October 24, 2016

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RE: Comments to the Carcinogen Identification Committee (CIC) on Possible Prioritization of Type I Pyrethroids

Dear Ms. Ramirez:

The Consumer Specialty Products Association[1] offers the following comments for the November 15, 2016 meeting of the Carcinogen Identification Committee (CIC). The CIC is being asked by California's Office of Environmental Health Hazard Assessment (OEHHA) to advise OEHHA on whether Type I Pyrethroids as a group, or specific individual compounds within the group, should be considered for listing at a future CIC meeting. The Consumer Specialty Products Association (CSPA) believes there is no scientific basis for prioritizing or listing Type I Pyrethroids as a group. Instead, CSPA believes the CIC should recommend to OEHHA that it

[1] CSPA is the premier trade association representing the interests of companies engaged in the manufacture, formulation, distribution and sale of more than $100 billion annually in the U.S. of familiar consumer products that help household and institutional customers create cleaner and healthier environments. CSPA member companies employ hundreds of thousands of people globally. Products CSPA represents include disinfectants that kill germs in homes, hospitals and restaurants; air fresheners, room deodorizers and candles that eliminate odors; pest management products for home, lawn and garden, and pets; cleaning products and polishes for use throughout the home and institutions; products used to protect and improve the performance and appearance of automobiles; aerosol products and a host of other products used every day. Through its product stewardship program, Product Care®, and scientific and business-to-business endeavors, CSPA provides its members a platform to effectively address issues regarding the health, safety and sustainability of their products.

consider only individual chemicals within this class as potential candidates for prioritization in accordance with OEHHA's Process for Prioritizing Chemicals for Consideration under Proposition 65 by the "State's Qualified Experts" (OEHHA, 2004).

CSPA's views are summarized below based on our scientific review of the carcinogenicity evidence for select Type I Pyrethroids summarized by OEHHA, the underlying documents and peer-reviewed studies on which the summaries are based, as well as other relevant peer-reviewed literature and regulatory documents relevant to those compounds specifically reviewed by OEHHA, as well as others in this class of chemicals. OEHHA's summary of the available scientific information is inadequate for prioritization of Type I Pyrethroids as a group.

Specifically, OEHHA's summary identifies eight individual chemicals that are not listed as carcinogens under Proposition 65.[2] There are at least three other chemicals in this group that are used in commerce and for which OEHHA summarizes no data, for a total of at least 11 chemicals in this group. OEHHA summarizes epidemiological data on only four of the eight chemicals it identified, and for three of these chemicals there is only one epidemiological study, which is of questionable value. OEHHA likewise summarizes no mechanistic data on four of these eight chemicals. While these chemicals share a chemical structure, the data summarized by OEHHA indicate that they do not share a mechanism of action (MOA) and that their potential for carcinogenesis varies significantly from one chemical to another.

CSPA therefore believes there is not a scientific basis for Type I Pyrethroids to be considered for listing as a group. Furthermore, CSPA believes that the CIC, as well as OEHHA, needs to keep in mind the important legal and policy issues that arise when a group of chemicals is listed collectively. Except under the rare situations where every chemical in the group is precisely as toxic as every other chemical in the group, or where the chemicals are always found in the same ratio to one another in a mixture to which Californians are exposed, it is impossible for OEHHA to develop a no significant risk level (NSRL) for the group of chemicals. It is equally improbable for a member of the regulated community to do so in order to determine whether its uses of one or more of the chemicals require a warning under Proposition 65, much less to justify such a level in defense of an enforcement action. As a result, the use of any chemical in the listed group will either be eliminated or result in warnings, even though the individual chemical may not meet the criteria for listing on its own much less

[2] One of the chemicals for which OEHHA summarizes data (resmethrin) was previously listed as a carcinogen under the authoritative bodies mechanism.

require a warning based on its individual toxicity characteristics and exposure scenarios. In addition, listing as a group would *likely* lead to over warning, a scenario that OEHHA recently addressed with the Clear and Reasonable Warning amendments. CSPA therefore believes that the CIC and OEHHA need to evaluate group listings with appropriate scientific skepticism and require a strong showing of consistent MOA and toxicity characteristics for every chemical in a group before a group should be listed.

GENERAL COMMENT 1: The animal tumor data and mechanistic data for the various Type I Pyrethroids tested demonstrate inconsistent results and diverse findings among these compounds, indicating that these compounds should not be considered as a group for listing as Proposition 65 carcinogens.

Comment 1a: A number of Type I Pyrethroids do not demonstrate significant increases in tumorigenicity in animal studies.

To justify the classification of a group of chemicals as carcinogens, there should exist some evidence that, for those members of the group that have been tested, each demonstrates tumorigenic responses in animals. In the case of Type I Pyrethroids, there are at least three compounds for which none of the animal carcinogenicity data are statistically significant: *d*-phenothrin (included in OEHHA's preliminary toxicology review), prallethrin and imiprophrin (neither of which were included in OEHHA's preliminary toxicology evaluation).

For *d*-phenothrin (a.k.a., Sumithrin), OEHHA cites positive liver tumor data in one of three 2-year rat feeding studies (OEHHA, 2016). The remaining two studies were negative for treatment-related tumorigenicity. In reviewing the single positive 2-year study, the USEPA noted that the increase in hepatocellular carcinomas only occurred at a dose level described as "excessively toxic limit dose of 20,000 ppm" of *d*-phenothrin, and did not reach statistical significance (EPA, 2008a). As a result of these studies, as well as chronic studies in dogs and mice that showed no statistically significant increase in tumors, the USEPA concluded *d*-phenothrin was not likely to be carcinogenic, and classified this Type I Pyrethroid as "Not likely to be carcinogenic to humans."

In the case of prallethrin, the USEPA and WHO reviewed the chronic toxicity data (lifetime dietary studies in rats and mice) and concluded there was no evidence of carcinogenicity in either species (Federal Register, 2000; WHO, 2004). Similarly, imiprothrin elicited no statistically significant tumorigenic or neoplastic changes in lifetime dietary exposure studies in rats (doses up to 219 mg/kg bw/day) or mice (doses up to 814 mg/kg bw/day) (Health Canada, 2003; EU, 2010). Therefore, the EU concluded that classification for carcinogenicity is not considered appropriate for imiprothrin.

Finally, the mixed Type I & II pyrethroid fenpropathrin (also not included in OEHHA's preliminary toxicology evaluation) tested negative for tumorigenicity in animal studies. As summarized by both USEPA and WHO, fenpropathrin administered via diet in chronic 2-year feeding studies failed to elicit significant increases in tumors at any sites in either CD-1 mice or CD rats (EPA, 2008b; WHO, 2012).

In summary, prioritizing the whole group of Type I Pyrethroids for consideration as potential carcinogens under Proposition 65 is unjustified given that there are members of this group that have been tested in animal carcinogenicity studies and were shown to elicit no tumorigenic responses. As OEHHA's prioritization process states: "It is unlikely that chemicals will be proposed for CIC [. . .] review that have been recently reviewed by an authoritative body and found to have insufficient evidence of carcinogenicity..." (OEHHA, 2004). It is clearly inappropriate for *d*-phenothrin, prallethrin, imiprothrin, or fenpropathrin to be prioritized for listing, much less listed. As such, the **group** based listing of Type I Pyrethroids is inappropriate.

Comment 1b: One of the Type I Pyrethroids included in the OEHHA summary, Metofluthrin, has already been evaluated for Proposition 65 carcinogen listing on two prior occasions and determined to be low priority. As USEPA concluded, the liver tumors in rats fed Metofluthrin are not relevant to humans given the underlying mechanistic data.

Under the authoritative bodies listing mechanism, OEHHA put forth Metofluthrin as a chemical under consideration for possible listing as a carcinogen (OEHHA, 2008). In a December 2008 notice, OEHHA stated that Metofluthrin "appear[s] to be 'formally identified' by USEPA in its reports as causing cancer." This conclusion was based on a 2006 USEPA Cancer Assessment Review Committee (CARC) document that summarized a 2-year feeding study that reported statistically significant increases in malignant and combined benign and malignant liver tumors in both male and female Wistar rats. The USEPA initially concluded Metofluthrin was "likely to be carcinogenic to humans" (EPA, 2006). (Note: There were no Metofluthrin-related increases in tumors observed in a 78-week CD-1 mouse feeding study.)

However, USEPA changed this conclusion in a 2007 report titled *METOFLUTHRIN: Second Report of the Cancer Assessment Review Committee*, reclassifying Metofluthrin as "Not Likely to Be Carcinogenic to Humans at Doses That Do Not Result in A Mitogenic Response" (USEPA, 2007). This change occurred after USEPA considered *in vivo* and *in vitro* mechanism of action (MOA) data (Hirose et al., 2009; Deguchi et al., 2009; Yamada et al., 2009).[3] The

[3] The MOA data were made available to USEPA prior to publication.

experiments demonstrated that the Metofluthrin-induced liver tumorigenesis MOA in rats is similar to that of other non-genotoxic CYP2B form inducers (e.g., phenobarbital), and that the key event of increased cell proliferation observed in rats would not occur in the human liver. Based on these findings, the USEPA made the following determinations:

- Treatment-related increases in liver tumors (benign and malignant) were seen in both sexes of Wistar rats at 900 ppm (38.1/47.4 mg/kg/day, M/F) and 1800 ppm (77.8/96.1 mg/kg/day, M/F), doses which were considered adequate to assess carcinogenicity;
- No treatment-related tumors were seen in male or female CD-1 mice at doses which were considered adequate to assess carcinogenicity;
- There is no mutagenicity concern; and
- The data are sufficient to support a mitogenic MOA for liver tumors (P450 induction leading to a proliferative response and ultimately to an increase in liver tumors). Metofluthrin does not operate via a cytotoxic or mutagenic MOA, nor does it cause peroxisome proliferation.

As a consequence of USEPA changing the cancer classification for Metofluthrin, OEHHA announced in January 2010 that it would not pursue the proposed Metofluthrin listing as "it no longer met the sufficiency criteria specified in Proposition 65 requiring the chemicals to be identified as carcinogens by an authoritative body" (OEHHA, 2010).

A year later, OEHHA published a preliminary toxicological evaluation of Metofluthrin for the CIC to consider prioritization for listing under Proposition 65 at a future CIC meeting (OEHHA, 2011a). While OEHHA included a brief statement of the underlying mechanism for Metofluthrin-induced rat tumors ("Liver tumors and mitogenic proliferative responses"), it did not indicate in its evaluation that this mechanism indicated the rat liver tumors were not relevant to humans. The CIC considered Metofluthrin a "low" priority chemical, presumably based on mechanism of action and low public exposure (OEHHA, 2011b).

Since OEHHA last considered Metofluthrin, there have been no additional positive tumor data published, nor have there been mechanistic data published refuting the MOA that illustrates that rat tumors are not relevant to humans. Because Metofluthrin has "been recently reviewed by an authoritative body and found to have insufficient evidence of carcinogenicity..." (OEHHA, 2004), and because there have not been any new data, much less "compelling new data," (OEHHA, 2004), Metofluthrin is another Type I Pyrethroid for which tumor data are inadequate for justifying prioritizing this group of compounds for listing.

Comment 1c: Some of the studies relied upon by OEHHA for evaluating Type I Pyrethroids have been shown to not be relevant to humans when factoring in mechanistic data.

In the case of transfluthrin, a 2-year rat study found a low incidence of urinary bladder papillomas and carcinomas at the highest dietary exposure level (2000 ppm) in females (reviewed by WHO, 2006). Further *in vivo* and *in vitro* studies were performed to elucidate the underlying mechanism of this effect. Yokohira et al. (2011) reported "clear cytotoxicity and necrosis of the urothrelial superficial cell layer[,] with focal accumulation of rounded cells detected by SEM indicative of focal, mild, simple hyperplasia" in rats fed 2000 ppm transfluthrin in their diet for 13 weeks. Histological analysis did not indicate formation of urinary crystals, but chemical analysis of the urine indicated the absence of transfluthrin, suggesting the observed bladder toxicity was due to a transfluthrin metabolite. The major metabolite of transfluthrin (tetrafluorobenzoic acid; TFBA) was detected at levels that elicited cytotoxicity in rat and human urothelial cell lines (MYP3 and 1T1, respectively). The results, the authors noted, "provide clear evidence in support of the cytotoxicity regenerative proliferation hypothesis regarding the mode of action for transfluthrin-induced neoplasia of the rat urinary bladder." The authors indicated that the TFBA metabolite occurs in rats but not humans, and thus concluded that the carcinogenic mode of action for transfluthrin is not relevant to humans. In 2014, the EU concurred with this conclusion, stating "None of the increased incidences of [tumors] reported in the rat 2-years [sic] study can be considered of human relevance."

OEHHA's summary notes that all the genotoxicity reviews of transfluthrin have been negative, leaving only one study in male and female mice showing an increase (with no tumor incidence stated) in liver adenomas in only the female mice. This would ordinarily not constitute a basis for prioritization of the listing of transfluthrin and accordingly OEHHA should not prioritize the listing of the group of Type I Pyrethroids to which transfluthrin belongs.

Comment 1d: Type I Pyrethroids should not be considered as a group for listing because there is no common tumor target for the Type I Pyrethroids with positive tumorigenicity study data.

Another aspect that is critical to understanding whether a whole group of chemicals warrants classification as a group is the consistency or diversity of the organ/tissue targets among them. Given that most of these compounds are not mutagenic or otherwise genotoxic (as reviewed and summarized by OEHHA, 2016), the tumor data for Type I Pyrethroids should indicate a common target tissue or tissues to justify prioritizing these compounds as a group for carcinogenicity listing under Proposition 65.

However, the tumor data reviewed by OEHHA for select Type I Pyrethroids illustrate that there is no target tissue common to these compounds, but rather a general diversity of tumor sites across the compounds for which statistically significant tumor data have been reported. Based on animal studies reviewed by OEHHA, various Type I Pyrethroids have elicited

tumorigenic responses in the liver, testis, bladder, and lung. Although tumorigenic responses were observed somewhat more frequently in the liver than in the other three tissues, even hepatocellular tumorigenicity did not occur consistently among the species and compounds tested. Therefore, it is clear that the carcinogenicity studies do not indicate a common carcinogenic endpoint for the subset of compounds for which there have been positive tumor responses reported; rather, the tumorigenic responses appear to be specific to the select compound studied (Tsuji et al., 2012).

Comment 1e: There is a paucity of evidence indicating a shared potential mechanism of action for carcinogenicity among Type I Pyrethroids.

An important factor in treating chemicals as a group "known to the state of California to cause cancer" should be a demonstrated common mechanism of action underlying the tumorigenicity evidence. For example, if these compounds were all or mostly mutagenic or otherwise genotoxic in some way, it may be inferred that they might share an underlying mechanism of action for the potential to elicit a tumorigenic response in animals, despite the observed diversity of tissue target sites (per Comment 1d). However, as summarized in OEHHA's own literature research, seven of these nine chemicals — including the one Type I Pyrethroid already listed as a known carcinogen by the State of California (resmethrin) — are negative in all mutagenicity and genotoxicity assays reported.

Given that most of the Type I Pyrethroids are devoid of mutagenic and genotoxic activity, by what other potential mechanisms could these compounds share as the basis for considering the group as a whole to be carcinogens? OEHHA researched the possibility that these compounds impacted endocrine systems in a common fashion, identifying two *in vitro*-based studies that evaluated this possibility: Kim et al. (2004) and Du et al. (2010). However, neither of these studies indicates that the Type I Pyrethroids share a common interaction with endocrine systems. Kim et al. (2004) tested seven pyrethroids (including four Type I Pyrethroids: bioallethrin, permethrin, *d*-phenothrin, and tetramethrin) and reported that none of them competitively bound to the estrogen receptor *in vitro*, and that only *d*-phenothrin (a.k.a., sumithrin) elicited weak estrogenic activity in breast cancer cell proliferation assays (with considerably lower potency and efficacy relative to estrogen positive control). In contrast, two other Type I Pyrethroids (bioallethrin and permethrin) inhibited estrogen-induced cell proliferation in this assay (demonstrating anti-estrogenic effects). Tetramethrin elicited neither estrogenic nor anti-estrogenic activity in this assay. These last observations contradict the mechanistic considerations summarized by OEHHA, as the Kim et al. (2004) results clearly do not support the conclusion that permethrin and tetramethrin are estrogen agonists (OEHHA, 2016). Furthermore, OEHHA indicated that Kim et al. (2004) concluded allethrin was an

estrogen agonist as well, except that bioallethrin – not allethrin – was not included in the study design.

In the other *in vitro* study, Du et al. (2010) examined the interactions of several pyrethroids (including the Type 1 pyrethroids tetramethrin and permethrin) at estrogen, androgen and thyroid receptors in reporter gene assays. For the estrogen and androgen receptor systems, tetramethrin and permethrin demonstrated stark differences: Tetramethrin was inactive in both endocrine system assays, whereas permethrin elicited concomitant agonist and weak antagonist effects in the estrogen receptor systems, and antagonist effects in the androgen system. The thyroid receptor assay was the exception, as both permethrin and tetramethrin tended to have antagonist effects at the thyroid receptor.

In summary, along with a considerable lack of consistent animal tumor data to justify treating Type I Pyrethroids as a group for priority carcinogenicity listing, the *in vitro* mechanistic study data cited by OEHHA fail to demonstrate a common mechanism by which this group could conceivably elicit tumorigenic responses. It is therefore inappropriate to consider prioritizing, much less listing, Type I Pyrethroids as a group.

GENERAL COMMENT 2: A single epidemiology study is cited for evaluating possible relationships between hematopoeitic cancers and exposures to three of the Type I Pyrethroids: allethrin, phenothrin, and tetramethrin (Ferreira et al., 2013). This study has critical design and reporting limitations that impede accurate measurements of true associations between disease and potential exposures and therefore does not provide a basis for considering Type I Pyrethroids as a group for listing as Proposition 65 carcinogens.

Comment 2a: The maternal exposure data collected by Ferreira et al. (2013) for seven Type I Pyrethroids are highly susceptible to recall bias and exposure misclassification, as they were based on self-reported recall of exposures of specific pesticide products and exposure durations going as far back as three years pre-diagnosis.

Ferreira et al. (2013) is a hospital-based multicenter case-control study of maternal pesticide exposure and risk of leukemia in offspring in Brazil. Mothers of 252 acute lymphoid leukemia (ALL) and acute myeloid leukemia (AML) cases and mothers of 423 controls were interviewed, and the objective of the study was to investigate the association between pesticide exposure during pregnancy and leukemia in children < 2 years of age. The exposure analysis presented by Ferreira et al. (2013) is retrospective and based on questionnaire responses from the mothers of both the case and control groups. Few details were provided on the type of survey instrument used, and no details were provided on the ways in which interviewer bias and recall bias may have been addressed. The mothers were asked to recall

exposures that potentially occurred during an ~15-month window (starting at three months prior to pregnancy, during each three-month trimester, ending with the three months following birth), the duration of these exposures, and the pesticide products they were exposed to during these time periods. For the mothers of cases, self-reporting of potential environmental exposures was conducted after the child (ages 0-23 months) was diagnosed with acute lymphoid leukemia (ALL) or acute myeloid leukemia (AML). The authors did not clearly indicate how long after diagnosis the mothers were asked to recall these exposures, but assuming questionnaires were completed shortly after ALL or AML diagnosis, recall would have at least ranged from 1-3 years. Since verification of self-reported exposures was not included in the study design (e.g., either through biomonitoring, or evaluation of household or occupational pesticide products at the time of the recall), it is more than likely that the specific self-reported pesticide exposures were susceptible to recall bias and exposure misclassification. Exposure misclassification can include misidentification of the product used, misremembering the duration and frequency of use, as well as forgetting relevant uses of products containing other pesticide classes that may or may not have carcinogenic potential.

It is well-documented that information obtained from case mothers and control mothers are subject to differential reporting and recall (Rothman et al., 2008, *Modern Epidemiology*). Case mothers will more frequently recall or report exposures perceived to be associated with the disease, more so than control mothers. Rothman et al. states, "*Recall bias is a possibility in any case-control study that relies on subject memory, because the cases and controls are by definition people who differ with respect to their disease experience at the time of their recall, and this difference may affect recall and reporting*" (p. 138). Recall bias is one limitation of Ferriera et al. (2013), and it is expected that differential recall will bias the measures of associations.

Comment 2b: Ferreira et al. (2013) do not present a quantitative dose-response analysis for the seven Type I Pyrethroids included in their study.

OEHHA's guidance to the State's Qualified Experts also states that the presentation of a dose-response analysis is an important factor for weighting epidemiology studies. While the exposure information in the Ferreira et al. (2013) study are based on self-reporting, no effort was made to define different exposure levels for any of the Type I Pyrethroids, even though data on event exposure durations and frequency were presumably collected via the questionnaire. The study authors indicated that "… *association with exposures during specific times of windows could not be accurately determined. Additionally, length of exposure was not evaluated in this study, so associations according to maternal cumulative exposure to pesticides could not be estimated.*" (p. 274, Ferreira et al., 2013). It is notable that the adjusted Odds

Ratios (ORs) were decreased generally for the duration of pesticide use. Higher ORs were reported for 0 to 11 months in comparison to 12 to 23 months, and some ORs in the longer duration of pesticide use were not of statistical significance. The absence of any trends in exposure level effects for each of the Type I Pyrethroids is another shortcoming that limits the utility of this study.

Comment 2c: As Ferreira et al. (2013) indicated, selection bias was likely to be introduced because controls were selected from hospitals. Selection bias is also discussed in terms of confounding; thus, it is also possible that residual confounding was present and impacted the study results. It is notable that cases versus control groups were relatively distinct populations based on social and economic status, and adjusted odds ratio calculations did not account for the significantly different incomes between the groups.

In Ferreira et al. (2013), the study authors indicated that cases were children less than 24 months of age with conclusive diagnosis of ALL (n=193) or AML (n=59). Controls (n=423) were selected among children less than 24 months of age with non-malignant diseases[4]; they were patients of general hospitals in the same cities as the cases or they were patients at the Brazilian National Health system centers where cases were recruited. Exclusion criteria included those with congenital syndromes, myelodysplasia, adoptive parents, or unknown biological mothers as well as controls with cancer diagnosis. It should be noted that in case-control studies, subjects are often selected after exposure and outcome has occurred, and thus there is potential for bias due to the combined effects of exposure and disease on participant selection. Controls should be selected from the same population, i.e. the source population, that gives rise to the study cases. However, improper selection of controls is a common issue for case-control studies, and Rothman et al. (2009) indicated that "*the source population for hospital- or clinic-based case-control studies is not often identifiable*." (p. 118, Rothman et al. 2009, Modern Epidemiology). In Ferreira et al. (2013), the study authors recognized that selection bias was probably introduced considering that controls were recruited from hospitals. Another aspect of selecting controls from a hospital setting is the consideration that individuals with disease outcomes related to the exposure(s) being studied should not be included in the study (Rothman et al. 2009). It is unclear whether the study authors in Ferreira et al. (2013) considered these factors for selection of controls.

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[4] Diseases of control children included infectious and parasitic diseases, non-malignant hematological diseases, asthma and bronchitis, hemangioma, severe diarrhea, cardiovascular diseases, and other non-malignant conditions (Ferreira et al., 2013).

Selection bias is often discussed in terms of confounding. It should be noted that there was a significant disparity in demographics between cases and controls, to the point that relatively distinct groups of people (aside from diagnosis) were apparently selected for cases and controls in this study. For example, the cases are represented by older, more educated and more financially secure mothers ($p<0.001$ for each of these characteristics). It was indicated that sensitivity analyses were conducted for various conditions in the controls (tuberculosis, GI ailments, etc.) to control for confounding by such social economic factors. However, the adjusted ORs did not account for the family income even though this was a significant indicator (higher among cases vs controls). The authors did not provide an explanation for why this variable was not adjusted for in the logistic conditional regression, and this is an important omission given that this disparity is a possible confounding factor that can impact the study results. In consideration of selection bias and residual confounding that is present in Ferreira et al. (2013), additional investigations are needed and the information from the current study is not sufficient for making definitive conclusions on the potential relationship between pesticide exposures and childhood leukemia.

Comment 2d: The authors in Ferreira et al. (2013) provide no biological justification for dividing the case and control populations into two age bins: 0-11 months and 12-23 months.

The authors do not justify the age-binning presented in their analysis of the Type I Pyrethroids. Given that half of all childhood leukemia cases are diagnosed within the first 3 years of life (Wigel et al., 2009), it appears that dividing the cases and controls into two separate age groups (<1 YO and 1-2 YO) was an arbitrary post-hoc analysis decision.

In summary, the single epidemiological study cited for three of the Type I Pyrethroids at issue is of questionable value, indicating that these three chemicals -- allethrin, phenothrin, and tetramethrin -- should not have passed OEHHA's epidemiological screen for prioritization (OEHHA, 2004). Because OEHHA relies on only the Ferreira et al. (2013) study with respect to these chemicals, it is inappropriate to consider prioritizing, much less listing, Type I Pyrethroids as a group.

Conclusion

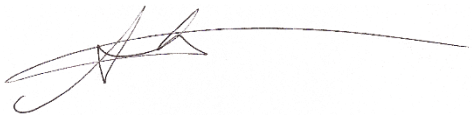
CSPA's review of the animal and human cancer and mechanistic studies identified by OEHHA for select Type I Pyrethroids shows that overall these compounds have been reported to be non-mutagenic and otherwise non-genotoxic. The animal data clearly show that not all Type I Pyrethroids elicit a significant tumor response in animals, and for those compounds that do, the animal tumors have either been determined to be irrelevant to humans, or cover such a diverse range of tissues as to indicate the underlying mechanisms of action are specific to the

individual compound and animal species tested, and do not illustrate a mechanism common to this group of compounds. In addition, the *in vitro* studies cited by OEHHA on potential mechanisms also do not provide evidence for a common MOA. Furthermore, the one human study that examined potential cancer associations with more than one Type I Pyrethroid (and thus the study most germane to question of whether it is appropriate to list these compounds as a group) had a number of study design and analysis shortcomings.

In their preliminary toxicology evaluation, OEHHA notes "Type I Pyrethroids **as a group** passed the human and animal data screens, underwent a preliminary toxicological evaluation, and are being brought to the Carcinogen Identification Committee (CIC) for consultation" (OEHHA, 2016) (emphasis added). But it is evident from reviewing the materials on which OEHHA relies that many of the individual Type I Pyrethroids evaluated would not pass the data screens had they been reviewed on an individual basis.

In summary, CSPA believes there is insufficient scientific basis to support consideration of Type I Pyrethroids as a group for prioritization and that OEHHA should only consider individual chemicals for prioritization.

Sincerely,



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cc: CSPA Scientific Affairs Committee Prop 65 Task Force
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References

1. Deguchi Y, Yamada T, Hirose Y, Nagahori H, Kushida M, Sumida K, Sukata T, Tomigahara Y, Nishioka K, Uwagawa S, Kawamura S, Okuno Y. (2009). Mode of action analysis for the synthetic pyrethroid metofluthrin-induced rat liver tumors: evidence for hepatic CYP2B induction and hepatocyte proliferation. Toxicological Sciences. 108(1):69-80.
2. Du GZ, Shen OX, Sun H, Fei J, Lu CC, Song L, Xia YK, Wang SL, Wang XR. (2010). Assessing Hormone Receptor Activities of Pyrethroid Insecticides and Their Metabolites in Reporter Gene Assays. Toxicological Sciences. 116:58-66.
3. Federal Register (2000). EPA Final Rule. Prallethrin [(RS)-2-methyl-4-oxo-3-(2-propynyl) cyclopent-2-enyl (1RS)-cis, trans-chrysanthemate]; Pesticide Tolerance. 40 CFR Part 180 [OPP–300987; FRL–6499–5]. June 26, 2000.
4. EPA. (2006). Cancer Assessment Document. Evaluation of the Carcinogenic Potential of Metofluthrin. Cancer Assessment Review Committee. Health Effects Division. Office of Pesticide Programs. June 6, 2006.
5. EPA. (2007). Metofluthrin: Second report of the Cancer Assessment Review Committee. Health Effects Division. Office of Pesticides and Toxic Substances, US EPA. July 26, 2007.
6. EPA. (2008a). Reregistration Eligibility Decision for d-Phenothrin. Office of Prevention, Pesticides and Toxic Substances. September 2008.
7. EPA. (2008b). Memorandum. Fenpropathrin: Human Health Risk Assessment for the Proposed Uses on Barley, Stone Fruit (Crop Group 12), Tree Nuts (Crop Group 14), Pistachio, Caneberries (Crop Subgroup 13-07A), Olive, Avocado, Black Sapote, Canistel, Mamey Sapote, Mango, Papaya, Sapodilla, and Star Apple. Office of Prevention, Pesticides and Toxic Substances. November 26, 2008.
8. EU. (2010). Imiprothrin: Product-type 18 (Insecticide). Directive 98/8/EC concerning the placing of biocidal products on the market. Inclusion of active substances in Annex I or IA to Directive 98/8/EC. Document 1. June 2010.
9. EU. (2014). Transfluthrin (insecticides, acaricides and products to control other arthropods). Regulation (EU) n°528/2012 concerning the making available on the market and use of biocidal products. Evaluation of active substances; Assessment Report. 13 March 2014.
10. Ferreira JD, Couto AC, Pombo-de-Oliveira MS, Koifman S. (2013). In utero pesticide exposure and leukemia in Brazilian children < 2 years of age. Environmental Health Perspectives. 121:269-275.

11. Health Canada. (2003). Regulatory Note: Imiprothrin. Pest Management Regulatory Agency. REG2003-05. May, 13, 2003.

12. Hirose Y, Nagahori H, Yamada T, Deguchi Y, Tomigahara Y, Nishioka K, Uwagawa S, Kawamura S, Isobe N, Lake BG, Okuno Y. (2009). Comparison of the effects of the synthetic pyrethroid Metofluthrin and phenobarbital on CYP2B form induction and replicative DNA synthesis in cultured rat and human hepatocytes. Toxicology. 258(1):64-9.

13. Kim IY, Shin JH, Kim HS, Lee SJ, Kang IH, Kim TS, Moon HJ, Choi KS, Moon A, Han SY. (2004). Assessing estrogenic activity of pyrethroid insecticides using in vitro combination assays. Journal of Reproduction and Development. 50:245-255.

14. OEHHA. (2004). Process for prioritizing chemicals for consideration under Proposition 65 by the "State's Qualified Experts". Office of Environmental Health Hazard Assessment California Environmental Protection Agency**.** December 2004.

15. OEHHA. (2008). Chemicals under consideration for possible listing via the authoritative bodies mechanism: Package 34. Reproductive and Cancer Hazard Assessment Branch Office of Environmental Health Hazard Assessment California Environmental Protection Agency. December 2008. Available at: http://oehha.ca.gov/proposition-65/crnr/chemicals-under-consideration-possible-listing-authoritative-bodies-mechanism-1#downloads

16. OEHHA (2010). Candidates for Listing Via the Authoritative Bodies Mechanism Found Not to Meet the Formal Identification Criteria: Clodinafop-Propargyl and Metofluthrin. January 1, 2010. Available at: http://oehha.ca.gov/proposition-65/crnr/candidates-listing-authoritative-bodies-mechanism-found-not-meet-formal

17. OEHHA. (2011a). Prioritization: Chemicals for Consultation by the Carcinogen Identification Committee. July 22, 2011. Available at: http://oehha.ca.gov/proposition-65/crnr/prioritization-chemicals-consultation-carcinogen-identification-committee

18. OEHHA. (2011b). Meeting Synopsis and Slide Presentations Carcinogen Identification Committee Meeting Held on October 12, 2011. Available at: http://oehha.ca.gov/proposition-65/events/carcinogen-identification-committee-meeting-scheduled-october-12-and-13-2011

19. OEHHA (2016). Prioritization 2016: Chemicals for Consultation by the Carcinogen Identification Committee. September 9, 2016. Available at: http://oehha.ca.gov/proposition-65/crnr/prioritization-2016-chemicals-consultation-carcinogen-identification-committee

20. Rothman KJ, Greenland S, Lash TL. (2008). Modern Epidemiology. 3rd edition. Lippincott Williams and Wilkins. Philadelphia, PA, USA.

21. Tsuji R, Yamada T, Kawamura S. (2012). Mammal toxicology of synthetic pyrethroids. Top Curr Chem. 314:83-111.

22. WHO. (2004). Prallethrin. WHO Specifications and Evaluations for Public Health Pesticides. Available at: http://www.who.int/whopes/quality/en/prallethrin_spec_eval_Nov_2004.pdf

23. World Health Organization (WHO, 2006). WHO specifications and evaluations for public health pesticides: Transfluthrin. Available at: http://www.who.int/whopes/quality/Transfluthrin_eval_specs_WHO_May_2016.pdf?ua=1

24. WHO. (2012). Fenpropathrin Monograph. In: Pesticide residues in food – 2012. Joint FAO/WHO Meeting on Pesticide Residues. Pgs 253-306.

25. Wigle DT, Turner MC, Krewski D. (2009). A systematic review and meta-analysis of childhood leukemia and parental occupational pesticide exposure. Environmental Health Perspectives. 117:1505–1513.

26. Yamada T, Uwagawa S, Okuno Y, Cohen SM, Kaneko H. (2009). Case study: an evaluation of the human relevance of the synthetic pyrethroid metofluthrin-induced liver tumors in rats based on mode of action. Toxicological Sciences. 108(1):59-68.

27. Yokohira M, Arnold LL, Lautraite S, Sheets L, Wason S, Stahl B, Eigenberg D, Pennington KL, Kakiuchi-Kiyota S, Cohen SM. (2011). The effects of oral treatment with transfluthrin on the urothelium of rats and its metabolite, tetrafluorobenzoic acid on urothelial cells in vitro. Food and Chemical Toxicology. 49(6):1215-23.