study data and exposure parameters presented in Table 1 is 0.030 per

[19] Section 25703(a)(8)

mg/kg-day. Inserting this number into the equation above results in an NSRL of 23 µg/day (rounded to two significant figures).

PROPOSED REGULATORY AMENDMENT

Section 25705(b)

The proposed change to Section 25705(b) is provided below, in underline.

(1) The following levels based on risk assessments conducted or reviewed by the lead agency shall be deemed to pose no significant risk:

Chemical name	Level (micrograms per day)
Acrylonitrile	0.7
…	
p-Chloro-α,α,α-trifluorotoluene (PCBTF)	23

PROBLEM BEING ADDRESSED BY THIS PROPOSED RULEMAKING

Proposition 65 does not provide guidance regarding how to determine whether a warning is required or a discharge is prohibited. OEHHA is the implementing agency for Proposition 65 and has the resources and expertise to examine the scientific literature and calculate a level of exposure, in this case a NSRL, that does not require a warning or for which a discharge is not prohibited.

ECONOMIC IMPACT ASSESSMENT (SEE BELOW)

NECESSITY

This proposed regulatory amendment would adopt an NSRL that conforms with the Proposition 65 implementing regulations and reflects the currently available scientific knowledge about *p*-chloro-α,α,α-trifluorotoluene. The NSRL provides assurance to the regulated community that exposures or discharges at or below this level are considered not to pose a significant risk of cancer. Exposures at or below the NSRL are exempt from the warning and discharge requirements of Proposition 65[20].

BENEFITS OF THE PROPOSED REGULATION

See “Benefits of the Proposed Regulation” under ECONOMIC IMPACT ANALYSIS below.

[20] Health and Safety Code sections 25249.9(b) and 25249.10(c)

TECHNICAL, THEORETICAL, AND/OR EMPIRICAL STUDIES, REPORTS, OR DOCUMENTS

The 2018 NTP report entitled "Toxicology and Carcinogenesis Studies of *p*-Chloro-α,α,α-trifluorotoluene in Sprague Dawley Rats (Hsd:Sprague Dawley SD) and B6C3F$_1$/N Mice (Inhalation Studies)"[21], and the publication by Anderson *et al.* (1983)[22] were relied on by OEHHA for calculating the NSRL for PCBTF. OEHHA also relied on information in the Hazardous Substances Data Bank (HSDB)[23] on the findings from genotoxicity tests of PCBTF. The NTP documents include data used in the potency calculation and information on mechanisms of carcinogenesis that are relevant to evaluating the most appropriate method for deriving the NSRL in the context of Section 25703. Anderson *et al.* (1983) provides equations to calculate inhalation rates for mice. Copies of these documents will be included in the regulatory record for this proposed action. These documents are available from OEHHA upon request.

OEHHA also relied on the following Economic Impact Analysis, included in this document, in developing this proposed regulation.

REASONABLE ALTERNATIVES TO THE REGULATION AND THE AGENCY'S REASONS FOR REJECTING THOSE ALTERNATIVES

The NSRL provides a "safe harbor" value that aids businesses in determining if they are complying with the law. The alternative to the proposed amendment to Section 25705(b) would be to not adopt an NSRL for this chemical. Failure to adopt an NSRL would leave the business community without a "safe harbor" level to assist businesses in complying with Proposition 65. No alternative that is less burdensome yet equally as effective in achieving the purposes of the regulation in a manner that achieves the purposes of the statute has been proposed.

REASONABLE ALTERNATIVES TO THE PROPOSED REGULATORY ACTION THAT WOULD LESSEN ANY ADVERSE IMPACT ON SMALL BUSINESSES

OEHHA is not aware of significant cost impacts that small businesses would incur in reasonable compliance with the proposed action. Use of the proposed NSRL by businesses is voluntary and therefore does not impose any costs on small businesses. In addition, Proposition 65 is limited by its terms to businesses with 10 or more employees (Health and Safety Code, section 25249.11(b)) so it has no effect on very small businesses.

[21] NTP (2018). Full citation provided in footnote 5.
[22] Anderson EL et al. (1983), full citation provided in footnote 19.
[23] HSDB, full citation provided in footnote 14.

EVIDENCE SUPPORTING FINDING OF NO SIGNIFICANT ADVERSE ECONOMIC IMPACT ON BUSINESS

Because the proposed NSRL provides a “safe harbor” level for businesses to use when determining compliance with Proposition 65, OEHHA does not anticipate that the regulation will have a significant statewide adverse economic impact directly affecting businesses, including the ability of California businesses to compete with businesses in other states.

EFFORTS TO AVOID UNNECESSARY DUPLICATION OR CONFLICTS WITH FEDERAL REGULATIONS CONTAINED IN THE CODE OF FEDERAL REGULATIONS

Proposition 65 is a California law that has no federal counterpart. There are no federal regulations addressing the same issues and, thus, there is no duplication or conflict with federal regulations.

ECONOMIC IMPACT ANALYSIS
Gov. Code section 11346.3(b)

It is not possible to quantify any monetary values for this proposed regulatory action given that use of the NSRL is entirely voluntary and the NSRL only provides compliance assistance for businesses subject to the Act.

Impact on the Creation or Elimination of Jobs/Businesses in California: This regulatory proposal will not affect the creation or elimination of jobs within the State of California. Proposition 65 requires businesses with ten or more employees to provide warnings when they expose people to chemicals that are known to cause cancer or developmental or reproductive harm. The law also prohibits the discharge of listed chemicals into sources of drinking water. PCBTF is listed as known to the state to cause cancer under Proposition 65; therefore, businesses that manufacture, distribute, sell or use products with PCBTF in the state must provide a warning if their product or activity exposes the public or employees to significant amounts of the chemical. The regulatory proposal does not create additional compliance requirements, but instead provides a “safe harbor” value that aids businesses in determining whether a warning is required for a given exposure.

Impact on the Creation of New Businesses or Elimination of Existing Businesses within the State of California: This regulatory action will not impact the creation of new businesses or the elimination of existing businesses within the State of California. The regulatory proposal does not create additional compliance requirements, but instead provides a “safe harbor” value that aids businesses in determining if they are complying with the law.

Impact on Expansion of Businesses within the State of California: This regulatory action will not impact the expansion of businesses within the State of California. The regulatory proposal does not create additional compliance requirements, but instead provides a “safe harbor” value that aids businesses in determining if they are complying with the law.

Benefits of the Proposed Regulation: The NSRL provides a “safe harbor” value that aids businesses in determining if they are complying with the law. Some businesses may not be able to afford the expense of establishing an NSRL and therefore may be exposed to litigation for a failure to warn of an exposure to or for a prohibited discharge of the listed chemical. Adopting this regulation will save these businesses those expenses and may reduce litigation costs. By providing a safe harbor level, this regulatory proposal does not require, but may encourage, businesses to lower the amount of the listed chemical in their product to a level that does not cause a significant exposure, thereby providing a public health benefit to Californians.