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Via Email and Hand-Delivery

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***RE: COMMENTS OF SUMITOMO CHEMICAL CO., LTD. AND BAYER CROPSCIENCE LP
REGARDING PRIORITIZATION OF TYPE I PYRETHROIDS***

Dr. Mack and Committee Members:

We are writing on behalf of Sumitomo Chemical Co., Ltd. (“Sumitomo Chemical”) and Bayer CropScience LP (“Bayer”) in response to the September 9, 2016 Notice entitled “Prioritization: Chemicals for Consultation by Carcinogen Identification Committee” (“Notice”). These companies and the undersigned representatives recommend that the group of chemicals referred to in the Notice as “Type I Pyrethroids” and the four Type I Pyrethroids discussed individually—Metofluthrin, Tetramethrin, d-Phenothrin (Sumithrin®) and Transfluthrin—not be considered for listing as chemicals “known to the state to cause cancer” for purposes of California’s Safe Drinking Water & Toxic Enforcement Act (“Proposition 65”), whether as a group or individually.

Each of these active ingredients plays an important public health role in controlling mosquitoes that vector diseases, including the Zika virus of current concern. Their public health uses result in low exposures to humans. To the extent that OEHHA or the Committee may wish to consider these chemicals sometime in the future, we suggest that they be assigned the very lowest priority. It is obvious on the present level of prioritization review that the extensive animal data that support their registrations in the United States, California and worldwide do not support a conclusion that they are “clearly shown” to cause cancer within the meaning of Proposition 65. The United States Environmental Protection Agency (“US EPA”) has classified Metofluthrin and d-Phenothrin as “not likely to cause cancer to humans.” Tumors observed in rats fed Tetramethrin are not malignant and therefore do not meet the CIC criteria for listing. Similarly, the mode of action (“MOA”) for bladder tumors observed in rats fed Transfluthrin is not relevant to humans under its conditions of use as an insecticide. The benign liver tumors observed in female mice fed Transfluthrin at a high dose level do not meet the CIC weight of the evidence criteria for listing under Proposition 65.

INTRODUCTION AND SUMMARY

Sumitomo Chemical produces Metofluthrin, Tetramethrin and d-Phenothrin, and holds registrations issued by the US EPA and the California Department of Pesticide Regulation (“DPR”) for insecticide products that contain these three active ingredients and protect humans and household pets against various insect pests that are a threat to public health, including mosquitoes, fleas, ticks, flies, bedbugs, ticks, ants, wasps and other insects, which carry diseases such as malaria, yellow fever, dengue fever, encephalitis, Lyme disease, Rocky Mountain Spotted Fever, West Nile Virus, and Zika virus. Bayer is a producer of Transfluthrin and this year has submitted applications for similar registrations to the US EPA and DPR for insecticide products that contain that pyrethroids as their active ingredient. As explained below, Metofluthrin and Transfluthrin are or will be incorporated into personal devices that protect their users from mosquitoes and supplement the use of traditional topical repellents.¹

OEHHA’s Notice asks the CIC for its recommendation as to “whether Type I Pyrethroids as a group, or specific individual compounds within the group should be considered for listing at a future meeting.” We present first below the reasons why four compounds that belong to the Type I Pyrethroids group should not be considered individually. It follows from that discussion that these four Type I Pyrethroids do not share a common mechanism of cancer; therefore, the chemical group referred to as Type I Pyrethroids should not be considered for listing as a class of chemicals, either.

- **Metofluthrin, Tetramethrin, d-Phenothrin and Transfluthrin should not be considered for listing individually.** Under Proposition 65 and its implementing regulations, a chemical is to be listed as a carcinogen only if it has been “*clearly shown*, through scientifically valid testing according to generally accepted principles, *to cause cancer* . . .”² The test is whether “the *weight of scientific evidence clearly shows that [the chemical] causes invasive cancer* in humans, or that it causes invasive cancer in animals (unless the mechanism of action has been shown not be relevant to humans).”³ “Scientifically valid studies of carcinogenesis” include “[e]pidemiological studies of carcinogenesis in humans,” and “[s]tudies of carcinogenesis in animals.”^{4,5} The “weight of evidence depends upon the degree to which

¹ Bayer and Sumitomo Chemical have conducted numerous state-of-the-art scientific studies with the four Type I Pyrethroids addressed in this letter to obtain and maintain the registrations required by US EPA, DPR and regulatory agencies in other countries to allow their sale and distribution as pesticides. Both companies are committed to sharing the results of those studies with regulatory bodies to support sound regulatory decisions, and in that spirit are pleased to make this submission to the CIC to assess the prioritization of Metofluthrin, Tetramethrin, d-Phenothrin and Transfluthrin. The Notice also references four other substances as being included in the chemical group of Type I Pyrethroids: Bifenthrin, Permethrin, Phenothrin, and Tefluthrin. The fact that this letter on behalf of Sumitomo Chemical and Bayer does not address those compounds should not be interpreted to state or imply any opinion regarding the carcinogenicity of those compounds, if any.

² California Health & Safety Code § 25249.8(b) (emphasis added).

³ Guidance Criteria for Identifying Chemicals for Listing as “Known to the State to Cause Cancer” (OEHHA March 2001), at 1 (emphasis added).

⁴ *Id.* at Section 2.A, B.

[various factors] can be verified or rejected with respect to *malignancies or tumors of malignant potential*.^{6, 7}

Applying these criteria to each of these chemicals individually, none of the four Type I pyrethroids meets the criteria for Proposition 65 listing:

Metofluthrin. US EPA (an authoritative body), DPR, the Chemicals Regulation Directorate (“CRD”) of the UK and the European Chemicals Agency (“EChA”) have reviewed Metofluthrin registration studies. EPA has classified Metofluthrin as “not likely to be carcinogenic to humans.” OEHHA concluded on January 1, 2010 that US EPA’s reviews of Metofluthrin data would not support listing under the Authoritative Bodies Listing Mechanism. On October 12, 2011, the Committee observed at a prioritization meeting that exposure to Metofluthrin is low and recommended that it receive the lowest priority for future review.⁸ Sumitomo Chemical-sponsored MOA studies conducted subsequently confirm that tumors observed in the chronic/oncogenicity rat study are not relevant to humans.

d-Phenothrin: US EPA has classified d-Phenothrin as “not likely to be carcinogenic to humans.” It is not genotoxic, and it is not carcinogenic in mice. Of three rat carcinogenicity studies, only one reported an increase in tumors at any site and then only at a dose level that exceeded the Maximum Tolerated Dose (“MTD”).

⁵ See also Cal. Code Regs., tit. 22, § 25305(e)(1),(2) indicating that “sufficient evidence of carcinogenicity” means that there are human studies to show “that there is a causal relationship between the chemical and cancer” or (2) animal toxicology data that demonstrate “an increased incidence of *malignant* tumors or *combined malignant and benign* tumors in multiple species or strains” (emphasis added).

⁶ *Id.* at Section 2.B.(ii).

⁷ See also, Cal. Code Regs. tit. 27, § 25305(e)(1),(2) “For purposes of this section, “as causing cancer” means that either of the following criteria has been satisfied:

(1) Sufficient evidence of carcinogenicity exists from studies in humans. For purposes of this paragraph, “sufficient evidence” means studies in humans indicate that there is a causal relationship between the chemical and cancer.

(2) Sufficient evidence of carcinogenicity exists from studies in experimental animals. For purposes of this paragraph, “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, 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.*

⁸ Transcript at pages 210-211.

Tetramethrin: Tetramethrin is not genotoxic. It is not carcinogenic in mice. The only tumors induced in male rats (testicular interstitial cell (Leydig) cell tumors) were benign and not expected to progress to malignancy. There was no evidence of decreased latency. For this reason, US EPA expressed the opinion in its review that Tetramethrin did not warrant the preparation of a cancer risk assessment.

Transfluthrin: Transfluthrin is not genotoxic. In a mouse oncogenicity study, liver tumors in female mice were benign. Rat bladder tumors apparently were the product of a metabolite formed uniquely in the rat's urine, which is not formed in humans.

- **The Type I Pyrethroids as a group should not be considered for listing as a class.** The data supporting the registration of Type I Pyrethroids also demonstrate that this group of chemicals should not be considered for listing *as a chemical class*. As Type I Pyrethroids, they share certain chemical similarities. Their acute toxicity profiles also share some similarities. None of the compounds has been shown to be genotoxic and their chronic toxicity profiles are more notable for their dissimilarity than similarity. Only one Type I Pyrethroid, Resmethrin, is classified as a carcinogen by US EPA (and thus was listed as a chemical “known to the state” to cause cancer for purposes of Proposition 65). The US EPA also has reviewed Metofluthrin and d-Phenothrin and classified them as “not likely to be carcinogenic to humans.” In addition, the tumorigenicity data on Tetramethrin and Transfluthrin do not point to a common biological mechanism of action.
- **Type I Pyrethroids as a class and the individual compounds above should be afforded the lowest priority for further review.** OEHHA traditionally has solicited advice from the CIC as to what “priority” (low, medium, or high) should be assigned to chemicals for future review. For the reasons above, we recommend that the Type I Pyrethroids not be reviewed as a class at all. If Metofluthrin, Tetramethrin, d-Phenothrin and Transfluthrin (as well as those other Type I Pyrethroids identified in the Notice) are to be reviewed in the future, notwithstanding the data discussed herein, then they should be assigned the lowest priority. The data and reviews by regulators and public health authorities simply do not support listing; thus, a further review would be a poor use of resources for the agency and the producers, and would distract agency resources away from more valuable work with other compounds and in other agency programs. Further to these points, we note that:

Other agencies, including an Authoritative Body, have reviewed these compounds for carcinogenic potential. Reviewing agencies for these compounds include US EPA, DPR, the Canadian Pesticide Management and Regulatory Agency (“PMRA”), the World Health Organization (“WHO”), EChA, and the Competent Authorities for the United Kingdom and the Netherlands. While their reviews do not ***preclude*** further review, the CIC and OEHHA can have confidence in the weight-of-evidence reviews conducted by these agencies and can direct the use of their resources to compounds that have not been reviewed so thoroughly already.

The cumulative assessment of all pyrethroids meets the FQPA safety standard.

US EPA determined that pyrethrins and pyrethroids share a common neurotoxic mechanism of action. The October 2011 Pyrethrins/Pyrethroid Cumulative Risk Assessment found that exposures from the many current uses of pyrethrins and pyrethroid insecticides do not pose risk concerns.

The Type I Pyrethroids are vital to protecting public health. The Type I pyrethroids, as a group, and the four Type I pyrethroids that are the subject of this submission individually and collectively are important public health insecticides.⁹

They play an important role by repelling or controlling adult mosquitoes that transmit disease, including the Zika virus. Pyrethroids demonstrate lower mammalian toxicity than organophosphate pesticides.

BACKGROUND: TYPE I PYRETHROIDS

The Type I Pyrethroids are synthetic molecules that are based on natural organic molecules. The term “pyrethrin” (or “pyrethrum”) is a generic description of the organic insecticidal ingredients that are found in or derived from flowers of certain species belonging to the genus *Tanacetum* (formerly *Chrysanthemum*). Six naturally occurring molecules having structural similarities and insecticidal properties have been extracted from plants of this genus and these molecules are called pyrethrins. Structure-activity research has led to the synthesis and commercial development of a number of derivatives of one of these, Pyrethrin 1, and those derivatives are referred to as Type I Pyrethroids.

The Type I Pyrethroid compounds were developed for their valuable insecticidal uses that protect public health and save lives. Type I Pyrethroids are esters of chrysanthemic acid that lack an alpha-cyano group. Pyrethroids with the alpha-cyano group are referred to as Type II Pyrethroids and have different insecticidal and toxicological properties than those of Type I. All pyrethroids are characterized by rapid biodegradation (principally in response to sunlight) and low mammalian toxicity compared to organophosphate pesticides. Type I and Type II Pyrethroids produce transient neurotoxic signs in mammals after acute oral dosing (tremor and convulsions (choreoathetosis) with profuse salivation, respectively).

The first synthetic pyrethroids were of Type I and were commercialized in the late 1960s and included Tetramethrin (first registered in 1968) and the Allethrin stereoisomers (registered in 1969). At present, over 40 pyrethroids have been used as insecticides. Ten active ingredients from the pyrethroid class of pesticides successfully completed EPA reregistration in 2008. Pyrethroids are considered by US EPA to share a common mechanism of toxicity for purposes of the cumulative risk assessment required by the Food Quality Protection Act (“FQPA”) but, as

⁹ Metofluthrin is the only insecticide currently registered for personal protection. D-Phenothrin is registered for wide-area use, including over agricultural lands. Tetramethrin is an essential partner to d-Phenothrin-based consumer aerosols, providing quick knockdown to complement d-Phenothrin’s killing action. The incorporation of Transfluthrin into a personal protective device will offer protection to military personnel in confined spaces.

explained below, that mechanism is specific to effects on the nervous system and is not associated with cancer etiology.

The Agency for Toxic Substances and Disease Registry (ATSDR) provided an excellent review entitled “Toxicological Profile for Pyrethrins and Pyrethroids.” According to this review, no reports were located regarding cancer in humans or animals following inhalation or dermal exposure to pyrethrins or pyrethroids. However, in the case of oral exposure to these chemicals, while no reports were located regarding cancer in humans, pyrethrins and some pyrethroids have been shown to cause tumors in rodent models. These data indicate that tumor induction does not appear to reflect a common carcinogenic endpoint for this particular subset of compounds. Instead, tumorigenic responses appear to be specific to the compound and test organism employed (Tsuji *et al.*, 2012).

Pyrethroids are registered for insecticidal uses that are vital to public health and save lives. As US EPA has noted, “[t]he use of pyrethrins and pyrethroids has increased during the past decade with the declining use of organophosphate pesticides, which are more acutely toxic to birds and mammals than the pyrethroids.”¹⁰

Pyrethroids Play an Important Public Health Role. Mosquitoes are clearly public health pests because they vector many diseases. In addition, mosquitoes can be extremely irritating. Although irritation is not a public health concern *per se*, it can hamper enjoyment of outdoor activities and, in some sensitive individuals, cause severe reactions, thus diminishing use of these products and their capacity to protect public health.

In the US, a number of species of mosquitos are present, which can transmit diseases to humans. The West Nile virus is carried by several species, notably members of the genus *Culex*. Other mosquito-borne diseases include Chikungunya virus, various species of viruses which cause forms of encephalitis and, most recently, the Zika virus. Although malaria does not occur in the US, two vector species (*Anopheles quadrimaculatus* and *Freeborni*) occur in many states. Accordingly, there is potential for transmission of malaria, should infected people enter the country. There also is the potential for transmission of dengue and dengue-hemorrhagic fever, with *Aedes aegypti*, the principal vector species, being present in many southern states.

METOFLUTHRIN

Metofluthrin is important in protecting public health. Among the registered uses of Metofluthrin is its use as an active ingredient in a personal pesticidal device that repels mosquitoes. The personal pesticidal device circulates air across a Metofluthrin-treated pad, releasing very low levels of the active ingredient. Metofluthrin will knock down and kill caged mosquitoes (Bibbs *et al.*, 2015). The personal protection device supplements or replaces traditional topical repellents that come in aerosol, pump spray, lotion, and sachet forms.

¹⁰ <https://www.epa.gov/ingredients-used-pesticide-products/pyrethrins-and-pyrethroids><https://www.epa.gov/ingredients-used-pesticide-products/pyrethrins-and-pyrethroids>.

Previously, Allethrins were used in mosquito coils and mats. These registrations have been phased out, however. Natural pyrethrins will be the only other available active ingredient for these types of products, and these compounds are subject to periodic worldwide shortages. Coils and mats are less expensive than other forms of personal mosquito control. The potential use of Metofluthrin in coils in the future will benefit less fortunate populations that are dependent on coils.

The animal data for Metofluthrin do not support listing. Carcinogenicity studies in rats and mice have been reviewed by the US EPA and the European Union with the United Kingdom as the rapporteur state. As noted in the OEHHA summary for metofluthrin, a 78-week study in CD-1 mice reported no treatment-related findings at any site in males or females.

Hepatocellular tumors were found to be increased in male and female Wistar rats. US EPA concluded that adenomas and carcinomas were increased in male rats at dietary concentrations of 900 and 1800 ppm. The hepatocellular tumor incidence in males is shown below:

<i>Hepatocellular Tumors in Male Rats</i>					
<i>Dose Level (ppm)</i>	0	20	200	900	1800
<i>Adenomas</i>	1/68	1/68	3/69	5/70	6/69
<i>Carcinomas</i>	0/68	0/68	0/69	3/70	8/69
<i>Combined</i>	1/68	1/68	3/69	8/70	12/69

The incidence of hepatocellular tumors in female rats was somewhat less. US EPA concluded that adenomas and carcinomas were increased due to treatment at the high dose level for adenomas and carcinomas and at the mid-dose level for adenomas. The hepatocellular tumor incidence in female rats is shown in the table below:

<i>Hepatocellular Tumors in Female Rats</i>					
<i>Dose Level (ppm)</i>	0	20	200	900	1800
<i>Adenomas</i>	1/38	1/32	0/40	3/38	7/46
<i>Carcinomas</i>	0/40	2/37	1/42	2/40	7/47
<i>Combined</i>	1/40	3/37	1/42	5/40	12/47

As discussed below, there are compelling reasons to doubt that these results in the rat are relevant to humans.

Metofluthrin is not genotoxic. OEHHA acknowledges that Metofluthrin has no potential for genotoxicity. The following assays were reviewed by US EPA in 2007:

- *Salmonella typhimurium*, reverse mutation assay (negative);
- *Escherichia coli* WP2uvrA reverse mutation assay (negative);
- *In vitro* chromosomal aberration assay in Chinese hamster lung cell (negative); and
- *In vivo* mouse micronucleus assay (negative).

Other relevant data demonstrate that Metofluthrin should not be listed. Sumitomo Chemical-sponsored studies demonstrate that the MOA of Metofluthrin-induced liver tumors in rats involves activation of the constitutive androstane receptor (“CAR”). This activation results in a pleiotropic response including the stimulation of cytochrome P450 (“CYP”) CYP2B isoforms and increased cell proliferation (“mitogenic proliferation”). This MOA is similar to that of other non-genotoxic liver CYP2B form inducer/CAR activators, such as phenobarbital (Holsapple *et al.*, 2006; Whysner *et al.*, 1996). In rodents, this etiology exhibits a clear threshold for the induction of hepatocellular tumors (Whysner *et al.*, 1996).

Importantly, substantial epidemiologic data are available for phenobarbital, which is administered to patients over a period of many years, frequently beginning in childhood and continuing for essentially the lifetime of the individual. Epidemiology studies have demonstrated that there is no evidence of increased liver tumor risk in these patients receiving phenobarbital for many years, even at doses producing plasma concentrations similar to those that are carcinogenic in rodents (IARC, 2001; La Vecchia and Negri, 2014; Olsen *et al.*, 1989).

Phenobarbital and Metofluthrin both activate the constitutive androstane receptor, induce hepatic CYP2B enzymes and have a mitogenic effect in rodents (Yamada *et al.*, 2009). Although the enzyme induction and resulting hypertrophic response occur in rat and human hepatocytes after *in vitro* exposure to these two substances, hyperplasia is not observed in human hepatocytes exposed to either phenobarbital or metofluthrin (Hirose *et al.*, 2009; Yamada *et al.*, 2015). Chimeric mice with human hepatocytes also proved refractory to the increase in replicative DNA synthesis after exposure to phenobarbital (Yamada *et al.*, 2014), and neither Metofluthrin nor phenobarbital induced Ki-67, a cellular marker for proliferation, in cultured human hepatocytes (Yamada *et al.*, 2015).

The carcinogenic response in the rat is not relevant to humans. These data provide further support for the conclusion that Metofluthrin-induced tumors seen in the rat are not relevant to humans. The doses of Metofluthrin that result in a mitogenic response in the rat are beyond the realm of human exposure. The dose at which exposure to Metofluthrin induces mitogenesis and other precursor events in rats exceeds a dietary concentration of 900 ppm, equivalent to 63.5/57.6 milligrams per kilogram in body weight per day (“mg/kg bw/day”) for males/females, and even this is characterized by the Agency as a “high-end worst case analysis.” By this analysis, the NOAEL for mitogenesis in the rat, in the worst-case, is 13,520-fold greater than any estimated exposures to humans (0.000939 mg/kg/day).

Moreover, a chronic toxicity study in the dog shows that neurological effects would be likely to occur in humans at doses far lower than the chronic dosing levels that would be

necessary to induce a mitogenic response. Therefore, it would be essentially impossible to expose humans to Metofluthrin at a level sufficient to cause cancer. In addition, the human hepatocyte appears to be refractory to the mitogenic response that is seen in the rat (Hirose *et al.*, 2009; Yamada *et al.*, 2014; Yamada *et al.*, 2015), and this is a necessary precursor event to carcinogenicity. Human hepatocytes in culture system or chimeric mice respond to known mitogens such as hepatocyte growth factor or epidermal growth factor (Hirose *et al.*, 2009; Yamada *et al.*, 2014, 2015).

Other agencies that have reviewed Metofluthrin, including an “Authoritative Body,” have not classified the compound as carcinogenic. Sumitomo Chemical implemented a research program designed to resolve any remaining uncertainties regarding the MOA for Metofluthrin. The initial results from this research program were submitted to the US EPA and consisted of, as the second EPA Carcinogenicity Assessment Review Committee (“CARC”) put it, a “preliminary study that could be used in conjunction with the main studies to further substantiate the proposed mitogenic mode of action for the liver tumors.” (US EPA 2007) Those data were evaluated and incorporated into US EPA 2007. Based on the new data, the CARC “reclassified metofluthrin as ‘***Not Likely To Be Carcinogenic to Humans at Doses That Do Not Result in a Mitogenic Response.***’”

The agency that regulates pesticides in the United Kingdom, CRD (a Directorate of the Health and Safety Executive (“HSE”)). The CRD found that “classification for [carcinogenicity] is not considered appropriate” (UK-CA 2008) for Metofluthrin. Accordingly, Metofluthrin was not given an R-phrase of R40 that is given to agents for which there is a concern for carcinogenicity. The CRD report notes the following:

- No changes in tumor incidence were observed in mice;
- The liver tumors in rats occurred against a background of hepatic enzyme induction and hepatocyte proliferation;
- There is no evidence of genotoxicity;
- The liver tumors in rats occurred as a result of a mode of action similar to that of phenobarbital; and
- Humans are much less sensitive than rats to liver tumor induction by this mode of action.

For these reasons, the CRD, after considering the available MOA data, did not classify Metofluthrin as a carcinogen. The EChA recently reached the conclusion that Metofluthrin should not be classified as carcinogenic based on available MOA data (EChA 2016).

D-PHENOTHHRIN

D-Phenothrin is valuable in protecting public health. Products containing d-Phenothrin are registered for use in a variety of formulations to control mosquitoes and other public health pests at many indoor and outdoor sites, including domestic, commercial, recreational, and institutional premise areas. (US EPA Registration Eligibility Decision, “US EPA RED” 2008).

There are d-Phenothrin-based products for use only by professional applicators as well products for use by consumers. There are no food uses, although there is a tolerance for food and feed crops, as explained under the Public Health section below.

D-Phenothrin is vital for mosquito control. As noted, mosquitoes are considered public health pests because they vector many diseases to animals and humans. Certain d-Phenothrin products are registered for wide-area mosquito adulticiding by truck-mounted and aerial ULV (ultra-low volume) applications. They are used extensively by mosquito abatement districts throughout the US. Important to its use as a ULV aerial adulticide, d-Phenothrin is approved for use over agricultural lands after field trials revealed that residue levels from samples taken below aerial-sprays were non-detectable, permitting a tolerance of 0.01 parts per million to be approved for food and feed crops.

Only a limited number of insecticides are registered for wide-area (adulticidal) mosquito control. Organophosphate pesticides registered for wide-area mosquito control programs are limited to malathion and naled. Pyrethroids registered for wide-area mosquito control programs include Permethrin, d-Phenothrin, Prallethrin and Etofenprox. The MOA of organophosphates is through inhibition of acetyl cholinesterase that regulates neurons.¹¹ Pyrethroids, by contrast, do not act upon acetyl cholinesterase. Pyrethroids also tend to knock down and kill insects more rapidly than organophosphates. Lastly, naled can be an irritant to the eyes and malathion can have an unpleasant odor, sometimes likened to cat urine.

A popular and more localized means of mosquito control around the home is the use of d-Phenothrin in residential mister systems. These systems consist of series of tubes linking insecticide reservoirs to nozzles set around the residence. When a pump is activated, the nozzles emit a fine mist. The timing and duration of emission are set to coincide with times of peak mosquito activity. Misters are installed and maintained by pest control professionals. D-Phenothrin-based aerosols for consumer use provide the lay person with a useful means of controlling mosquitoes around the home.

D-Phenothrin also is valuable in controlling other public health pests. D-Phenothrin-based aerosols for consumers are also labeled for the control of a variety of other public health pests, including flies, cockroaches, fleas, wasps, hornets, yellow jackets, and bed bugs.

The animal studies for d-Phenothrin do not support listing. D-Phenothrin has been thoroughly tested for carcinogenicity and genotoxicity and the weight of the evidence supports a finding that it is not carcinogenic. The results of these studies are described below.

An oncogenicity study with d-Phenothrin in the B6C3F₁ mouse did not show evidence of carcinogenicity. A small increase in female mice with either carcinoma or adenoma in the high dose group was within the historical incidence of hepatocellular tumor incidence for this strain of mouse. Of the three carcinogenicity studies that have been conducted in rats only one of the studies found an increase in tumors at any site and in that case the tumors were only found at a

¹¹ The application rates of malathion and naled for mosquito control generally are regarded at levels that do not pose any risk to humans.

dose level that exceeded the MTD. The tumor incidence for hepatocellular tumors in female rats is shown below.

Hepatocellular Tumors in Female Rats				
	Control	50 mg/kg	500 mg/kg	1000 mg/kg
Number examined	50	50	50	50
Adenoma	2	0	1	3
Carcinoma	0	0	1	8*
Adenoma or carcinoma	2	0	2	11*
*p,0.01				

The 1000 mg/kg dose level was excessively toxic, based on a severe decrease in body weight gain of 40%, clinical signs of toxicity, and extensive changes in serum biochemical parameters. Decreased body weight gain in the range of 10-15% is desirable to show that the high dose was sufficiently high to elicit a carcinogenic response without disrupting the physiology of the test animal (Rhomberg *et al.*, 2007). An increase in tumors in excess of the MTD, however, is not predictive of a carcinogenic hazard because stress or distress has a documented effect, unrelated to the test substance, on the outcome of a carcinogenicity study (OECD 116). As shown below by the body weight gain data for female rats, animals at the high dose exceeded the MTD.

Body Weight Gain (% of control) for Female Rats			
Weeks on Test	Target Dose Levels		
	50 mg/kg/day	500 mg/kg/day	1000 mg/kg/day
Weeks 0-13	99	83	72
Weeks 0-94	100	86	60

D-Phenothrin is not genotoxic. An extensive battery of genotoxicity studies support a finding that d-Phenothrin is not genotoxic.

- A mutagenicity test with *Escherichia coli* and *Salmonella typhimurium* using d-Phenothrin was negative.
- In a host-mediated assay using *S. typhimurium* G46, the bacterial mutation frequency in d-Phenothrin-treated mice was not increased compared to the control group.
- A DNA-repair test with *Bacillus subtilis* did not inhibit the growth of any strain at any dose level.

- D-Phenothrin did not induce chromosomal aberrations *in vivo* using mouse bone marrow cells.
- In an *in vitro* chromosomal aberration test, Chinese hamster ovary cells were treated with d-Phenothrin. A significant increase in the number of cells with chromosomal aberrations was not observed.
- The ability of d-Phenothrin to induce sister-chromatid exchanges was tested in cultured mouse embryonic cells *in vitro*. D-Phenothrin did not induce SCEs.
- In a study of unscheduled DNA synthesis, HeLa S3 cells were treated with d-Phenothrin. There was no significant increase in DNA synthesis in cells exposed to d-Phenothrin.

The carcinogenic response to d-Phenothrin is not relevant to humans. The increase in liver tumors at the limit dose in rats is not predictive of a carcinogenic hazard because the dose level exceeded the MTD. No significant increase in tumor incidence was seen at lower dose levels in this study or in a study in mice. D-Phenothrin is not genotoxic. In short, the weight of the evidence supports the conclusion that d-Phenothrin is not carcinogenic.

Other agencies that have reviewed d-Phenothrin, including an Authoritative Body, have not classified the compound as carcinogenic. US EPA (2006) concluded that d-Phenothrin is “not likely to be carcinogenic to humans” based on the finding that the only treatment-related tumors that occurred were at an excessively toxic dose of 20,000 ppm (1,000 mg/kg/day) in rats. US EPA also noted that “no genotoxic potential for d-Phenothrin was indicated.” (US EPA 2008).

The EU also determined that d-Phenothrin was not carcinogenic, noting “Carcinogenicity and long term toxicity of d-Phenothrin have been investigated in the rat and mouse. No treatment related change was seen in the incidence of tumors in either species.” (EU 2013).

Canada’s PMRA also reached the same conclusion as US EPA, concluding in the recent re-evaluation: “There was no evidence to suggest that d-phenothrin damaged genetic material and it is not considered to be a human carcinogen.” (PMRA PRVD2015-05, proposed re-evaluation decision).

TETRAMETHRIN

Tetramethrin is valuable in protecting public health. The registered uses for products containing Tetramethrin include many indoor and outdoor residential and commercial sites in pump and pressurized formulations. There are Tetramethrin-based products registered for professional applicators only, as well as products registered for use by consumers. There are no food uses for Tetramethrin.

Tetramethrin is valuable in protecting humans and household pets from infectious diseases carried by flying insects such as flies, mosquitoes, wasps, hornets, and yellow-jackets. Tetramethrin was developed primarily for controlling muscoid flies in and around the home. Its

quick knockdown action, when coupled with another insecticide to provide killing action, makes it a useful chemical for fly control. Tetramethrin-based aerosols for consumer use also are registered for the control of a variety of other public health pests, including mosquitoes, wasps, hornets, and cockroaches.

Tetramethrin's attribute of quick knockdown is essential for treating certain insects, such as paper wasps (*Polistes* species), hornets (*Dolichovespula* species) or yellowjackets (*Vespula* species), since survivors can administer a vicious sting to the applicator. Tetramethrin is therefore frequently formulated in "jetstream" sprays for treating individual insects or their nests. In these products, Tetramethrin is often pre-mixed with d-Phenothrin, discussed above. Tetramethrin functions to knockdown the insect and the d-Phenothrin functions to kill the insect.

The animal studies would not support listing. A two year oncogenicity study in B6C3F₁ mice did not show evidence of carcinogenicity (Yamada, 2016). A small increase in Harderian gland tumors was seen at the high dose, but the incidence was within the historical control range at the laboratory and was not considered to be biologically significant. No other tumor-type was increased as a result of treatment. A second dietary carcinogenicity study in mice was conducted with the CD-1 strain, and it also showed no evidence of carcinogenicity .

An association has been found between dietary exposure to Tetramethrin in rats and the induction of benign testicular interstitial cell (Leydig) cell tumors. In the first carcinogenicity study in the rat (Yamada, 2016), Sprague-Dawley rats were obtained as weanlings from females that had been dosed during gestation. In addition, the animals were dosed in the diet throughout their 104 week lifespan. The incidence of Leydig cell tumors for each dose level is shown in the table which appears in US EPA 1988, and is reproduced below:

Incidence of Leydig Cell Adenomas in Two-Year Study in Male Rats				
Dose (mg/kg/day)	0	42	125	230
No. examined	42	30	36	35
No. w/ Leydig cell tumor	2	3	9	14
Percentage	5	10	25	40
p=	0.0000	0.1313	0.0034*	0.000**
*Significance of trend noted at control and significance of pair-wise comparison in treated animals				
**p<0.01				

A subsequent study used both the Sprague Dawley and Long-Evans strains of rats (Yamada, 2016). This study also began with *in utero* exposure. After weaning, rats received Tetramethrin in the diet for up to 104 weeks. Increases were again seen in Leydig cell tumors in male rats. The incidences of Leydig cell tumors in the two strains in this study are shown in the table below:

Incidence of Leydig Cell Tumors in Two-Year Study in Male Rats				
Sprague-Dawley				
Intake (mg/kg/day)	0	7.5	35	180
No. animals	39	40	40	30
No. animals with Leydig cell tumor	4	3	4	4
Percentage	18	17	7	41
p=	0.0006**	0.5951	0.1415	0.0229*
Long Evans				
Number on study	42	44	39	43
No. animals with Leydig cell tumor	4	3	4	22
Percentage	10	7	7	51
p=	0.0000	0.4736	0.6011	0.0000**
* Significance of trend noted at control and significance of pair-wise comparison in treated animals				
** p<0.01				

Tetramethrin is not genotoxic. Tetramethrin is non-genotoxic in studies of prokaryotic and eukaryotic cells. *In vivo* chromosomal aberration studies in male mice dosed intraperitoneally also were negative for genotoxicity.

Leydig cell tumors do not progress to malignancy. No increase in carcinoma of the Leydig cell was seen in either of the Tetramethrin studies in the rat. In fact, although the baseline incidence of Leydig cell tumors approaches 100% in some strains of rats such as the Fischer 344 strain, the tumor rarely progresses to malignancy (Cook *et al.*, 1999). Cytologic features of hyperplasia and adenoma are similar and the primary distinction between the tumor and hyperplasia is the size of the lesion. Testicular tumors are rare in humans, and the Leydig cell tumors constitute only 1 - 3% of testicular tumors. The incidence of testicular Leydig cell tumors is 0.00004% in humans.

The lack of progression to malignancy in these studies is particularly relevant in considering whether Tetramethrin should be listed as a chemical “known to the state to cause cancer.” The CIC listing criteria include the following as one of five considerations in the weight of the evidence to be considered by the CIC:

“The tumors produced are more aggressive than those occurring in the absence of exposure. Benign tumors may be included if the type is known to progress to malignant tumors of the same cell type.”

The criteria document notes that a single study in one species might be sufficient for listing “if malignant tumors occurred to an unusual degree with respect to frequency, type, location, age at onset, or low dosage, or in a strain not otherwise prone to such tumors.” Again, the criteria emphasize evidence of malignancy in making the decision to list a chemical as a carcinogen. The tumor of interest here occurred at a late stage in the Tetramethrin studies and treatment did not cause a reduction in latency of onset.

The Leydig cell tumor in the rat rarely becomes malignant and appears to be a poor predictor of carcinogenicity of the testes in humans. Several currently used pharmaceuticals such as flutamide, cimetidine and ketoconazole induce this tumor type in rats but appear to have no effect on Leydig cell tumor incidence in humans (Foster *et al.*, 1999). The weight of the evidence clearly indicates that humans are not sensitive to the induction of Leydig cell tumors.

Other agencies that have reviewed Tetramethrin but have not opined that a cancer risk assessment is warranted because the Leydig cell tumors did not progress to malignancy. Regulatory agencies including US EPA, PMRA and the EChA agree that Tetramethrin exposure is not associated with carcinogenicity in mice.

“The US EPA concluded that tetramethrin should be classified as Group C, ‘possible human carcinogen’ based on statistically significant dose-related increases in Leydig cell tumors in rats, but that no cancer risk assessment was needed. The EPA noted that this decision was based on (1) the fact that this type of tumor is a benign tumor that does not progress to a malignant tumor in rats; (2) the tumors occurred at a later stage of the study; (3) the exposures started *in utero*; and (4) the treatment did not cause a reduction in latency.”

EChA concluded that Tetramethrin should be classified in Carcinogenicity Category 2 (“Suspected of Causing Cancer”), based on the increased incidence of Leydig cell tumors in rats and, because the underlying mechanism is not known, concluding that the relevance of the tumors to humans cannot be ruled out. Nevertheless, the WHO International Programme on Chemical Safety evaluated Tetramethrin and concluded that:

“There is no evidence of malignancy in three rat studies and no evidence of this type of tumor in mice. It can be concluded that the tumorigenic effect, if real, is most unlikely to be relevant to human exposure.”

(WHO, 1990)

TRANSFLUTHRIN

Transfluthrin is valuable in protecting public health. Although Transfluthrin is not yet registered with US EPA, Bayer submitted an application in August 2016 to register the technical

grade as a new active ingredient. Another company has applied to register a personal pesticidal device that will use this active ingredient. All products are for use against public health pests and will be for consumers. A brief description of each product and its uses follows.

Indoor spatial repellent device (passive diffuser) and Personal Insect Repellent Kit (“PIRK”). A fabric in the device is impregnated with Transfluthrin. The device diffuses and emits the active ingredient. Transfluthrin’s vapor pressure is 9×10^{-4} Pa at 20°C. The device repels, knocks down, and kills mosquitoes. A protective plastic film protects the device until it is activated, and a manual closure cap allows it to be de-activated to preserve the reservoir of Transfluthrin and allow the user to control release, as desired.

Indoor and outdoor aerosol. This product is a water-based aerosol containing 0.04% Transfluthrin and 0.025% Cyfluthrin for perimeter and crack-and-crevice treatments. The target pests include mosquitoes and cockroaches. The product is intended for intermittent (4-6 second) use indoors and for total release outdoors (*i.e.*, as a fogger).

Indoor mini-aerosol. This 20 ml aerosol contains a concentrated (10-25% AI) formulation. It is for indoor use against mosquitoes, flies, and other pests. Intermittent activations of the aerosol valve emit 10-25 mg of Transfluthrin at a time. Each activation is effective for 4-8 hours.

Indoor/outdoor liquid – barrier spray. The liquid product contains 0.1-1.0% Transfluthrin and is for use as a surface or as a residual spray for perimeters and spot areas. The product relies upon contact and vapor phase to achieve efficacy. It is labeled for mosquitoes and biting insects and is effective for up to 8 hours. The liquid is applied at a rate of 3 g/second/foot².

Transfluthrin is effective in controlling public health pests. Pests against which Transfluthrin has been shown to be effective include mosquitoes, sandflies, and stable flies. Furthermore, Transfluthrin has demonstrated efficacy against public health pests with documented resistance to other active ingredients. All of these pests are designated in US EPA’s PR Notice 2002-1 as “public health pests.” The following are the principal public health pests targeted by Transfluthrin end-use products.

Mosquitoes. In view of the disease potential of mosquito bites, the Transfluthrin-based products, especially the Bayer spatial repellent device and the PIRK, will protect individuals from mosquitoes. As noted earlier, one of the most widely used types of repellent products are skin-applied (“topical”) products. The military has observed deployed troops not using topical repellents. Again, the cancellation of the Allethrins will make Transfluthrin all the more necessary for personal and spatial insect repellent devices.

Sandflies. The PIRK also will be labeled for use against sandflies and stable flies. Sandflies of the genus *Phlebotomus* are important as vectors of leishmaniasis in many parts of Asia, the Middle East, Africa and southern Europe. There are several species of *Leishmania*.

These protozoan parasites cause two forms of leishmaniosis: cutaneous (in which papules or nodules can develop into ulcers) and visceral (which results in weight loss, enlargement of the spleen and liver, anemia and weight loss). Leishmaniosis rarely occurs in the US. Nevertheless, the disease was a serious impediment to US troops deployed in Afghanistan and Iraq in the 2000's. Most of these cases were of the cutaneous form.

Stable Flies. Stable flies (*Stomoxys calcitrans*) do not carry any diseases, but are painful biters and their rapid flight and evasive tactics make them harder to swat than mosquitoes. They are frequently found in outdoor residential settings and can be numerous where there are animal feces or piles of rotting tidal wrack. Stable flies can be a considerable nuisance at barbecues and other outdoor gatherings.

Transfluthrin is not genotoxic. Transfluthrin was non-genotoxic in *in vitro* studies examining reverse mutation, cytogenicity, mitotic recombination, unscheduled DNA synthesis, induction of micronuclei, sister chromatid exchange, and in three *in vivo* genotoxicity studies testing micronucleus formation in mice and post-labeling adduct formation in rat liver and urinary bladder DNA (Driver *et al.*, 2016).

A species-specific metabolite induces the bladder tumors through irritation of the rat urothelium. On the basis of genotoxicity testing, metastatic carcinomas in lifetime feeding studies are not expected and they were not observed. Instead, there were statistically-significant increases in adenomas in the livers of mice at the highest dose tested and benign papillomas and malignant carcinomas of the bladder in rats at the highest dose. There is no dose-response curve for either tumor (*i.e.*, the effect was only observed at the highest dose tested). The following table from Driver *et al.*, 2016 shows the incidence of bladder tumors at the dietary levels tested in the two-year carcinogenicity study in rats.

Incidence of Bladder Tumors in Two-Year Carcinogenicity Study in Rats								
Sex	Males				Females			
Dose level (ppm)	0	20	200	2000	0	20	200	2000
No. examined	58	59	58	57	59	60	60	60
No. w/ papilloma	0	0	0	2	0	0	0	1
HCD	0				2			
No. w/ carcinoma	0	0	0	1	0	0	0	2
HCD	1				0			
HCD = historical control data obtained for 30 two-year studies in Wistar rats conducted from 1981 to 1989 in the same lab (n = 3,000)								

The putative carcinogen in rat urinary bladders resulting from Transfluthrin metabolism is the metabolite TFBA (2,3,5,6-tetrafluorobenzoic acid). There are several facts that implicate TFBA as the rat urinary bladder carcinogen, including its inherent irritant properties, the sensitivity of rat urothelial cells to irritants compared to mice or primates, the fact that TFBA is cytotoxic to bladder urothelial cells in all species tested at concentrations observed in the rat, the

ability of rats to concentrate TFBA in urine much more than in mice or humans and, perhaps most importantly, that rats alone appear capable of metabolizing Transfluthrin to TFBA. Therefore, the occurrence of this tumor in rats is not relevant to humans.

In vitro (liver bead) comparative metabolism by rat, mouse, dog and human cells shows that only rodents produce detectable levels of TFBA (Driver *et al.*, 2016). The difference between rat and human production of TFBA *in vitro* is at least 8-fold, *i.e.*, at the limit of detection there was no production of TFBA in human liver cells, while rat cells produced 8-fold higher concentrations. TFBA is concentrated by rat kidneys in urine to levels that are cytotoxic following 13 weeks of feeding at the 2000 ppm dose, which produces rat bladder tumors (Yokohira *et al.*, 2011).

Rat urothelial cells are extremely sensitive to irritation, much more so than urothelial cells in mice or primates (Cohen, 1995; DeSesso, 1995). TFBA produces not only irritation, but cytotoxicity *in vitro* in bladder urothelial cells (Cohen and Arnold, 2010). As a result, rats have a greater tendency than other species to experience irritation and cytotoxicity to the cells lining the bladder, resulting in an increased rate of cell turnover, which progresses to tumor formation.

Following oral dosing, TFBA is concentrated 2-fold higher in urine of rats than in mice given 4-fold higher dosages (Driver *et al.*, 2016). Rats are unique in their ability to more highly concentrate organic and organometallic acids in urine via active secretion, compared to mice or humans. As a result of enhanced metabolism to TFBA and urinary concentration, the MOA for bladder tumors observed in rats is species-specific and not relevant to humans. There was no evidence of chronic irritation of urinary bladders in either mice or dogs that received daily doses of transfluthrin on a chronic basis.

Dietary cancer bioassays are of questionable relevance for intended use of Transfluthrin. It also is important to note that TFBA has only been detected in rats dosed via the oral route and that exposure to transfluthrin will be predominantly via inhalation. While the toxicity at high exposure level of the subchronic inhalation study was determined by unequivocal neuroexcitatory effects, these were not observed in the respective feeding study at markedly higher doses. Conversely, the toxicity of the feeding study was predominantly hepatotoxicity and some changes indicative of nephrotoxicity. These organs were not affected at all in the respective subchronic inhalation study. This absence of any coherence of findings supports the conclusion that each route of exposure produces its own characteristics of toxicity due to a hepatic first-pass metabolism (Pauluhn, 2016).

The liver tumors in the mice were benign and only increased in females. A significant increase in benign liver tumors occurred only in females and only at the highest dietary level. Hepatocellular adenoma was the only tumor type observed in female mice that was increased from control incidence in chronic feeding studies, and there was no progression of the adenoma to carcinoma (malignancy) following lifetime dosage with Transfluthrin. The following table from Driver *et al.*, 2016 shows the incidence of liver tumors at the dietary levels tested in the two-year carcinogenicity study in mice.

Incidence of Liver Tumors in Two-Year Carcinogenicity Study in Mice								
	Males				Females			
Dose level (ppm)	0	10	100	1000	0	10	100	100
No. examined	49	50	50	50	50	48	50	50
Hepatocellular adenoma (b)	5	4	5	5	4	2	2	13*
HCD	0-11				0-9			
Hepatocellular carcinoma (m)	5	8	7	7	2	2	4	4
HCD	3-11				0-5			
b = benign; m = malignant; HCD = historical control data obtained for 13 two-year studies in B6C3F1 mice conducted from 1986 to 1987 in the same lab (n = 50)								
* = p < 0.05 (Fisher's exact test, two-tailed)								

Thus, the data show that humans are exposed intermittently via inhalation to Transfluthrin, and at five orders of magnitude lower dosages than mice or rats that developed tumors in carcinogenicity bioassays by the oral route of exposure. The MOA for bladder tumors is rat-specific, and not relevant to humans under conditions of use for Transfluthrin as an insecticide / insect repellent. The benign liver tumors observed in female mice at a high dose level do not meet the following criteria for inclusion in the weight of the evidence for listing under Proposition 65:

“an increased incidence of *malignant* tumors or *combined malignant and benign* tumors in multiple species or strains.”

Other agencies that have reviewed Transfluthrin have concluded that tumors observed in the rat were not relevant to humans. The EU reviewed Transfluthrin in 2014 with the Netherlands as the rapporteur state and concluded: “None of the increased incidences of tumors reported in the rat 2-years study can be considered of human relevance” and “None of the increased incidences of tumors reported in mouse 2-years study can be considered to biological significance.” With regard to bladder cancer the EU report noted:

“Mechanistic studies indicate that transfluthrin may have a tumour promoting action and clearly support a) urothelial cytotoxicity and associated regenerative proliferation caused by high, sustained urinary concentrations of TFBA as the mechanism of urinary bladder tumour formation in rats exposed for two years to a very high dose level of transfluthrin, coupled to b) the weight of evidence that this process should not be extrapolated to man.”

THE TYPE I PYRETHROIDS SHOULD NOT BE CONSIDERED FOR LISTING AS A CLASS

There are no common methods of action for carcinogenesis that would provide a basis for considering all Type I Pyrethroids for listing as a class. As noted, the Notice asks for comments on whether CIC should consider Type I Pyrethroids as a chemical group. Type I Pyrethroids, however, do not share a common site in laboratory animals for tumors. Pyrethroids of Types I and II do share a common mechanism for acute toxicity based on their effect on the mammalian neuron, but long-term exposure of laboratory animals to high levels of Type I

Pyrethroids results in a variety of effects. Toxicity that may be seen after long term dosing vary among this group of pesticides, and may be associated with compound-specific metabolites that are produced after the hydrolysis of the ester functionality found in most pyrethroids. We discuss and demonstrate below that several of the tumors that are found after dosing are considered not to be relevant to humans.

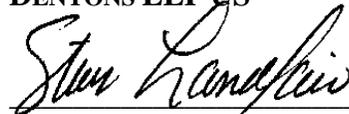
There are no epidemiological data that would support listing as a class. Because pyrethroids are relatively new and more limited in use and exposure than most agricultural pesticides, there are few relevant epidemiological studies of the pyrethroids. A retrospective, case-control, hospital-based study in Brazil examined the association between exposure to several Type I Pyrethroids (based on recall) and acute lymphoid and myeloblastic forms of childhood leukemia in children less than two years old (Ferreira *et al.*, 2013). Controls were recruited from hospitals in the same cities and included children with infectious diseases, asthma and bronchitis, diarrhea, hematological and cardiovascular disease. Pesticide exposure was classified based on the mother's recall of any contact with specific pesticides during the three months before pregnancy, throughout each pregnancy trimester and for three months after birth. Although increases were occasionally reported for some Type I Pyrethroids in the adjusted odds ratios, the numbers of cases were small and independent ascertainment of exposure did not occur. Selection bias in the matching of cases and controls and recall bias by parents of children with leukemia may have been present.

CONCLUSION

For all of the reasons above, Bayer and Sumitomo Chemical, represented by the undersigned, believe that the Type I Pyrethroids should not be considered for listing as a class of chemicals, and that none of the individual Type I Pyrethroids identified in the Notice should be considered for listing, either. If OEHHA should decide nevertheless to consider the chemicals for listing, we believe this group of compounds should be assigned the lowest priority for review.

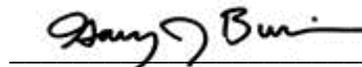
Respectfully submitted,

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STUDY TITLE:

Transfluthrin Oncogenic Weight of Evidence Evaluation

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July 29, 2015

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BAYER ES-001-15

Page 1 of 16

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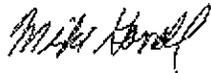
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Company: Bayer CropScience LP

Company Agent: Mike Gorrell

Title: Regulatory Manager

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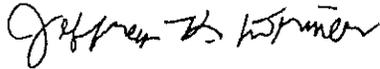
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The following evaluation of data is not subject to the principles of 40 CFR 160, GOOD LABORATORY PRACTICE STANDARDS (FIFRA), as promulgated in Federal Register, 54, No. 158, 34067-34704, 17 August 1989.

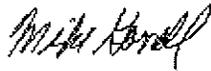
AUTHOR:



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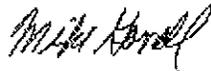
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I. Introduction

Transfluthrin (2,3,5,6-tetrafluorobenzyl (1R,3S)-3-(2,2-dichlorovinyl)-2,2-Dimethylcyclopropanecarboxylate; CAS No. 118712-89) is a novel type I pyrethroid currently registered in the European Union (EU; see CAR 2010) and marketed worldwide, except in the United States (U.S.), for domestic uses. Core formulations are aerosols, coils, liquid vaporizers/plug-in, anti-moth paper, and impregnated fibers/papers. Transfluthrin is produced by Bayer CropScience and sold to third parties including SC Johnson, Fumakilla, Endura, Sara Lee, Zobebe Group and the key brands are Baygon[®], Raid[®], Good Knight[®], Earth[®], and Fumakill[®].

This report includes the following:

- 1) an evaluation of the existing toxicology database for transfluthrin with regard to Weight Of Evidence (WOE) for the two neoplasms observed in experimental animals;
- 2) a description of the mechanistic basis for considering these adverse effects as threshold phenomena, supporting the use of a Margin of Exposure (MOE) risk metric, rather than linear extrapolation for risk assessment; and
- 3) a presentation of the scientific evidence for non-relevance of observed neoplasms to humans, thus, qualifying these effects as such in any long-term (chronic) health risk analyses for transfluthrin, and with respect to application of EPA's Guidelines for Carcinogen Risk Assessment (EPA 1986; EPA 2005).

II. Factors that both Tumor Types Have in Common

Tumors observed with statistical significance following lifetime dosing with transfluthrin (rat bladder and mouse liver) have some common features. First, in this WOE discussion those common features will be discussed. The common features include the lack of genotoxicity, the lack of dose-response in oncogenicity studies, the species-specific nature of the tumors, the lack of a common Mechanism of Action (MOA), and the intermittent, low-level exposures in humans compared to the bolus nature of nocturnal feeding of rodents. In addition, there are unique MOA issues that make those tumors more likely in that particular test species and unlikely in humans.

Transfluthrin was non-mutagenic in eight *in vitro* studies examining reverse mutation, cytogenicity, mitotic recombination, unscheduled deoxyribonucleic acid (DNA) synthesis, induction of micronuclei, and sister chromatid exchange and additionally in three *in vivo* genotoxicity studies testing micronucleus formation in mice and post-labeling adduct formation in rat liver and urinary bladder DNA (Wason, 2012). Table 1 provides a summary of the genotoxicity study results for transfluthrin.

Table 1: Summary of Genotoxicity Studies Conducted with Transfluthrin

Test Type	Reference	Organism	Range Tested (µg/mL)	Effect Level (µg/mL)
<i>In vitro</i>				
Micronucleus	Watters, 2012	Human lymphocyte	200-240	230 ^a
Clastogenicity	Herbold, 1990	Human lymphocyte	50-200	200 ^b
Sister Chromatid	Murli, 1989	Hamster CHO	0.67-200	none ^c
Forward mutation	Lehn, 1989	Hamster CHO	25-100	none ^d
Unscheduled DNA synthesis	Brendler, 1992	Rat hepatocyte	1-500	none ^e
Ames	Herbold, 1986	<i>S. typhimurium</i>	20-12,500	none ^f
Ames	Herbold, 1987a	<i>S. typhimurium</i>	20-12,500	none ^g
Mitotic recombination	Herbold, 1987b	<i>S. cerevisiae</i>	625-10,000	none ^h
<i>In vivo</i>				
Test Type	Reference	Organism	Range Tested (mg/kg)	Effect Level (mg/kg)
Micronucleus	Herbold, 1988	Mouse bone marrow	375	none ⁱ
Micronucleus	Roth, 2012	Mouse bone marrow	62.5-437.5	none ⁱ
Post label adduct	Radi <i>et al.</i> , 1995	Rat liver	100-250	none ^j
Post label adduct	Radi <i>et al.</i> , 1995	Rat bladder	100-250	none ^j

^a A statistically significant increase in multinucleated binucleate cells was observed at 230 µg/mL with 39% cytotoxicity. The cytotoxic dose response was extremely steep - going from 7% at 200 µg/mL to 63% at 240 µg/mL.

^b Inconsistent dose response in Table I of the report (with or without S9), but good dose response without S9 in Table 6.

^c Cytotoxicity observed at 67 µg/mL without S9 and 200 µg/mL with S9.

^d Cytotoxicity observed at 50 µg/mL.

^e Cytotoxicity observed at 500 µg/mL.

^f Using strains TA 1535, TA 100, TA 1537 and TA 98.

^g Using strains TA 1535, TA 100, TA 1537 and TA 98. Cytotoxic (bacteriostatic) at concentrations from 775-12,500 µg/mL, with some strains more sensitive than others.

^h Cytotoxicity was observed sporadically at 10,000 µg/mL.

ⁱ Although there was no excess formation of micronuclei, the highest doses tested produced marked adverse effects in the mice including tremors.

^j No effect was observed on DNA labeling in the key tissues examined, although there was clear evidence of absorbed transfluthrin and metabolites in blood serum.

Thus, on the basis of genotoxicity testing, one would not expect metastatic carcinomas in lifetime feeding studies, and indeed they were not observed. Instead, there were statistically-

significant increases in adenomas in the livers of mice at the highest dose tested and benign papillomas and malignant carcinomas of the bladder in rats at the highest dose. There is no dose-response for either tumor (see Table 2 for rats and Table 3 for mice), i.e., the effect was only observed at the highest dose tested (at or above the maximum tolerated dose or MTD). This pattern of dose response is associated with compounds that have exceeded the body's ability to detoxify or repair damage, i.e., there is a threshold dose above which tumors are observed.

Tumors induced by lifetime feeding of transfluthrin were species-specific, i.e., bladder tumors in rats but not mice or dogs (Eiben et al., 1993; Schladt et al., 1999; Ruf, 1993). Excess liver tumors were observed in mice, but not rats or dogs. The unique physiologic differences between species that influences the proclivity to develop tumors in certain organs in response to chemical stressors is discussed in detail for bladder, as well as liver, tumors below. There is not a common MOA for liver tumors in mice and bladder tumors in rats. There is a rational explanation for how the tumors form in liver vs. bladder associated with the normal physiologic differences of mice vs. rats, and why those tumor types produced from chronic exposure to transfluthrin are not relevant to humans.

Both rats and mice in chronic studies ingested their doses as near bolus daily, since they consume food almost exclusively at night over a few hours' duration in a series of eating "bouts" (Ulman et al., 2008). By comparison, based on the proposed pesticide use patterns and products for transfluthrin, humans could potentially be exposed primarily by inhalation over daily durations up to 24 hr and then only intermittently, i.e., there is a defined window of time in the year when pests such as mosquitoes proliferate and require a repellent/insecticide. Lacking un-repaired DNA damage or carryover of un-repaired cell damage, the observed tumors are effects clearly associated with a defined threshold. As such they should be evaluated (and regulated) as non-linear effects rather than assuming that the effects can occur at any dose level to zero. Moreover, extensive MOA studies demonstrate why oncogenic effects are not relevant to humans. MOA studies will be discussed sequentially – first for bladder tumors in rats and then for liver tumors in mice.

III. Bladder Tumors in Rats

The putative proximate carcinogen in rat urinary bladders resulting from transfluthrin metabolism is the metabolite TFBA (2,3,5,6-tetrafluorobenzoic acid). There are several facts that implicate TFBA as the rat urinary bladder carcinogen, including its inherent irritant properties, the sensitivity of rat urothelial cells to irritants compared to mice or primates, the fact that TFBA is cytotoxic to bladder urothelial cells in all species tested at concentrations observed in the rat, the ability of rats to concentrate TFBA in urine much more than in mice or humans, and perhaps most importantly that rats alone appear capable of metabolizing transfluthrin to

TFBA in liver cells. Each of these factors is discussed in the following section in more detail, with reference to the supporting documentation.

TFBA has a pK_a of ~ 1.8 (<http://en.chembase.cn/molecule-100455.html>) and thus is strongly ionic at physiologic pH, and is a potent irritant on mucous membranes (e.g., rabbit eye; Bayer, 1999; Sigma Aldrich MSDS). The MSDS uses the signal word “danger” to indicate the corrosive nature of TFBA. Rat urothelial cells are extremely sensitive to irritation, much more so than urothelial cells in mice or primates (Cohen, 1995; 1998; Desesso, 1995). Indeed TFBA produces not only irritation, but cytotoxicity *in vitro* in bladder urothelial cells (Cohen and Arnold, 2010; Scholtz, 2002; Wirnitzer and Hartmann, 2002). As a result, rats have a greater tendency than other species to experience irritation and cytotoxicity to the cells lining the bladder, resulting in increased rate of cell turnover, which progresses to tumor formation. However, even in rats the bladder tumors were only observed at the highest dose level (Table 2).

Table 2: Summary of Bladder Tumors in Rats (from Eiben et al., 1993)

Sex	Males				Females				
	Dose level (ppm)	0	20	200	2000	0	20	200	2000
# Examined		58	59	58	57	59	60	60	60
<i>papilloma (b)</i>					2				1
<i>HCD</i>		0				2			
<i>carcinoma (m)</i>					1				2
<i>HCD</i>		1				0			

b = benign; m = malignant; HCD = Historical control data obtained for 30 two-year studies in Wistar rats conducted from 1981 to 1989 in the same lab (n = 3,000) from Bomhard and Rinke (1993).

Transfluthrin is well-absorbed following oral ingestion, as evidenced by the ratio of urinary excretion following oral vs. intravenous dosing, with the absorption efficiency from the gastrointestinal (GI) tract is estimated at $\sim 90\%$ in rats (Koester et al., 2009). Absorbed transfluthrin is efficiently cleared by liver esterases, and the alcohol moiety is conjugated with glucuronide for biliary and renal excretion (Koester, 2009), as summarized in Figure 1. TFBA is the primary metabolite in rats and is excreted primarily via the urinary route. The glucuronide of benzyl alcohol is the second-most abundant metabolite, and is excreted about $1/4^{\text{th}}$ (25%) as much as TFBA. The glucuronide of the benzyl alcohol moiety has sufficient molecular weight to allow it to be excreted in bile. Combined factors of molecular weight >325 g/mole of the conjugated benzyl alcohol metabolite that can readily be hydrolyzed in the GI tract and observed fecal

excretion following iv administration (Ecker et al., 1997), make enterohepatic circulation a virtual certainty.

In vitro (liver bead) comparative metabolism by rat, mouse, dog and human cells shows that only rodents produce detectable levels of TFBA (Totis, 2009). The difference between rat and human production of TFBA *in vitro* is at least 8-fold, i.e., at the limit of detection there was no production of TFBA in human liver cells, while rat cells produced 8-fold higher concentrations. TFBA is concentrated by rat kidneys in urine to levels that are cytotoxic following 13 weeks of feeding at the 2000 ppm dose, which produces rat bladder tumors (Yokohira et al., 2011).

Following oral dosing, TFBA is concentrated 2-fold higher in urine of rats than in mice given 4-fold higher dosages (Eigenberg, 2010). Rats are unique in their ability to more highly concentrate organic and organometallic acids in urine via active secretion, compared to mice or humans (Arnold et al, 1997; 1999; Cohen, 1995; 1998). Transporters in the kidney are able to move anions from the blood against concentration gradients into urine (Shitara et al., 2006). These compounds are also bladder irritants that produce bladder tumors in rats. The cytotoxic concentration of TFBA in the bladders of rats is not achievable in humans because humans are not exposed to transfluthrin at the high dosages rats received, they make little if any TFBA, and the TFBA would not be concentrated by the kidney in humans to the extent it is in rats (Cohen and Arnold, 2010).

As a result of enhanced metabolism to TFBA and urinary concentration, the MOA for bladder tumors observed in rats is species-specific and not relevant to humans. There was no evidence of chronic irritation of urinary bladders in either mice or dogs that received daily doses of transfluthrin on a chronic basis.

IV. Liver Tumors in Mice

Hepatocellular adenoma was the only tumor type observed in female mice that was statistically different from control incidence in chronic feeding studies, and there was no progression of benign (adenoma) to carcinoma following lifetime dosage with transfluthrin (Schladt et al., 1999). B6C3F1 mice used in the chronic study have known high incidences of spontaneously-occurring liver tumors, i.e., control B6C3F1 mice always have a measurable incidence of liver adenomas (Schladt et al., 1999; Wason and Lautraite, 2010). Hypertrophy of periportal hepatocytes was observed at 12- and 24-month sacrifices in the chronic study in both sexes. This effect is associated with exposure to high concentrations of inducers of metabolic enzymes in the liver, and has been demonstrated with other pyrethroids (Yamada et al., 2009). Shown in Table 3 is the dose response for mouse liver adenomas and historical control incidence of that tumor type. Excess liver tumors occurred only in females and only at the highest dietary level. Had the same tumor been observed in both sexes, it would have added to the WOE for a potentially-significant hazard to humans (EPA, 1986).

Table 3: Summary of Mouse Liver Tumors

Sex	Males				Females			
Dose level (ppm)	0	10	100	1000	0	10	100	1000
# Examined	49	50	50	50	50	48	50	50
Hepatocellular adenoma (b)	5	4	5	5	4	2	2	13*
HCD	0-11				0-9			
Hepatocellular carcinoma (m)	5	8	7	7	2	2	4	4
HCD	3-11				0-5			

b = benign; m = malignant; HCD = Historical control data obtained for 13 two-year studies in B6C3F1 mice conducted from 1986 to 1987 in the same lab (n = 50); * = p < 0.05 (Fisher's exact test, two-tailed).

The primary route of exposure to transfluthrin in humans is via inhalation, which would result in a much lower concentration in the liver, compared to the levels associated with ingestion of the same dose. There are multiple reasons for higher liver concentrations following oral dosing than following inhalation. First, an oral dose is absorbed from the small intestine and taken directly to the liver via the portal vein (first-pass), resulting in extremely high localized concentrations in the liver. By comparison, inhalation exposure results in absorption by the pulmonary vein that goes to the heart sending blood to the entire body, with only a fraction going first to the liver. Second, human inhalation exposure occurs continuously over an extended duration, while rat dietary exposure reflects a series of bolus doses. Finally, the oral absorption has been measured at ~90% in rats (Koester et al., 2009), while uptake and retention efficiency via inhalation averages ~50% in humans over a wide range of chemistry (Ross et al., 2001). While the absorption efficiency of transfluthrin by the inhalation route has not been measured, it is very unlikely that it exceeds the upper bound of measurements for reactive vapors like formaldehyde, which is still ≤75%.

V. Conclusions

Humans are exposed intermittently to transfluthrin, and at five orders of magnitude lower dosages than mice or rats that developed tumors in the carcinogenicity bioassays. The MOA for liver tumors is mouse-specific, and is not relevant to humans under conditions of use for transfluthrin as an insecticide / insect repellent. This is because the B6C3F1 strain of mouse is well-known to spontaneously-develop benign liver tumors, and only developed excess liver tumors over the incidence in controls when dosed with transfluthrin at the equivalent of 20 mg/kg daily for a lifetime. Similarly, the MOA for bladder tumors is rat-specific, and not relevant to humans under conditions of use for transfluthrin as an insecticide / insect repellent. This is due to the fact that humans metabolize little if any transfluthrin to TFBA, unlike rats in which it is the primary urinary metabolite. Additionally, rats excrete highly-concentrated urine, relative to other species, and the high concentration of TFBA in the bladder produces irritation leading to cytotoxicity, cell proliferation and ultimately neoplasms.

The results from extensive genotoxicity testing indicate transfluthrin does not affect DNA. Lacking un-repaired DNA damage as a causal mechanism, the defining characteristic of tumor development in both rats and mice is carryover of un-repaired cell damage, so that the observed tumors are effects with a defined threshold. As such, the tumors observed in rats and mice should be regulated as non-linear effects, rather than assuming that the effects can occur at any dose to zero. Moreover, the liver and bladder tumor dose-response observed in mice and rats, respectively, are not relevant to humans and thus, should be qualified as such in any long-term (chronic) health risk analyses for transfluthrin, and with respect to conclusions and descriptors or descriptions resulting from application of EPA's Guidelines for Carcinogen Risk Assessment (EPA 1986; EPA 2005).

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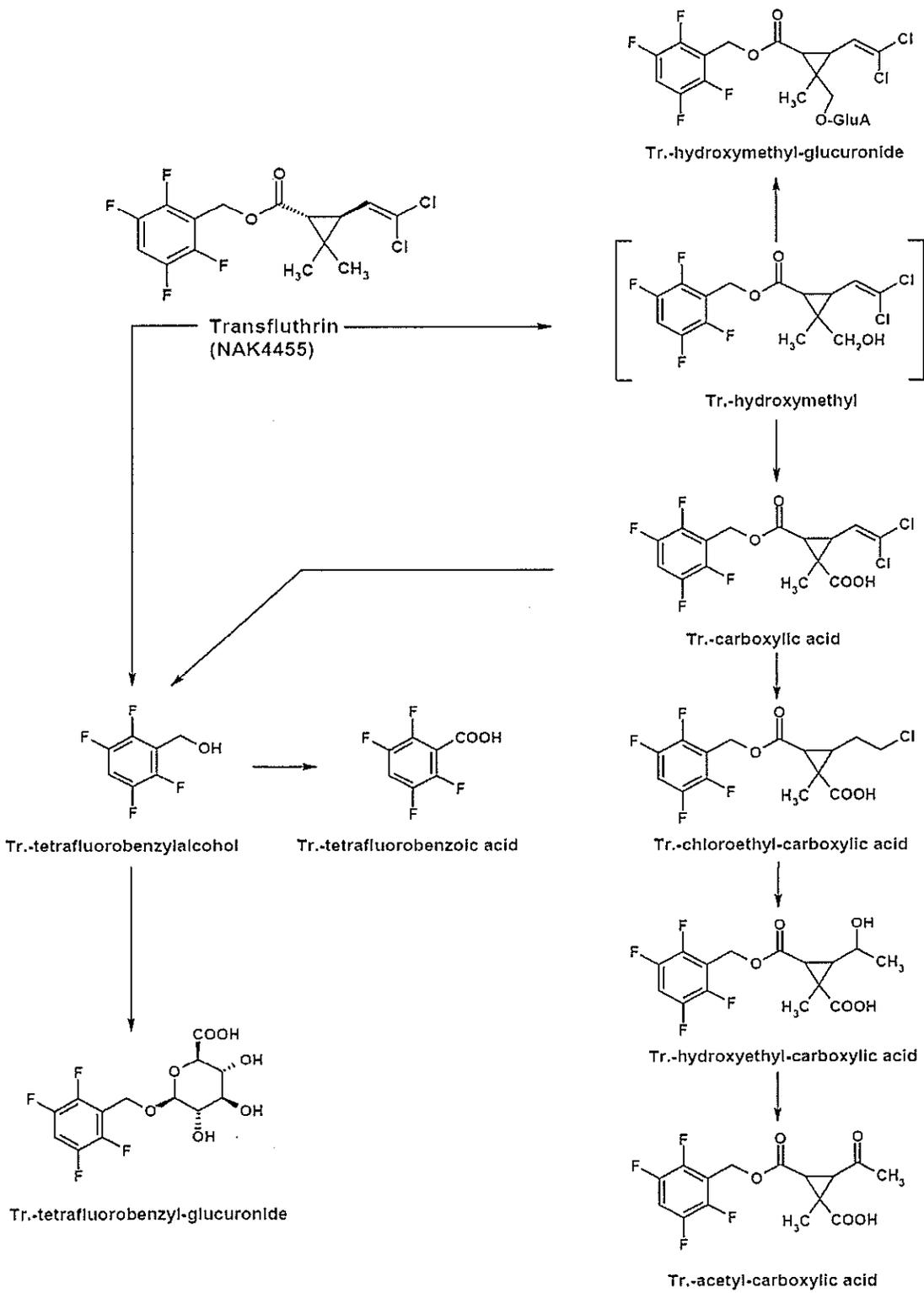
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Figure 1: Metabolic Flow Scheme of Transfluthrin in the Rat (from Koester, 2009)



[Tr. = Transfluthrin]