Responses to Public Comment on the Draft Cancer Inhalation Unit Risk Factor for *p*-chloro-α,α,α-trifluorotoluene (Parachlorobenzotrifluoride, PCBTF)

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Introduction

On October 18, 2019, the Office of Environmental Health Hazard Assessment (OEHHA) released the draft document, *p Chloro-α,α,α-trifluorotoluene (p-chlorobenzotrifluoride, PCBTF) Cancer Inhalation Unit Risk Factor* to solicit public comment. Written comments on the draft Inhalation cancer Unit Risk Factor (IUR) for PCBTF were received from the American Coatings Association (ACA).

The Air Toxics Hot Spots statute (Health and Safety Code Section 44360(b)(2)) requires the Office of Environmental Health Hazard Assessment (OEHHA) to develop guidelines for conducting health risk assessments carried out within the Hot Spots program. To meet this requirement, OEHHA published a Technical Support Document (TSD) in 2009 that reviews the methodology the office has used over the years to derive cancer potency factors. The TSD also provides updated calculation procedures for estimating cancer potency factors, including procedures for evaluating the increased susceptibility of infants and children to carcinogens.

The methods recommended in the TSD are generally similar to those described in the US Environmental Protection Agency's (US EPA) Carcinogen Risk Assessment Guidelines (2005). The TSD therefore refers to US EPA (2005) for additional discussion of various procedures that are also used by OEHHA. The TSD provides more detailed guidance in cases where OEHHA recommendations are different from those of US EPA.

The guidelines presented in the 2009 TSD were used to derive an IUR for PCBTF.

Responses to ACA Comments

In the following sections, OEHHA summarizes the substantive issues raised in the ACA comment letter and provides responses to these issues.

ACA Comment 1

ACA asserts that in deriving the proposed IUR, OEHHA has:

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

For example, ACA states:

> "In the estimation of the Cancer Slope Factor (CSF) or Inhalation Unit Risk (IUR) for PCBTF, OEHHA (2019) has applied linear low-dose extrapolation. This default assumption is incorrect, because it assumes that PCBTF is mutagenic. The available data show that PCBTF is not mutagenic."

And further:

> "When a chemical is not mutagenic - as is the case with PCBTF - the application of non-threshold or linear approaches are inappropriate. This opinion is shared by other authorities such as the United States Environmental Protection Agency (USEPA). […] The USEPA (2005) guidelines indicate that linear extrapolation should be used for agents that are DNA-reactive and have direct mutagenic activity. However, when a chemical is not mutagenic - as is the case with PCBTF - USEPA (2005) provides guidelines for a nonlinear approach."

Response to Comment 1

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

In addition, OEHHA provides the following point of clarification regarding its use of genotoxicity (and mutagenicity) information in cancer risk assessment. As noted above, OEHHA's methods are generally consistent with US EPA's 2005 Guidelines for

Carcinogen Risk Assessment. However, OEHHA diverges somewhat from US EPA in regard to use of genotoxicity information. Unlike US EPA, OEHHA's cancer methodology does not depend upon making a sharp distinction between genotoxicity and mutagenicity. The TSD, at page 18, states:

> "Genetic damage in exposed organisms includes both gene mutations (point or frameshift), and larger scale effects such as deletions, gene amplification, sister-chromatid exchanges, translocations and loss or duplication of segments or whole chromosomes. These genetic effects of chemical exposures are deleterious in their own right. In addition, since carcinogenesis results from somatic mutations and similar genetic alterations, agents that cause genetic damage generally have carcinogenic potential."

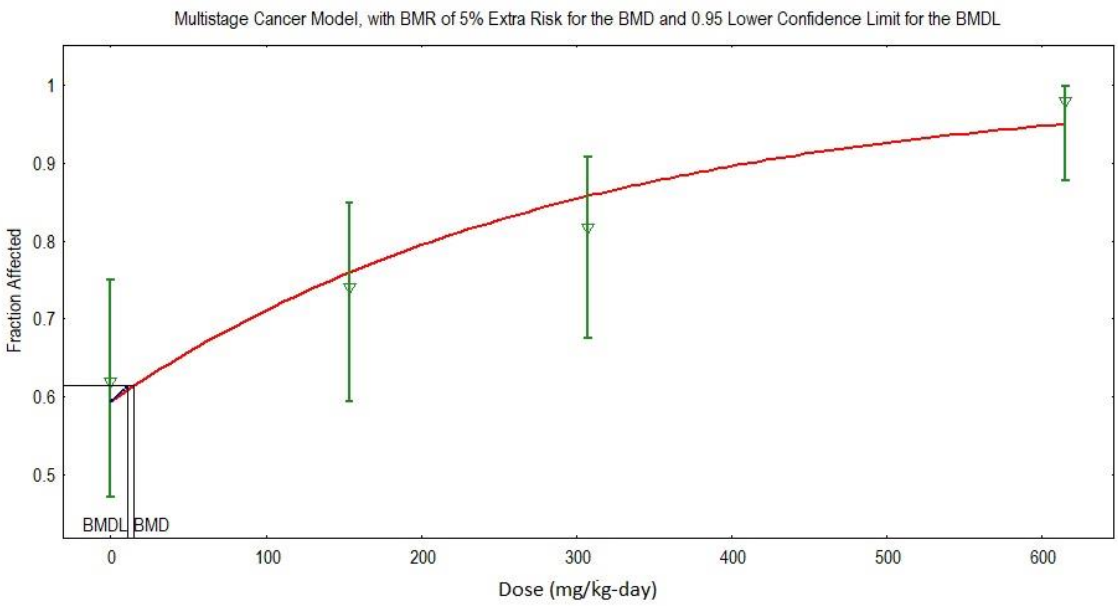
Contrary to ACA's assertion regarding the use of a low-dose linear risk model, OEHHA's use of the model in this case is consistent with US EPA's 2005 guidelines on page 3-21, which state:

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

OEHHA guidelines over the years have also noted that the linear low-dose assumption used with the multistage cancer model, is "an appropriate method for dose extrapolation in most cases" (see TSD, page 75).

As the following dose-response graph (adapted from Figure 2 of the IUR document) illustrates, the data for mouse liver tumors, from which the IUR value was derived, does not indicate the presence of a threshold for PCBTF tumor induction.

BMDS dose-response graph for liver tumors in male mice exposed to PCBTF



ACA Comment 2

ACA challenges OEHHA's assessment of the available genotoxicity data as providing "some evidence" that PCBTF is a genotoxic substance. ACA states that OEHHA's conclusion contradicts that of the NTP:

> "OEHHA's approach is inconsistent with conclusions reached by NTP (2018), which found that PCBTF is neither mutagenic nor more generally genotoxic."

ACA's further criticism focuses on the small proportion of studies that reported positive genotoxic outcomes, as well as the quality of the studies reporting positive results. In particular, ACA takes issue with the positive genotoxicity results obtained for unscheduled DNA synthesis (UDS) by Benigni et al. (1982), for sister chromatid exchanges (SCE) by Litton Bionetics (1979) and for micronucleus formation by NTP (2018).

Response to Comment 2

OEHHA's review of the available genotoxicity information on PCBTF included the Benigni et al. (1982) study that was apparently not considered by NTP (2018) and which

reported a positive finding for unscheduled DNA synthesis in human embryonic epithelial cells.

The UDS results obtained by Benigni, et al. (1982) are presented in the following table. A monotonic dose-response can be seen for concentrations between 0 and 2 µl/ml. The three highest concentrations showed a statistically significant increase in UDS. The positive, but relatively decreased response at 10 ul/ml may be due to cytotoxicity given that the method tests a range of concentrations leading up to, but below concentrations that produce excessive cell loss due to cytotoxicity (San and Stich, 1973).

UDS Results for PCBTF (Benigni, et al., 1982)

Concentration (µl/ml)	Mean net grains per nucleus	Standard error of replicates
0	1.78	0.53
0.2	3.08	1.7
1	10.02 *	2.21
2	19.82 *	2.18
10	11.94 *	1.33

* Significant at p=0.01 by t-test.

However, OEHHA notes that the concentrations of PCBTF tested by Benigni, et al. (1982) are well above concentrations that would have been attained in the blood of the rats and mice exposed in the NTP (2018) cancer studies. For example, female rats exposed to 50 ppm PCBTF for six hours had blood levels of 6 µg/ml (0.0045 µl/ml) (Newton, et al. 1998); modeled blood concentrations at 250 ppm exposure for 6 hours were approximately 36 µg/ml (0.027 µl/ml) (Knaak, et al. 1998).

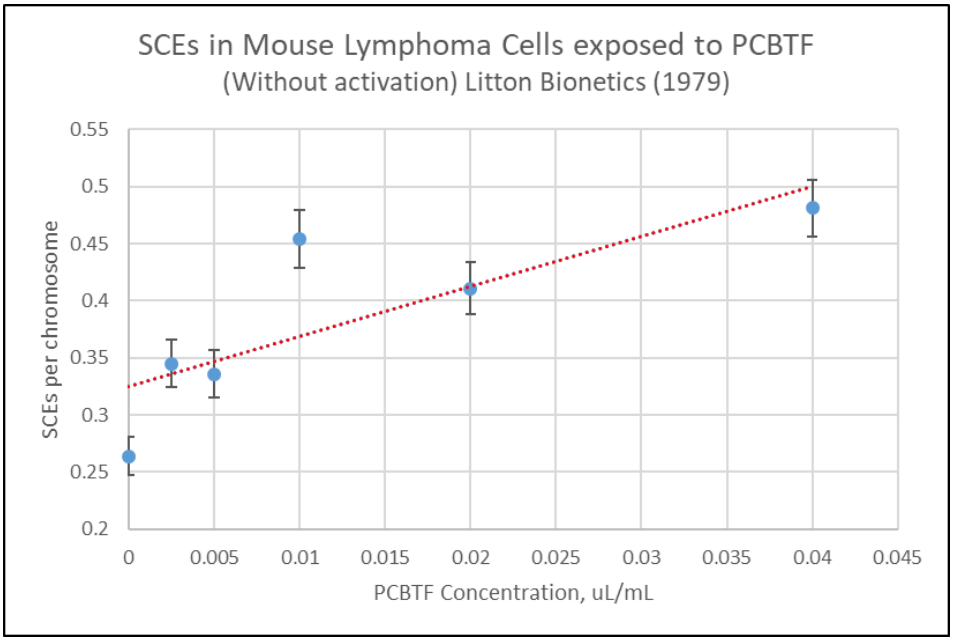
Nonetheless, this additional positive result along with the other limited positive test data, led us to conclude that there was “some evidence” of genotoxicity.

In addition, as we noted in the IUR document, two of the more sensitive genotoxicity assays, namely the “single-cell, gel electrophoresis” (comet) test for DNA-strand breaks and tests measuring oxidative DNA damage or DNA-adduct formation, have apparently not been completed for PCBTF or its metabolites. This represents a data gap in the PCBTF genotoxicity database.

In its comments on the Benigni, et al. (1982) study, ACA incorrectly claims that, “incidences of UDS did not increase with increasing concentration.” ACA additionally hypothesizes that all the positive results in Benigni may be due to cytoxicity. However,

this seems unlikely since measurements are to be taken at the exposure time that triggers the highest level of DNA-repair synthesis without substantial lethality, according to San and Stich (1973).

In its assessment of the Litton Bionetics (1979) SCE study, ACA correctly observes that SCEs per chromosome in the test without microsomal activation were significantly increased compared to controls for all tested concentrations of PCBTF (t-test p-values < 0.01). ACA notes as well that 3 of 5 tested concentrations with activation displayed elevated SCEs. However, ACA incorrectly asserts that the increases in the non-activated test did not display a dose-response trend. As shown in the following chart, the data do indicate a clear trend. (The trend line in the chart is based on a linear regression and the error bars represent the standard error of the replicates).



Regarding the *in vivo* micronucleus tests in rats and mice, NTP (2018) observed significantly increased micronuclei only in male mice. The NTP report, at page 72, states:

> "In mice from the 3-month study, small but statistically significant increases in micronucleated mature erythrocytes were seen [in males and females] at the highest exposure concentration (2,000 ppm), but the observed values for the female mice were within historical control ranges […] and were not considered to be biologically significant […] For male mice, the observed response was outside the historical control range for the laboratory and was therefore judged to be positive."

ACA notes that postive results were obtained in the male mouse at an exposure concentration above those used in the NTP (2018) carcinogenesis study, "suggesting micronuclei are not part of the mode of action for the observed tumors in rodents."

OEHHA agrees that the positive result for male mice at 2000 ppm exposure are greater than the levels of exposure used in the NTP (2018) lifetime mouse studies (≤ 400 ppm). We would also point out, however, that the micronucleus test was based upon a subchronic exposure. Positive results may have been observed at lower exposure concentrations had the test been completed after a chronic exposure to PCBTF.

Notwithstanding our disagreement with various specific elements of ACA's overall genotoxicity commentary, OEHHA concurs with ACA that there is "at best, limited evidence *in vitro* that PCBTF is genotoxic." To this we would add that the result for micronucleus formation in the male mouse, *in vivo*, (NTP 2018) also provides limited evidence. Accordingly, OEHHA has revised the wording of its conclusion from "some evidence," to "limited evidence" that PCBFT is genotoxic.

However, as already noted, OEHHA does not require a positive finding of genotoxicity (or mutagenicity) in order to apply the low-dose linear assumption in cancer dose-response modeling. Evidence that a chemical is either genotoxic or mutagenic can provide added support for low-dose linearity, but lack of such evidence does not rule out its use.

ACA Comment 3

ACA states:

> "In its report, OEHHA (2019) noted concern regarding the generation of a reactive and genotoxic metabolic intermediate that could potentially be of concern in determining the mutagenic potential of PCBTF. However, the potential for a mutagenic metabolite is not supported by the available evidence provided in Table 4 of OEHHA (2019)…"

Response to Comment 3

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

ACA Comment 4

OEHHA did not consider all available data for the mouse liver tumors. Specifically, OEHHA did not conduct a proper assessment of the Constitutive Androstane Receptor (CAR) mode of action for mouse liver tumors proposed by NTP (2018), which is supported by available data. For example, ACA states:

> "The available science for PCBTF is consistent with a mode of action (CAR activation) proposed by the NTP (2018) for male mice liver tumors (the endpoint relied upon for the OEHHA recommended IUR). Further, tumors occurring by this mode of action in rodents are not relevant to human health. As such, OEHHA should either abandon use of the mouse liver tumor data when developing the CSF/IUR 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."

Response to Comment 4

First, ACA is incorrect to say that NTP (2018) "proposed" a CAR-based mode of action (MOA). NTP discussed some of the evidence indicating that PCBTF may be a CAR activator in rats and mice. The relevant paragraph of the NTP report at page 76 states:

> "There is evidence that [PCBTF] inhalation exposure can lead to CYP2B induction in the liver of Sprague-Dawley rats […] ; liver microsomes from male rats exposed to 250 ppm [PCBTF] had approximately six times higher CYP2B activity compared to controls, with little activity seen at lower exposure concentrations or in females. Other CYP isoforms evaluated also showed higher activity in exposed animals; however the strongest induction was CYP2B. CYP2B activation via the constitutive androstane receptor (CAR) is a known mechanism of tumor promotion activity in the liver of rodents [...] The potential for [PCBTF] to activate CAR was evaluated in the Tox21 screening program but results were inconclusive [...] Liver weights and nonneoplastic lesions observed in the current 3-month and 2-year studies are also consistent with a potential CAR-mechanism of action and similar responses have been observed in other studies with CAR/CYP2B inducers..."

In the same report section, NTP concludes that, "further mechanistic studies are needed to better understand [PCBTF-induced] hepatocellular carcinogenesis."

Second, it has not been adequately demonstrated that rodent liver tumor data from chemicals fitting the putative CAR adverse outcome pathway (AOP) are irrelevant to human cancer risk assessment.

The main elements of the CAR AOP are:

- Activation of the constitutive androstane receptor (CAR)
- Altered expression of hepatic, CAR-dependent genes related to cell cycle control (associated events: CYP2B and CYP3A induction, increased liver weight, and hepatocellular hypertrophy)
- Increased mitogenic cell proliferation of hepatocytes
- Increased pre-neoplastic liver foci
- Increased hepatocellular adenomas or carcinomas

Recent studies in CAR/PXR[1] humanized mice indicate that induction of mouse and human CAR/PXR lead to very similar responses. Luisier et al. (2014) examined early and late transcriptomic responses to sustained phenobarbital (PB) exposure (90 days) in liver tissue from double knockout CAR and PXR, double humanized CAR and PXR, and wild-type C57BL/6 mice. Transient induction of genes associated with DNA replication, cell cycle, and mitosis, and the proliferation-related nuclear antigen Mki67 were observed in both humanized CAR/PXR mice and wild-type mice. These responses are consistent with hepatocyte proliferation. Peak expression occurred between 1 and 7 days of PB exposure. All of these responses were absent in the knockout mouse livers and were reversible in wild-type and humanized mice with a 4-week recovery period following exposure. These data suggest that the activation of both mouse and human CAR by PB leads to very similar hepatic xenobiotic and proliferative transcriptional responses in a C57BL/6 mouse genetic background (Luisier et al., 2014).

In another study, male transgenic mice expressing human CAR and PXR were used to investigate possible differences between wild-type and humanized mice in their responses to PB (Braeuning et al., 2014). In this tumor initiation/promotion study, a single initiating dose of N-nitrosodiethylamine was given, followed by PB treatment for 10 months. The authors state that the tumor response in PB-treated humanized mice was less pronounced regarding tumor volume fraction and tumor multiplicity, but that "phenobarbital-mediated tumor promotion clearly occurs in mouse liver expressing the human CAR and PXR receptors" (Braeuning et al., 2014). Specifically, the liver tumor incidences observed in mice treated with the initiator alone were 7/15 adenomas in wild-type mice and 12/15 adenomas in humanized mice, and in mice treated with the initiator

[1] PXR: the Pregnane X Receptor.

and with PB promotion the incidences were 14/14 liver adenomas in wild-type mice and 15/15 liver adenomas in humanized mice.

Third, even if the assumption were made that rodent liver tumor data for chemicals fitting the putative CAR adverse outcome pathway (AOP) are not relevant to human cancer risk assessment, the evidence supporting the CAR MOA for PCBTF liver tumor formation in mice is still incomplete.

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

More generally, alternative MOAs should be considered and studied before concluding that a single mechanism, such as the CAR AOP, is operative for any particular tumor type. A broader approach is necessary to identify other potential pathways of tumor induction. This can be accomplished, for example, through the use of genome-wide, chromosome-wide, and transcriptome-wide association studies (Shen, et al. 2015).

One example of such an approach was applied by Nesnow et al. (2009) to three CAR activators, namely phenobarbital (PB), triadimefon, and propiconazole. These investigators looked at transcriptional profiles in animals treated with these compounds, and found the profiles differed significantly across the three CAR activators. This work led Nesnow et al. (2009) to conclude that the mechanisms of tumorigenic action were likely to differ across the three CAR activators, and to investigate novel MOAs for propiconazole, based on transcriptomics and metabolomics data (Nesnow 2013).

ACA Comment 5

In footnote 2 of its comment letter, ACA cites an unpublished 1992 epidemiological report[2] of Occidental Chemical Corporation workers. ACA states that the results from this study:

> "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 [...] 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."

Response to Comment 5

OEHHA obtained and reviewed this unpublished study (Occidental Chemical Corporation, 1992) after we released our draft IUR document. The study was commissioned by Occidental Chemical and carried out by researchers from the University of Pittsburgh. It evaluated cancer incidence in approximately 4,000 predominantly male workers at the Occidental Chemical Corporation plant in Niagara, NY. Statistically significant increases in respiratory system and stomach cancers were found in the study cohort.

As noted in ACA's comment, the workers in this study were exposed to a large number of chemicals in addition to PCBTF. OEHHA adds that these chemicals included various known or suspected carcinogens, such as: benzene, trichloroacetic acid, trichloroethylene, perchloroethylene, lindane, mirex, and asbestos. Individual chemical risks could not be identified in the study due to the lack of chemical-specific, worker or workstation exposure data.

ACA asserts that since workers in this study did not display elevated levels of the tumor types observed in laboratory animals, the study provides evidence that PCBTF is not carcinogenic to humans.

OEHHA disagrees. Had the workers in this study been exposed to PCBTF alone, the observed elevated rates of respiratory and stomach cancer would provide qualitative evidence of PCBTF's carcinogenic potential. In the absence of a quantitative worker exposure assessment, the NTP (2018) animal study results should be used to carry out

[2] This study was actually completed by the researchers in 1984 but submitted to the company in 1992.

a dose-response assessment, irrespective of the lack of cross-species tumor-site concordance.

Tumor-site concordance is not required for cancer hazard or risk assessment. Although the basic cellular mechanisms of carcinogenesis are similar among mammals, this does not imply that exposure to a chemical carcinogen will always produce cancer in the same organ in different species (US EPA, 2005). Accordingly, there is no expectation of tumor-site concordance when using animal studies to predict human cancer risk (OEHHA, 2009).

However, given that plant workers were actually exposed to unknown concentrations of multiple potential carcinogens (including PCBTF), this study provides no useful information with which to assess PCBTF's carcinogenicity.

ACA Comment 6

ACA asserts that "OEHHA did not use generally accepted modeling approaches." Specifically, ACA says that OEHHA relied upon draft (2014) BMDS guidance instead of US EPA's final BMDS guidelines (US EPA 2012). For example, ACA states:

> "When selecting a dose-response model, OEHHA (2019) appears to have used methods taken from a 2014 draft operating procedure for USEPA subcontractors […] 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."

Regarding the use of Akaike's Information Criterion (AIC) for model selection, ACA further states:

> "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."

Response to Comment 6

OEHHA generally follows US EPA guidance on the proper use of its BMD software. This includes the 2012 BMDS technical guidelines (US EPA 2012), the user manuals for BMDS version updates, US EPA on-line tutorials, and the various guideline addenda

published by US EPA's BMDS program. (This does not mean however, that we rigidly adhere to every recommendation in these guidelines. For example, OEHHA normally prefers to use a benchmark response rate of 5% in fitting models to data from NTP cancer studies in rodents, whereas US EPA recommends a default value of 10%.)

The 2014 US EPA document to which ACA refers in its commentary is titled: "Choosing Appropriate Stage of a Multistage Model for Cancer Modeling (BMDS Technical Guidance)" (US EPA 2014). It is a technical memo that represents a minor addendum to the 2012 BMDS technical guidance and provides a standard procedure for analysts in choosing the appropriate stage of the multistage cancer model. It recommends that in some cases the analyst should forego the use of the AIC to choose the final model. (The AIC is a calculated value that can be used to identify, from a set of well-fitting models, a model that provides an optimal balance between model-fit and model-parsimony.)

According to US EPA, this guideline "has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication." (See US EPA web page, https://cfpub.epa.gov/ncea/bmds/recordisplay.cfm?deid=308382). OEHHA contacted US EPA BMDS staff about the status of the 2014 guidance memo, and they verified that it has been officially recommended by the Agency Statistical Workgroup (AGS) for use in US EPA risk assessments.

ACA is incorrect in stating that we only used Chi-squared measures of fit (i.e., p-values) to judge the fit of the multistage models to the data. We also used:

- The scaled residual for the dose nearest the benchmark dose (BMD), whose absolute value should be < 2.
- Visual inspection of the overall curve fit, particularly in the low-dose region.
- AIC comparison to consider model parsimony, when recommended by the 2014 BMDS guidance addendum.

OEHHA also notes that using the 2014 BMDS guideline for male mouse liver tumors, upon which the proposed IUR is based, produces the same BMDL value as is obtained by using only the 2012 guidelines.

OEHHA also fixed a typographical error in the IUR document (pointed out by ACA) that referred to the 2014 guidance as "US EPA 2016."

Additionally, OEHHA added a column to Table 8 of the IUR document, indicating cases in which the AIC or an alternative method was used to choose the model for each tumor

site. We also provided text to the Model Calculations section of the Document describing the reasons for those choices.

ACA Comment 7

ACA stated that OEHHA ignored its own peer-reviewed final guidance (OEHHA 2009) on dose-response modeling. Specifically, ACA states:

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

Response to Comment 7

OEHHA used two standard methods to adjust the tumor-incidence data for differential early mortality in the animal studies. The "effective number" method was used for mice and the "poly-3" method was used for rats. These methods, which are described in more detail in the IUR document, have been used regularly by OEHHA, US EPA and researchers in the field. For example, OEHHA recently used the effective-number method in developing IURs for perchloroethylene, t-butyl acetate, and cobalt compounds. US EPA used effective-number for biphenyl, pentachlorophenol, and RDX.

As noted in the IUR document, OEHHA uses the poly-3 method in cases where differential mortality across dose groups is greater than roughly 15 percent prior to study-week 85 (or time-to-tumor modeling may be used when differential mortality is more severe).

ACA stated that the effective-number and poly-3 methods are "not recommended" in either US EPA (2005) or OEHHA's TSD. More precisely, these methods are not addressed in the guidelines.

US EPA does however, discuss the use of these methods in some of its Integrated Risk Information System (IRIS) toxicological reviews. For example, in the IRIS review for trichloroethylene (US EPA 2011, Appendix G, page G-1), US EPA discusses when the poly-3 method (or time-to-tumor modeling) is preferred over the effective-number method:

> "In cases in which there is high early mortality or differential mortality across dose groups and the individual animal data are available, a more involved analysis that takes into account animals at risk at different times (ages) is preferred (e.g., the poly-3 approach or time-to-tumor modeling…"

Regarding the use of time-to-tumor models, US EPA (2005) mentions them briefly in a single passage on page 3-15, discussing mathematical models and the need to sometimes use alternative models to get reliable results. Here, US EPA states:

> "when there are large differences in survival across dose groups […] models that include time-to-tumor or time-to-event information *may be useful*." [emphasis added]

The TSD and previous guidelines used by OEHHA -- such as the 1985 California Department of Health Services guidelines (CDHS 1985) -- also discuss the use of time-to-tumor models. The TSD, at page 75, notes that in CDHS (1985):

> "Several models were proposed for extrapolating low-dose human cancer risk from animal carcinogenicity data [...] The [1985] guidelines stated that time-to-tumor models (i.e., a Weibull-in-time model) should be used for low-dose extrapolation in all cases where supporting data are available, particularly when survival is poor due to competing toxicity."

> "However, the [1985] guidelines also noted the difficulty of determining the actual response times in an experiment. Internal tumors are generally difficult to detect in live animals and their presence is usually detected only at necropsy. Additionally, use of these models often requires making the determination of whether a tumor was the cause of death, or was found only coincidentally at necropsy when death was due to other causes. Further, competing causes of death, such as chemical toxicity, may decrease the observed time-to-tumor for nonlethal cancers by allowing earlier necropsy of animals in higher dose groups."

In short, both OEHHA and US EPA guidelines present time-to-tumor analysis as an option (not a requirement) that may be used when survival is poor in some dose groups, and when the appropriate information to run the model is available.

ACA Comment 8

ACA notes: "PCBTF was developed as a substitute for use in ACA member products precisely because it assists in reducing the public health effects of ground level ozone. Currently, there are no viable alternatives available to replace PCBTF where it is used

as an exempt solvent […] Over-regulating this chemical to avoid an uncertain hazard (i.e., potential health effects in humans) will only bring about the near-certain public health impacts of increased ground level ozone."

Response to Comment 8

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

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