AmericanCoatings ASSOCIATION℠

January 23, 2019

Julian Leichty
Office of Environmental Health Hazard Assessment
P.O. Box 4010, MS-12B
Sacramento, California 95812-4010

Submitted electronically through https://oehha.ca.gov/comments

Re: Notice of Intent to List: p-Chloro-α,α,α-trifluorotoluene (Para-Chlorobenzotrifluoride, PCBTF) (November 23, 2018)

Dear Mr. Leichty:

The American Coatings Association (ACA) offers the following comments on the Office of Environmental Health Hazard Assessment (OEHHA) Notice of Intent to List: p-Chloro-α,α,α-trifluorotoluene (Para-Chlorobenzotrifluoride, PCBTF) (CASRN 98-56-6).[1]

ACA's comments may be summarized as follows:

1. Use of PCBTF in paint, sealant, and similar products assists in reducing ambient concentrations of ozone, thereby providing important public health benefits that may be eliminated unnecessarily if PCBTF is listed. Currently, there are no viable alternatives available to replace PCBTF in those formulations in which it is being used.

2. OEHHA is required to perform a weight of evidence analysis, considering the record as a whole, to determine whether PCBTF should be listed as known to cause cancer.

[1] ACA is a voluntary, nonprofit trade association working to advance the needs of the paint and coatings industry and the professionals who work in it. The organization represents paint and coatings manufacturers, raw materials suppliers, distributors, and technical professionals. ACA's mission includes programs and services that support the coatings industry's commitment to environmental protection, sustainability, product stewardship, health and safety, corporate responsibility, and the advancement of science and technology. Additional information is available on the ACA website, https://www.paint.org.

3. The available record as a whole does not provide "sufficient evidence" of carcinogenicity as required by the "authoritative body" regulation (27 CCR 25306). OEHHA is required to "determine which chemicals have been formally identified by an authoritative body as causing cancer under 27 CCR 25306(c). "As causing cancer" means "sufficient evidence" of carcinogenicity exists from studies in experimental animals. "Sufficient evidence" means studies in experimental animals indicate that there is an increased incidence of malignant tumors or combined malignant and benign tumors: (1) in multiple species or strains; (2) in multiple experiments (e.g., with different routes of administration or using different dose levels); or (3) to an unusual degree, in a single experiment with regard to high incidence, site or type of tumor, or age at onset (27 CCR 25306(e)(2)).

    a. <u>PCBTF has not been "formally identified."</u> The National Toxicology Program (NTP) Report on which OEHHA relies does not "formally identify" PCBTF as an animal carcinogen because the Report does not conclude that PCBTF causes cancer after applying a proper weight of evidence analysis.

    b. <u>OEHHA lacks sufficient evidence in "multiple species."</u> The NTP Report, which discusses the study that the NTP conducted as well as the scientific literature for PCBTF at the time of the report, does not demonstrate sufficient evidence of carcinogenicity in "multiple species" – malignancy in particular – as required in the authoritative body regulation. Results were produced in mice and rats, but NTP concluded that there is only "some evidence" of carcinogenicity in the rat. Further, because historical control data were not available for the rat, NTP could not clearly determine whether the observed tumors were occurring at rates above background. Importantly there was not substantial evidence of a progression to malignancy. Accordingly, the rat data do not demonstrate an "increased incidence" of malignant tumors as required by the authoritative body regulation at 27 CCR 25306(e)(2) and therefore the "multiple species" requirement is not satisfied.

    c. <u>OEHHA lacks sufficient evidence in "multiple experiments."</u> The NTP Report does not demonstrate sufficiency of evidence in "multiple experiments" utilizing different routes of administration or different dose levels, as required by the authoritative body regulation. While the 2-year mouse bioassay found evidence of tumors in both sexes of the mouse, this finding has not been replicated in two or more independent studies carried out at different times or in different laboratories or under different protocols. Further, all of the results in the mouse involved the same route of administration (inhalation) and the same three dose

levels, yet they failed to produce a consistent tumor response across doses within the species. And even if male and female mouse data from a single study were to be considered "multiple experiments," such data are not definitive proof of causality alone. This is particularly true for PCBTF when the same route of administration and dosing were utilized, the observations are inconsistent, the tumor types are known to commonly occur in this strain of mice spontaneously, and the most plausible mode of action suggested by the NTP is of questionable relevance.

d. No Mode of Action Has Been Identified. PCBTF was not found to be genotoxic, leading NTP to propose no mode of action and to suggest that further mechanistic studies are needed. Although the NTP did not propose a mode of action at this time for the liver tumors in the mouse, the agency noted that the data are consistent with a potential constitutive androstane receptor (CAR)-mode of action, which is not considered relevant to humans.

e. Exposure Levels are Not Representative of Human Exposures. The observed effects occurred at concentrations orders of magnitude higher than human exposures, and further review is required to determine whether the observed animal tumors are relevant to human health and whether there is a threshold below which carcinogenicity would not be expected.

For these reasons, ACA urges OEHHA to determine that the NTP Report is not a sufficient basis for listing PCBTF. These points are discussed in detail below. To develop these points, the ACA enlisted the assistance of Ramboll US Corporation (f/k/a Environ International Corporation, Inc.). Attached and incorporated into this letter is a memorandum prepared by Ramboll (hereinafter "the Ramboll report") evaluating the sufficiency of the NTP Report as support for the proposed listing.

PCBTF Uses

To improve air quality, attain federal and state ozone standards and protect public health, air quality regulatory agencies such as the South Coast Air Quality Management District (SCAQMD), adopt regulations that limit emissions of VOCs and oxides of nitrogen (NOx), which form ground level ozone in the atmosphere. Certain VOCs are less reactive in the atmosphere and, therefore, do not contribute significantly to the formation of ozone. Exempting solvents with negligible reactivity helps agencies meet air quality goals while allowing manufacturers the flexibility to formulate products meeting strict VOC content limits. Industries affected by VOC regulations petition air quality regulators to exempt from the VOC definition compounds that have been deemed negligibly reactive by EPA.

One of those exempt compounds is PCBTF. Currently, there are no viable alternatives available to replace PCBTF in those formulations in which it is being used. If the substance is listed by OEHHA, air quality regulators may be prompted to remove the exemption, eliminating the public health benefits from ozone reductions that flow from use of PCBTF in paint, sealant, and similar products. The Proposition 65 statute was intended to protect public health. See *California Chamber of Commerce v. Brown*, 196 Cal. App. 4th 233, 258 (2011). Use of PCBTF in paint, sealant, and similar products provides important public health benefits, through related reductions in ambient ozone that may be eliminated unnecessarily if PCBTF is listed. Prior to listing PCBTF, OEHHA should perform a thorough weight of evidence analysis as required by the authoritative body regulations.

Weight of Evidence Analysis

The 1990 Statement of Reasons underlying the OEHHA authoritative body regulation explains that the regulation "utilizes the EPA's Classification System for Categorizing Weight of Evidence for Carcinogens From Human and Animal Studies (51 Fed. Reg. 33999 (Sept. 24, 1986))" (p.15) (hereinafter "EPA's 1986 Cancer Classification Guidelines"). In describing this system, EPA stated:

> EPA has developed a system for stratifying the weight of evidence . . . This classification is not meant to be applied rigidly or mechanically. At various points in the above discussion, EPA has emphasized the need for an overall, balanced judgment of the totality of the available evidence . . . Therefore, the hazard identification section should include a narrative summary of the strengths and weaknesses of the evidence as well as its categorization in the EPA scheme (51 Fed. Reg. 33996).

The 1990 Statement of Reasons also explains that "Under the regulation, there is no automatic adoption of an authoritative body's list. The Agency [i.e., OEHHA] will investigate to make certain that there are sufficient animal or human data" (p. 17).

Similarly, the courts have recognized that OEHHA must scrutinize the whole record compiled by an authoritative body to determine whether there is substantial evidence to support a listing. In *Exxon Mobil v. OEHHA*, 169 Cal. App. 4th 1264, 1278, 1280-81 (2009) (emphasis in original):

> [O]nce the chemical is "formally identified" by an authoritative body . . . *OEHHA* reviews the scientific record before the authoritative body to determine whether there is substantial evidence to support a listing.
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> Nothing in [the authoritative body regulation] suggests, however, that OEHHA must base this conclusion *solely* on the authoritative body's report. Rather, as OEHHA suggests, the language of [the regulation] is

> broad enough to allow OEHHA to premise its conclusion on the authoritative body's report *and other factors*, such as the scientific literature on which the authoritative body relied and OEHHA's knowledge of the authoritative body's methodology. In other words, so long as OEHHA is able to conclude on the basis of the authoritative body's report *and the underlying scientific record* that an authoritative body has identified a chemical . . . and that the identification takes the regulatory criteria into account, OEHHA may list it . . .
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> We do not agree . . . that the authoritative body's *report* is the only permissible evidence that the authoritative body made the regulatory findings. Rather, as we have said, we believe that OEHHA properly can conclude that the authoritative body made the necessary findings based on OEHHA's review of the scientific literature on which the authoritative body relied and its knowledge of the authoritative body's methodology. So long as OEHHA can conclude, on the basis of the *entire record* before it, that the authoritative body made the [required] findings, it may list a chemical pursuant to the authoritative body provision of the statute.

With respect to PCBTF, consideration of the scientific body of evidence reported by NTP in the agency's technical report leads to a conclusion that the available evidence is not sufficient to list PCBTF as a carcinogen, for reasons to which we now turn.

The NTP Report and OEHHA Authoritative Body Regulation

OEHHA's Notice of Intent to List PCBTF relies on the NTP report, which presents the results of animal testing and discusses the available scientific body of literature at the time of the NTP report. OEHHA's authoritative body regulation for listing based on determinations by an authoritative body consist of several elements:

1. OEHHA is required to "determine which chemicals have been formally identified by an authoritative body as causing cancer;"

2. A chemical is "formally identified" by an authoritative body when [OEHHA] determines that the chemical has been included on a list of chemicals causing cancer issued by the authoritative body; or is the subject of a report which is published by the authoritative body and which *concludes* that the chemical causes cancer or reproductive toxicity; or has otherwise been identified as causing cancer or reproductive toxicity by the authoritative body in a document that indicates that such identification is a final action;

3. "As causing cancer" means "sufficient evidence" of carcinogenicity exists from studies in experimental animals;

4. "Sufficient evidence" means studies in experimental animals indicate that there is an increased incidence of malignant tumors or combined malignant and benign tumors in multiple species or strains, [or] in multiple experiments (e.g., with different routes of administration or using different dose levels), or, to an unusual degree, in a single experiment with regard to high incidence, site or type of tumor, or age at onset (27 CCR 25306(c)-(e)). (Emphasis added.)

The NTP report and associated record do not satisfy these listing requirements.

First, NTP does not "formally identify" PCBTF as an animal carcinogen within the meaning of the "authoritative body regulation because the required weight of evidence (as discussed above) was not performed by NTP.[2] Further, the NTP Report does not specifically conclude that PCBTF "causes cancer." NTP merely finds "clear evidence" of carcinogenicity in mice, and "some evidence" in rats. These conclusions are explained in the Report as follows:

> **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
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> **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence (p. 13).

Accordingly, while the NTP Report and associated record describe the strength of the evidence provided by the animal testing, NTP does not apply a weight of the evidence approach to determine that the evidence is sufficient, as defined in the authoritative body regulation, to conclude that PCBTF is an animal carcinogen.[3] Therefore, NTP did

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[2] At present, PCBTF has not been added to the NTP Report on Carcinogens, and NTP has not proposed to do so. The NTP Criteria for listing a substance as a "reasonably anticipated" human carcinogen, on the basis of animal studies alone, are nearly identical to the OEHHA criteria for "sufficient evidence" in animals.[2] However NTP has not yet performed that weight of the evidence analysis. See https://ntp.niehs.nih.gov/pubhealth/roc/process /index.html.

[3] The 1990 Statement of Reasons notes that "if an authoritative body properly applies a strength-of-the-evidence approach, the Agency will not substitute its judgment on the basis of negative data, unless new data not considered by the authoritative body clearly establishes that there is not sufficient evidence in either animals or humans" (p. 17). In this case, however, the NTP approach does not rise to the level of a proper "weight of evidence" analysis or meet the criteria for sufficiency in the OEHHA regulations. Further, the evidence against listing PCBTF is not limited to negative data, but also includes the limitations of the positive data, as discussed further throughout these comments.

not “formally identify” PCBTF because it did not conclude that the chemical causes cancer.[4]

Second, a proper weight of evidence analysis of the entire NTP record indicates that the evidence is insufficient to support listing at this time because the “as causing cancer” requirement is not met. As discussed above, “as causing cancer” means “sufficient evidence” of carcinogenicity exists from studies in experimental animals (27 CCR 25306(e)). “Sufficient evidence” means studies in experimental animals indicate that there is an increased incidence of malignant tumors *or* combined malignant and benign tumors: (1) in multiple species or strains; (2) in multiple experiments (e.g., with different routes of administration or using different dose levels); *or* (3) to an unusual degree, in a single experiment with regard to high incidence, site or type of tumor, or age at onset. Given the NTP database, Element 3 is not relevant here.[5]

The evidence provided in the NTP Report is not sufficient for listing under Elements 1, 2, or 3.[6] With respect to Element 1, clear evidence of carcinogenicity has not been demonstrated in “multiple species.” As explained further in the attached analysis of the NTP record prepared by Ramboll US Corporation, which is incorporated herein by reference, the NTP record does not provide “sufficient evidence” because, among other things, it fails to “indicate that there is an increased incidence of *malignant* tumors *or* combined *malignant and benign* tumors *in multiple species* or strains.” (Emphasis added.)

The NTP does not consider the tumors observed in rats as clear evidence, only providing some evidence. The increase in thyroid and adrenal tumors that were noted to support the conclusions of carcinogenic activity were almost all benign. Only a few animals, including a control, developed a malignant tumor. Hence, substantial evidence of a progression to malignancy was not found. Further, because historical control data were not available for the rats, NTP could not definitively determine whether the observed tumors were occurring at rates above background. Accordingly, the rat data do not demonstrate an “increased incidence” of malignant tumors as required by the authoritative body regulation. Thus, the rat data provide “limited” evidence, not “sufficient” evidence, and therefore should not be relied upon to support listing PCBTF as a carcinogen.

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[4] If OEHHA is in fact arguing that the NTP Report was a “list” or “final action” pursuant to 27 CCR 25306(d), OEHHA has not met its burden. Including PCBTF in the NTP Report does not, in and of itself, render the chemical eligible for listing on NTP’s Report on Carcinogens. Additionally, publishing the NTP report is not considered “final action” by NTP.

[5] The NTP results do not demonstrate any unusual degree of incidence, site or type of tumor, or age at onset. Specifically, as explained in the attached Ramboll report, the liver tumors observed in mice do not represent an increase in rare or unusual tumors, but rather tumors that NTP has noted are common in this strain of mice, so do not represent tumors to an unusual degree from a single experiment. The age of first incidence of the combination of malignant tumors considered in the treated mice is also similar to the age of first incidence in the corresponding control mice; therefore, there does not appear to be a difference in age of onset.

[6] Element 3 is not met for reasons explained immediately above, in footnote 5.

Nor can listing be justified under sufficiency Element 2, which requires positive results in "multiple experiments" utilizing different routes of administration or dose levels. The evidence in the mouse upon which OEHHA expressly relied in its Notice of Intent to List is limited mainly to a combination of liver tumors in a single strain of mice with varied response across sexes within that strain. Liver carcinomas in male mice were the only tumor type that was significantly increased at the lowest concentration tested. In contrast, a similar dose-response relationship for carcinomas was not observed in female mice, with the incidence significant only at the highest concentration tested. These results do not justify listing under Element 2, as explained below.

The NTP findings are not the result of "multiple experiments," as that term is properly understood in the historical context in which the sufficiency criteria were adopted. As noted above, OEHHA's 1990 Statement of Reasons supporting adoption of the authoritative body regulation explains that the regulation is based on EPA's 1986 Cancer Classification Guidelines. Indeed, the language of the OEHHA sufficiency criteria is identical to the EPA criteria for sufficiency of animal evidence (51 Fed. Reg. 33999). The EPA criteria, in turn were drawn from the criteria developed by the International Agency for Research on Cancer (IARC) (51 Fed. Reg. 33996). In its 1986 Cancer Classification Guidelines, EPA explicitly acknowledges its reliance on IARC, making clear to OEHHA and the regulated community the origin and meaning of EPA's and OEHHA's sufficiency criteria. IARC describes the "multiple experiment" criterion as follows:

> The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms (as described on p.23) in (a) two or more species of animals ***or*** (b) <u>in two or more independent ***studies*** in one species carried out at different times or in different laboratories or under different protocols</u>.[7] (Emphasis added.)

The NTP study does not meet this requirement – the mouse data were generated as part of *single study*. As the Methods and Materials section of the NTP report shows, both sexes of mice were exposed at the same laboratory, beginning at the same timepoint, for the same duration, using the same protocol.[8] If OEHHA wants to adopt an interpretation of the sufficiency criteria that differs from the interpretation the agency provided when it promulgated the regulation, the agency should provide notice and accept public comments, rather than adopting and implementing this different interpretation on a case-by-case basis.

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[7] "IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans," Supp. 7 p. 30 (1987).

[8] As discussed in the attached Ramboll Report, standard carcinogenicity testing guidelines require testing in both sexes of a species as part of the standard protocol for a long-term animal experiment. NTP's standard protocol for a chronic toxicity and carcinogenicity study requires testing in multiple species, in both sexes for each species and with multiple exposure or dosing groups.

Further, there's no mention in the sufficiency criteria of reliance on the results from "two sexes"' of the same species from a single study, except under extraordinary circumstances in which malignancy is found "to an unusual degree, in a single experiment with regard to high incidence, site or type of tumor, or age at onset." As explained in the attached Ramboll report, the NTP database does not meet this requirement. If the agency wants to adopt a criterion that permits consideration of data from two sexes of the same species generated through a single study under less than extraordinary circumstances, the agency should amend the regulation and permit public notice and comment, rather than implementing such a criterion on a case-by-case basis.

Even if OEHHA wanted to interpret the mice data as having been generated through separate "experiments," the NTP experiments would not satisfy the plain language of the sufficiency criteria. All of the testing involved the same route of administration: inhalation. And both sexes received the same three dose levels.[9] Yet, if OEHHA wants to ignore or minimize these concerns, the fact that the experiments did not produce consistent observations of tumors across species or the same dose-response patterns within species -- as explained above and in detail in the attached Ramboll report -- should still cause the agency to question whether the NTP report provides substantial evidence of causality.

Further, a finding of sufficiency also would be inconsistent with the Chemical identification Committee "Guidance Criteria for Identifying Chemicals for Listing As 'Known to the State to Cause Cancer'" (March 2001), guidance which, unlike the authoritative body regulation, explicitly provides for consideration of tumors found in significant excess in both sexes of a species. However, the CIC Guidance describes the evidence accorded to a finding in two sexes of the same species as part of the discussion of the proper weighting of a list of characteristics, stating that "<u>none of these individual characteristics provides an absolute criterion of causality by itself</u>."[10] (Emphasis added.) A blanket rule allowing listing whenever tumors are found in only the two genders of a single species, tested as part of a single study, conducted in the same laboratory, and utilizing the same exposure pathway and dose levels, does not provide substantial evidence of causality. That is particularly true where, as here, the findings in a single species are extremely limited – for example, the liver tumors observed in mice do not represent an increase in rare or unusual

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[9] Moreover, as IARC has explained, the three dosing levels are part of a single experiment, and *not* separate experiments themselves.

> The primary purpose of a long-term carcinogenicity experiment is to determine if the administration of a test substance to animals of some species alters the normal pattern of tumour development in that species. <u>In a typical long-term carcinogenicity experiment, a pool of animals is divided by randomization into several groups. One group serves as a concurrent control group, while the remaining groups are exposed to various dose levels of the test substance by some appropriate route of administration</u>.[9] (Emphasis added.)

[10] See also, EPA, "Guidelines for Carcinogenic Risk Assessment" (2005).

tumors (i.e., they commonly occur in mice), there appears to be no meaningful difference in the age of onset between the treated and controlled mice, the three dose levels failed to produce a consistent tumor response within the species, and the most plausible mode of action is of questionable relevance.

Apart from our concerns about the lack of substantial evidence from multiple species or multiple experiments, there are other reasons to consider the NTP Report an insufficient basis for listing at this time. The NTP report does not propose a mode of action. Further, the NTP report indicates that the mode of action is unlikely to be genotoxic. *It is also possible that the mode of action is species-specific*. The data in the NTP Report do not indicate that PCBTF is genotoxic, and the results from the analysis of liver tumors observed in mice indicate a ***decrease*** in gene mutations with increasing PCBTF exposure. As a result of this analysis and the results from other assays, NTP proposed no mode of action for the reported animal tumors but concluded that the mode of action for the tumors observed is unlikely to be driven by genotoxicity and suggested that further mechanistic studies are needed. However, as noted in the Ramboll report, NTP suggested that the PCBTF data are consistent with a potential constitutive androstane receptor (CAR)-mechanism of action. Liver tumors induced in rodents via CAR-activation are not considered relevant to humans.[11] Thus the limited available evidence on mode of action further calls into question the sufficiency of the evidence to support the proposed listing.

In addition, the observed effects occurred at concentrations orders of magnitude higher than human exposures (100 ppm in mice and rats compared to 1.15 ppm occupational exposure). Further review of the evidence is required to determine whether the observed animal tumors are relevant to human health and, because PCBTF is not genotoxic, whether there is a threshold above current human exposures below which an increased risk of carcinogenicity would not be expected.

Accordingly, as demonstrated in the attached Ramboll report and in these comments, a proper analysis of the weight of the evidence in the NTP Report considered as a whole indicates that the NTP record does not currently support listing of PCBTF.

Conclusion

ACA and its members take their environmental stewardship responsibilities very seriously. 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 for this purpose. Accordingly, it is imperative that OEHHA's listing decision is based on sufficient evidence within the meaning of the authoritative body regulation. ACA urges OEHHA to review the NTP Report carefully in the context of the Proposition 65 listing

[11] EPA's 1986 Cancer Classification Guidelines also note that mouse liver tumors may be questionable as a result of high spontaneous background incidence, and may be considered limited evidence where, as here, warranted by the specific information available (51 Fed. Reg 33999 n.2).

criteria, and to consider additional information such as we have provided. We believe that such an analysis will show that the National Toxicology Program (NTP) Report on PCBTF, and the data it provides, do not satisfy the OEHHA listing criteria.

Respectfully submitted,

David Darling,
Vice President of Health, Safety and Environmental Affairs

ATTACHMENT

RAMBOLL

MEMO

To **David Darling**
American Coatings Association
From **Robinan Gentry, PhD**

1. Summary

At the request of the American Coatings Association (ACA), Ramboll US Corporation (Ramboll) conducted a review of the NTP (2018)[1] Technical Report to evaluate the conclusions by NTP (2018)[1] regarding the strength of evidence of carcinogenicity for p-chloro-α,α,α-trifluorotoluene (PCBTF) based on the results provided in the Technical Report for Sprague Dawley rats and B6C3F1/N mice. This memorandum was prepared to support ACA's Comments on the Proposed Listing of PCBTF recently announced by the Office of Environmental Health Hazard Assessment (OEHHA).

The results of the NTP study were evaluated to determine how they inform sufficiency criteria for listing a chemical under Proposition 65 as known to cause cancer. These sufficiency criteria are focused on the observation of malignant or malignant and benign tumors combined in multiple species or the observation of tumors in multiple studies in the same species. The only evidence of statistically significant increases in malignant tumors was limited to liver tumors in mice in the NTP (2018)[1] study. In comparing the results from the mice to the rats, no significant increase in the incidence of liver tumors was reported in male or female rats and only statistically significant increases in benign tumors of the thyroid and adrenal gland were reported in rats, mainly at the highest concentration tested (1000 ppm). In drawing conclusions regarding evidence of carcinogenic activity for PCBTF, NTP (2018)[1] concluded that there was *clear evidence of carcinogenic activity* in male and female mice, based on the incidence of hepatocellular tumors (individual incidences or combinations of adenoma, carcinoma or hepatoblastoma), with only *some evidence of carcinogenic activity* in male and female rats. Consideration of these results alone does not provide sufficient evidence needed to list PCBTF as known to cause cancer under Proposition 65.

2. Results of Review and Discussion

In the 2-year carcinogenicity inhalation study conducted in rats, NTP (2018)[1] reported several tumor types with statistically significant increased incidences, compared to incidences in control animals (Table 1). In male rats, there were statistically significant increases in the incidence of thyroid adenomas and carcinomas (combined) exposed to 1000 ppm when compared to incidences of these tumors in the corresponding control group. However, these tumors were largely benign, with a single malignant carcinoma observed in the control group, as well as in a single animal from the 300 and 1000 ppm exposure groups. Statistically significant increases in the incidence of C-cell adenoma of the thyroid were reported in female rats exposed to 1000 ppm, in the incidence of C-cell adenoma and carcinoma (combined) of the thyroid in females exposed to 100 or 1000 ppm, and benign pheochromocytoma of the adrenal medulla in animals exposed to

[1] NTP. 2018. NTP Technical Report on the Toxicology and Carcinogenesis Studies of *p*-Chloro-*α,α,α*-Trifluorotoluene (CAS NO 98-56-6) in Sprague Dawley (Hsd:Sprague Dawley SD) and B6C3F1/N Mice (Inhalation Studies). National Toxicology Program. NTP TR 594. June.

100 ppm. As with the male rats, these tumors were largely benign, with 2 thyroid carcinomas reported in females exposed to 100 ppm and 1 in females exposed to 1000 ppm. While not statistically significantly increased when incidences in exposed groups were compared to incidences in controls, a significant trend was reported for the incidence of alveolar/bronchiolar carcinoma in male rats and adenocarcinoma in the uterus in female rats.

Regarding the observation of thyroid tumors in male and female rats, according to NTP (2018)[1], historical control tumor incidences are typically considered when interpreting the results of studies; however, there are no inhalation historical control data available for the Hsd:Sprague Dawley rats. Therefore, NTP (2018)[1] could not determine if the incidence of thyroid C-cell tumors reported in male and female rats were occurring at rates higher than historical controls.

In the 2-year carcinogenicity inhalation study conducted in mice, NTP (2018)[1] also reported several tumor types with statistically significant increased incidences compared to controls (Table 2). However, the tumors observed were different than those reported in rats. In male mice, statistically significant increases in the incidence of hepatocellular carcinoma were reported in animals exposed to 100, 200 or 400 ppm, hepatocellular hepatoblastoma in animals exposed to 400 ppm, and hepatocellular adenoma, carcinoma or hepatoblastoma (combined) in animals exposed to 200 or 400 ppm. In female mice, there were significant increases in the incidence of hepatocellular adenoma in animals exposed to 200 or 400 ppm, hepatocellular carcinoma in animals exposed to 400 ppm, hepatocellular hepatoblastoma in animals exposed to 400 ppm, and hepatocellular adenoma, carcinoma or hepatoblastoma (combined) in animals exposed to 200 or 400 ppm. A similar dose-response relationship for these tumors was not observed in the female mice compared to the male mice, with the incidence of hepatocellular carcinomas significant only at the highest concentration tested (400 ppm). Significant increases in the incidence of Harderian gland adenoma or adenocarcinoma (combined) were also reported in female mice exposed to 200 or 400 ppm.

NTP (2018)[1] reports that hepatocellular adenomas and carcinomas are the most common primary liver tumors, both spontaneously occurring, and treatment related, in B6C3F1/N mice and they occur more commonly in male mice compared to females. NTP (2018)[1] evaluated specific genetic mutations from hepatocellular carcinomas (genetic *Hras* or *Ctnnb 1* mutations) from both control and exposed groups of mice reported in the NTP (2018)[1] study in order to provide some information regarding the potential mechanisms of the hepatocellular carcinomas observed in mice following exposure to PCBTF. Results of the NTP evaluation indicated a statistically significant trend and pairwise differences in the ***negative*** direction for *Hras* mutations between spontaneous hepatocellular carcinomas in chamber control mice and hepatocellular carcinomas in treated mice, suggesting a decrease in mutations with increasing PCBTF exposure and additional evidence of a lack of the involvement of mutagenicity in the development of the mouse liver tumors. No significant changes were noted in *Ctnnb 1* mutations in mouse hepatocellular carcinomas. NTP (2018)[1] offered no conclusion based on this genetic testing and suggested, in light of the negative genotoxicity results for PCBTF, further mechanistic studies are needed to better understand PCBTF-induced liver tumors.

Based on the results of the PCBTF 2-year inhalation carcinogenicity study in rats and mice, NTP (2018)[1] concluded that there was ***some*** evidence of carcinogenicity in male and female rats based on the incidence of thyroid tumors and ***clear*** evidence of carcinogenicity in male and female mice

based on the incidence of liver tumors. In considering these results in informing the strength of evidence of carcinogenicity to support listing under Proposition 65 as known to cause cancer, these results alone do not provide sufficient evidence. Under the OEHHA regulations, "sufficient evidence" of carcinogenicity from studies in experimental animals exists if there is an increased incidence of malignant tumors or combined malignant and benign tumors in multiple species or strains, in multiple experiments (e.g., with different routes of administration or using different dose levels) or, to an unusual degree, in a single experiment with regard to high incidence, site or type of tumor, or age of onset. The NTP (2018) results do not provide clear evidence of carcinogenicity in multiple species, as the tumors observed in the rats were almost all benign with little progression to malignancy demonstrated and mainly observed in animals receiving the highest concentration tested (1000 ppm). Thus, there is not sufficient evidence of malignancy in two species. In addition, the liver tumors observed in mice do not represent an increase in rare or unusual tumors, but rather tumors that NTP has noted are common in this strain of mice, so do not represent tumors to an unusual degree from a single experiment. The age of first incidence of the combination of malignant tumors considered in the treated mice is also similar to the age of first incidence in the corresponding control mice; therefore, there does not appear to be a difference in age of onset.

In considering the results reported in male and female mice, this would not be considered multiple studies or experiments. In reviewing documentation from the International Agency for Research on Cancer (IARC) that is consistent with the definition of sufficient evidence of carcinogenicity in experimental animals in the OEHHA regulations, multiple experiments are considered to be conducted in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols (IARC 1987)[2]. In addition, standard carcinogenicity testing guidelines provided by the OECD (2018)[3] and the U.S. Environmental Protection Agency (USEPA) Office of Prevention, Pesticides and Toxic Substances (OPPTS) (USEPA 1998)[4] require testing in both sexes of a species as part of the standard protocol. NTP's standard protocol for a chronic toxicity and carcinogenicity study (NTP 2011)[5] requires testing in multiple species, in both sexes for each species and with multiple exposure or dosing groups. Further, the Guidance Criteria for Identifying Chemicals for Listing as "Known to the State to Cause Cancer" (March 2001), indicates that the observation of tumors in two genders of a species does not provide an absolute criterion of causality by itself.

According to NTP (2018)[1], there are no reports of the carcinogenic potential of PCBTF in animals in any other reports provided in the literature. Therefore, the evidence of carcinogenicity in animals is limited to the tumors reported by NTP (2018)[1]. In addition, NTP (2018)[1] further discusses an epidemiological assessment conducted in a cohort of workers (4000) exposed to PCBTF in a mixture with more than 80 other chemicals. The results from this study do not provide any evidence of higher than expected rates of the cancer types reported in NTP (2018)[1], even though the workers were exposed to a large number of chemicals, including PCBTF. Therefore, because

[2] IARC. 1987. IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. World Health Organization, International Agency for Research on Cancer. Supplement 7. Lyon, France.

[3] OECD. 2018. OECD Guideline for the Testing of Chemicals: Carcinogenicity Studies. Test No. 451. Available at: https://read.oecd-ilibrary.org/environment/test-no-451-carcinogenicity-studies_9789264071186-en#page1.

[4] USEPA. 1998. Health Effects Test Guidelines OPPTS 870.4200 Carcinogenicity. United States Environmental Protection Agency, Prevention, Pesticides and Toxic Substances (7101). EPA 712-C-98-211. August 1998.

[5] NTP. 2011. Specification for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program (NTP).

the evidence is limited to one study conducted in animals, with only clear evidence concluded by NTP (2018)[1] for the mouse, the results from the NTP (2018)[1] study do not provide sufficient evidence of carcinogenicity. In addition, as similar tumor responses were not observed across species, it is possible that the mode of action associated with PCBTF exposure and the occurrence of liver and thyroid tumors in mice or rats may be species-specific and not relevant to humans.

In considering data reported in NTP (2018)[1] that may be relevant in further evaluating the sufficiency of the evidence, as well as understanding the potential mode of action for the cancers observed in rats or mice and whether these observations may be relevant to humans, NTP (2018)[1] reported that the available data do not indicate that PCBTF is genotoxic, based on the results from standard *in vitro* assays. In addition, no significant increases in micronucleated erythrocytes were observed in peripheral blood samples from male and female rats exposed to PCBTF for 3 months via inhalation. While NTP (2018)[1] did not propose a mode of action for the tumors observed in mice and rats, NTP (2018)[1] concluded that the mode of action for carcinogenicity observed in the animals in the current study is unlikely to be driven by genotoxicity. This, in combination with the observation of the majority of the tumors reported in animals following exposure to high concentrations of PCBTF, suggests a potential mode of action resulting from repeated cytotoxicity and cell regeneration and therefore, provide support for a nonlinear mode of action. NTP (2018)[1] notes strong nonneoplastic responses in the lung and liver of both sexes in both rats and mice suggestive of inflammation and cytotoxicity. NTP (2018)[1] also notes that PCBTF has been reported to increase CYP2B activity and CYP2B activation via the constitutive androstane receptor (CAR) which is a known mechanism of tumor promotion activity in the liver of rodents. They further note that the liver weight changes and nonneoplastic lesions observed in the 3-month and 2-year studies for both rodent species is consistent with a potential CAR-mechanism of action. While NTP proposes further mechanistic studies to investigate the mode of action for the liver tumors observed in mice, the development of liver tumors in rodents that are induced via CAR-activation is not considered relevant to humans.[7] Integration of the available data for PCBTF from other studies, as well as the results from the NTP (2018)[1] study, may provide additional evidence for a mode of action for the carcinogenicity observed in animals that is animal-specific and may also indicate a threshold below which no increase in tumor incidence would be expected. Therefore, the assumption of linearity in low-dose extrapolation (e.g., any exposure is associated with some level of risk of cancer), which is the default assumption for most regulatory assessments if a chemical is genotoxic, is inconsistent with the NTP (2018)[1] results for PCBTF, which provide support for a non-linear mode of action for carcinogenicity. 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.

Of additional importance is that the observed tumors were not consistent across animal species. While significant increases in liver tumors in male mice and liver and Harderian gland tumors in female mice were reported, no significant increase in these tumors was reported in rats, further suggesting a possible mode of action for liver carcinogenicity that could be mouse-specific and raise questions of relevance to human health (Klaunig et al. 2003[6]; Holsapple et al. 2006[7]; Corton

[6] Klaunig JE, Babich MA, Baetcke KP, Cook JC, Corton JC, David RM, DeLuca JG, Lai DY, McKee RH, Peters JM, Roberts RA, Fenner-Crisp PA. 2003. PPARα agonist-induced rodent tumors: modes of action and human relevance. Critical Reviews in Toxicology, 33(6): 655-780.

[7] Holsapple MP, Pitot HC, Cohen SM, Boobis AR, Klaunig JE, Pastoor T, Dellarco VL, Dragan YP. 2006. Mode of action in relevance of rodent liver tumors to human cancer risk. Toxicological Sciences, 89(1): 51-56.

et al. 2018[8]). The lack of genotoxicity evidence for PCBTF suggests a potential nonlinear mode of action by which carcinogenic effects may occur following exposure to high concentrations above a threshold concentration. This threshold could possibly be higher than expected human exposures. The National Research Council (2014)[9] notes the importance of assessing evidence that environmental chemicals can cause adverse health effects based on what is known about current human exposure levels. The observed effects reported in NTP (2018)[1] occurred at concentrations orders of magnitude higher than human exposures (100 ppm in mice and rats compared to 1.15 ppm occupational exposure) (Lee 2015)[10]. Further review of the evidence relevant to the mode of action of PCBTF is required to determine both if the tumors observed in animals are relevant to people and if the results from NTP (2018)[1] demonstrate a threshold higher than expected exposure concentrations in humans and below which carcinogenicity would not be expected.

[8] Corton JC, Peters JM, Klaunig JE. 2018. The PPARα-dependent rodent liver tumor response is not relevant to humans: addressing misconceptions. Archives in Toxicology, 92(1): 83-119.

[9] National Research Council. 2014. Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC: The National Academies Press.

[10] Lee EG, Lewis B, Burns DA, Kashon M, Kim SW, Harper M. 2015. Assessing Exposures to 1-chloro-4-(trifluoromethyl) benzene (PCBTF) in U.S. Workplaces, Journal of Occupational and Environmental Hygiene, 12:7 D123-D130.

Table 1. Male and Female Rats Tumor Incidence (NTP 2018)				
Endpoint	**0 ppm**	**100 ppm**	**300 ppm**	**1000 ppm**
Male Rats				
Thyroid gland C-cell adenoma	2/50[a,b]	5/49	3/49	12/50**
Thyroid gland C-cell adenoma and carcinoma (combined)	3/50[a,b]	5/49	4/49	13/50**
Lung alveolar/bronchiolar carcinoma	0/50	0/50	0/50	2/50
Female Rats				
Thyroid gland C-cell adenoma	2/50[b]	8/50	8/50	14/50**
Thyroid gland C-cell adenoma or carcinoma (combined)	2/50[b]	10/50*	8/50	15/50**
Adrenal medulla benign pheochromocytoma	0/49[b]	3/50	4/50	6/50*
Uterus adenocarcinoma	1/50[b]	1/50	0/50	5/50

[a] Incidence data are presented as number of animals with tumor over number of animals examined
[b] Statistically significant trend

*Statistically significant at $p < 0.05$**Statistically significant at $p < 0.001$

Table 2. Male and Female Mice Tumor Incidence (NTP 2018)				
Endpoint	**0 ppm**	**100 ppm**	**200 ppm**	**400 ppm**
Male Mice				
Hepatocellular carcinoma	8/50[a,b]	19/50*	16/50*	35/50**
Hepatoblastoma	1/50[b]	1/50	1/50	15/50**
Hepatocellular adenoma, carcinoma or hepatoblastoma (combined)	31/50[b]	37/50	40/50*	48/50**
Female Mice				
Hepatocellular adenoma	12/50[b]	14/50	24/50*	34/50**
Hepatocellular carcinoma	7/50[b]	8/50	12/50	34/50**
Hepatoblastoma	0/50[b]	0/50	1/50	8/50*
hepatocellular adenoma, carcinoma or hepatoblastoma (combined)	18/50[b]	18/50	29/50*	46/50**
Harderian gland adenoma or adenocarcinoma (combined)	2/50[b]	6/50	9/50*	8/50*

[a] Incidence data are presented as number of animals with tumor over number of animals examined

[b] Statistically significant trend

*Statistically significant at $p < 0.05$

**Statistically significant at $p < 0.001$