

Albany
Atlanta
Brussels
Denver
Los Angeles

McKenna Long
& Aldridge^{LLP}
Attorneys at Law

101 California Street • 41st Floor • San Francisco, CA 94111
Tel: 415.267.4000 • Fax: 415.267.4198
www.mckennalong.com

New York
Philadelphia
Sacramento
San Diego
San Francisco
Washington, D.C.

STANLEY W. LANDFAIR
(415) 267-4170
slandfair@mckennalong.com

May 5, 2009

CHRISTIAN VOLZ
(415) 267-4108
cvolz@mckennalong.com

Thomas M. Mack, M.D., M.P.H., *Chairperson*
Committee Members
CARCINOGEN IDENTIFICATION COMMITTEE

RE: FMC COMMENTS ON PRIORITIZATION OF PERMETHRIN

Dear Chairman Mack and Committee Members:

We are submitting the following comments on behalf of our client FMC Corporation (“FMC”), to recommend that the compound known as permethrin (CAS No. 52645-53-1) not be advanced to the next stage of the listing process under Proposition 65 or, alternatively, that it be assigned a low priority for review.

SUMMARY

Under this Committee’s well-established guidance criteria, a chemical may be listed as a carcinogen only if the weight of scientific evidence clearly shows, through scientifically valid testing, that the chemical causes invasive cancer in humans, or invasive cancer in animals (unless the mechanism of action has been shown not to be relevant in humans). The goal of the Prioritization Process is to identify chemicals for this Committee’s expedited consideration that will at least potentially meet this weight of evidence standard for listing.

Permethrin clearly does not satisfy the selection criteria of the Prioritization Process. OEHHA advises, correctly, that there are no epidemiology data that suggest permethrin causes cancer in humans. Therefore, the Prioritization Process selection criteria require that permethrin be shown to cause invasive cancer in “positive animal cancer bioassays,” *i.e.*, studies showing “an increased incidence of malignant or combined malignant and benign tumors” The animal studies OEHHA has listed for permethrin, however (and FMC agrees that these are the best and most relevant studies), do not show a significant increase in malignant tumors in any species. Similarly, the genotoxicity studies listed by OEHHA show no genotoxicity except at exposure levels that also cause cytotoxicity. In summary, the animal data taken as a whole are not persuasive evidence that permethrin causes cancer, and the chemical is not genotoxic.

The fact that permethrin was classified by the United States Environmental Protection Agency (“US EPA”) in 2002 as “likely to be carcinogenic to humans” does not change the foregoing conclusion, or mandate either priority review or ultimate listing of permethrin under

Proposition 65. Permethrin is not here proposed for listing on the basis of an “authoritative body” identification; this Committee must decide whether the human and animal data satisfy the Committee’s own guidance criteria for listing, and the criteria of the Prioritization Process for review. As we explain in detail below, the data do not satisfy those criteria. Moreover, numerous expert agencies other than US EPA have reviewed the same body of data and have reached a contrary conclusion.

Finally, and particularly relevant to the Committee’s decision on whether to make a review of permethrin a *priority*, recent and ongoing research suggests that the mechanism of action by which permethrin (and other pyrethroids) produces tumors in rodents is not relevant to humans. Based on such research, US EPA recently revisited the cancer classification for metofluthrin, a pyrethroid referenced by OEHHA as structurally similar to permethrin, and concluded that pyrethrins and metofluthrin are “not likely to be carcinogenic to humans” FMC is currently generating similar mode of action data for permethrin and anticipates that US EPA will reach a similar conclusion. Considering the importance of permethrin to protect both humans and crops from insects and diseases, this Committee would be justified in assigning a low priority to permethrin so that its review can await the development of such valuable new data.

I. Permethrin Is A Valuable Compound Used To Protect Public Health And To Protect Agricultural Commodities From Insect Infestation Under Safeguards Already Imposed Under Federal And State Law

A. Permethrin Is Widely Used to Protect Humans and Crops from Harmful Insects

Permethrin is a synthetic pyrethroid insecticide. The compound is effective against a broad spectrum of insect pests. As an aid to agriculture, permethrin is effective in the control of aphids, Japanese beetles, bagworms, caterpillars, ground beetles, termites and sod webworms. More importantly, permethrin also is effective in controlling insect pests that are a threat to public health, such as mosquitoes, fleas, flies, bedbugs, ticks, ants, and wasps,¹ and in controlling fleas, ticks and other insects in household pets and other domestic animals. Permethrin also is effective in the control of bedbugs. As a pharmaceutical agent in shampoos,

¹ See generally, U. S. Environmental Protection Agency (US EPA 2007). Reregistration Eligibility Decision (RED) for Permethrin. EPA 738-R-06-017. Prepared by Office of Prevention, Pesticides and Toxic Substances, Washington, D.C.

permethrin is effective in the control of head lice and scabies. Permethrin thus is an important tool in the control of insect-borne diseases that constitute a threat to public health, such as malaria, yellow fever, dengue fever, encephalitis, Lyme disease, Rocky Mountain Spotted fever, and West Nile Virus.

Permethrin also is the only insecticide that may be used lawfully in the United States for treating fabrics to make them pest-resistant. The compound thus is approved by the Armed Forces Pest Management Board and used by military personnel for treating field uniforms, mosquito netting, tents, and other protective equipment to make them resistant to mosquitoes and other disease-bearing insects listed above.²

Permethrin is referred to as a synthetic pyrethroid insecticide because, while man-made, it resembles naturally-occurring chemicals with insecticidal properties, called pyrethrins, which are found especially in chrysanthemums. Pyrethrins are one of the oldest classes of organic insecticides known. They work by quickly paralyzing the nervous systems of insects, producing a quick “knockdown” effect on insect pest populations, and by acting as a stomach poison when ingested by insects or as a contact poison through direct contact. The insecticidal activity of this material lasts up to twelve weeks after application.

Permethrin has a long history of being applied agriculturally to control against pests in the production of fruits, vegetables, and other crops. It has not been known to cause any chronic toxic effects to humans. Mild eye and skin irritation may occur with exposure to permethrin which can be treated by washing the eyes and skin thoroughly with water after contact. When properly used, it is of very low toxicity to household pets and is virtually non-toxic to birds. It is toxic to fish and the label recommends caution in applying the product in areas that would result in aquatic exposure. Permethrin binds tightly to soil, making it unlikely to leach or contaminate groundwater.

The majority of permethrin, however, is used in non-agricultural settings. Of these uses, 55% is applied by professional applicators, 41% by homeowners, and 4% in mosquito abatement areas. Permethrin is the most widely used mosquito adulticide in the U.S. due to its low cost, high efficacy, and low incidence of pest resistance.³

² Armed Forces Pesticide Management Board Technical Bulletin No. 36, available on-line at http://www.afpmb.org/coweb/guidance_targets/ppms/TG36/TG36.htm#_Toc6820321.

³ *See generally*, U. S. Environmental Protection Agency (US EPA 2007). Reregistration Eligibility Decision (RED) for Permethrin. EPA 738-R-06-017. Prepared by Office of Prevention, Pesticides and Toxic Substances, Washington, D.C.

B. US EPA and California DPR Have Approved Permethrin for these Uses under Federal and State Law

Permethrin was first registered by US EPA under the Federal Insecticide, Fungicide and Rodenticide Act (“FIFRA”) in 1979 for use on cotton. Since then, permethrin has been registered for use on over fifty crops and foods, including numerous fruits, tree nuts, vegetables and livestock.

US EPA recently completed an exhaustive review and re-evaluation of the scientific data on permethrin and of all the compound’s registered uses, as it was required to do for all pesticides first registered prior to 1984. This review culminated in a Re-registration Eligibility Decision in which EPA concluded that permethrin products are eligible for re-registration. In reaching this conclusion, US EPA considered the significance of the many uses of permethrin and conducted a risk-benefit balancing analysis. US EPA noted that permethrin is very valuable to agricultural users because it controls a broad spectrum of pests, while many other competing pesticides have either become unavailable, or control only specific insects or fewer pests. Permethrin is also particularly useful because its unusually brief, one-day “pre-harvest interval” allows for effective pest control immediately prior to harvest of crops. US EPA also noted permethrin’s importance as a mosquito adulticide, and concluded that the loss of permethrin would adversely affect mosquito abatement programs in some situations.^{4, 5}

II. Numerous Agencies Have Reviewed Permethrin for Carcinogenic Potential

It will be obvious to the Committee upon review of the materials cited in OEHHA’s March 2009 Notice that permethrin was classified in 2002 by the US EPA as “Likely to Be Carcinogenic to Humans,” and remains so classified now under that Agency’s 2005 Guidelines for Carcinogen Risk Assessment.⁶ Deeper inquiry will show, however, that permethrin has been reviewed many times previously under predecessor guidelines published by the same agency, as well as by the International Agency for Research on Cancer (“IARC”) and the World Health

⁴ *Id.*

⁵ The distribution, sale and use of permethrin for pesticidal purposes in California also is subject to registration and other requirements under the California Food & Agricultural Code. The pattern of registration activity in California under California law is not materially different from that under federal law (with the exception that California law does not impose the requirement for reregistration), so is not summarized here.

⁶ US Environmental Protection Agency, Guidelines for Carcinogen Risk Assessment, Risk Assessment Forum (March 2005), at 7.

Organization (“WHO”). Based on virtually the same data, these bodies, agencies and panels did not reach the same conclusion as USEPA.

We demonstrate in Section II below that the data the US EPA reviewed in reaching its 2002 conclusion do not satisfy the criteria for listing permethrin as a chemical “known to the State to cause cancer” for purposes of Proposition 65. Thus, the US EPA classification of permethrin does not compel a conclusion that permethrin should be listed as a carcinogen under Proposition 65. As background for explaining and understanding this distinction, we have summarized below the history of the various reviews that have been conducted on permethrin and the conclusions that have been reached, as recounted in a 2002 Report of the US EPA Carcinogen Assessment Review Committee (hereinafter referred to as “US EPA CARC” or “CARC”).⁷

1. 1988 US EPA Carcinogenicity Peer Review Committee (1988)

In December, 1988 the Carcinogenicity Peer Review Committee (“CPRC”) met to evaluate the database for permethrin to determine its potential for carcinogenicity. The CPRC concluded that permethrin should be classified in Group C under the 1986 Guidelines then in effect.⁸ This classification bore the descriptor “Possibly Carcinogenic in Humans,” and was described as follows:

“This group is used for agents with limited evidence of carcinogenicity in animals in the absence of human data. It includes a wide variety of evidence, *e.g.*, (a) a malignant tumor response in a single well-conducted experiment that does not meet conditions for sufficient evidence, (b) tumor responses of marginal statistical significance in studies having inadequate design or reporting, (c) *benign but not malignant tumors with an agent showing no response in a variety of short-term tests for mutagenicity*, and (d) responses of marginal statistical significance in a tissue known to have a high or variable background rate.”⁹

⁷ *Id.*

⁸ US Environmental Protection Agency, Guidelines for Carcinogen Risk Assessment, Risk Assessment Forum (September 1986), published at 51 Federal Register 33992 (September 24, 1986).

⁹ *Id.* at 20.

2. FIFRA Scientific Advisory Panel (1989)

The FIFRA Scientific Advisory Panel considered permethrin in May, 1989 and considered the CPRC's assessment. The SAP similarly recommended that permethrin be classified as a Group C oncogen. Importantly, the SAP did not recommend any quantitative risk analysis, because of the relatively weak carcinogenicity and the lack of any data showing mutagenicity.¹⁰

3. US EPA Carcinogenicity Peer Review Committee (1989)

In June, 1989, the CPRC met again to consider the comments and recommendations of the FIFRA SAP. The CPRC "reaffirmed" its prior classification of permethrin as a Group C Possible Human Carcinogen, based on the same data, and recommended that a quantitative risk assessment be performed.

4. World Health Organization (1990)

A World Health Organization Task Group on Environmental Health Criteria for certain pesticides evaluated permethrin in July, 1988. The report, published in 1990, comments as follows:

"There were indications, from three long-term mouse studies, of oncogenicity in the lungs of one strain of mouse (females only) at the highest dose level (5g/kg/diet). Studies in rats revealed no oncogenic potential in either sex."

Based on these data, the report concluded that:

"Toxicological evidence from mutagenicity studies and from long-term mouse and rat studies suggests that permethrin's oncogenic potential is very low, is limited to female mice, and is probably epigenetic."¹¹

¹⁰ U.S. Environmental Protection Agency (US EPA, 2002), *Permethrin: Report of the Cancer Assessment Review Committee (Third Evaluation)*, Cancer Assessment Review Committee, Health Effects Division, Office of Pesticide Programs, October 23, 2002, at 14-15.

¹¹ World Health Organization (WHO 1990), *Environmental Health Criteria for Permethrin*.

5. International Agency For Research On Cancer (1991)

The International Agency for Research on Cancer (“IARC”) concluded that permethrin was associated with a marginal increase in pulmonary adenomas in mice and that no genotoxic effect was observed in the limited number of short-term tests that were available. IARC concluded that there was inadequate evidence for the carcinogenicity of permethrin in laboratory animals and that permethrin is not classifiable as to its carcinogenicity to humans.¹²

6. WHO Joint Meeting on Pesticide Residues (1999)

The Joint Meeting on Pesticide Residues (“JMPR”), conducted under the auspices of the World Health Organization Food and Agriculture Organization, concluded that permethrin was not carcinogenic in the rat but that the evidence in mice was conflicting. JMPR noted that no genotoxic effects were observed in an adequate battery of genotoxicity studies and concluded “Thus, the weight of the evidence supports the conclusion that permethrin has a very weak carcinogenic potential and the probability that permethrin has oncogenic potential in humans is remote.”¹³

7. Cancer Assessment Review Committee (2002)

During the period between the first US EPA review above and 2002, the US EPA revised its Guidelines for Carcinogen Risk Assessment. In addition, FMC requested re-classification. Accordingly, the federal agency revised its process for re-evaluating pesticides, and re-considered permethrin again, this time under US EPA’s 1999 Interim Final Guidelines for Carcinogen Risk Assessment, which are substantially similar to the 2005 Guidelines in effect now. The CARC’s conclusion is reproduced in part below:

“In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July 1999), the CARC, by majority vote, considered permethrin as “Likely to Be Carcinogenic to Humans” by the oral route. There was considerable discussion among the CARC about the merits of a “Suggestive” instead of “Likely” classification. Some members felt that since only benign lung and liver tumors were observed in only one species (*i.e.*, mouse), no carcinomas were observed (*i.e.*, no progression to malignancy), and since permethrin is not mutagenic, the

¹² International Agency for Research on Cancer (1991). Volume 53: Occupational Exposures in Insecticide Application, and Some Pesticides. World Health Organization, Lyon, France.

¹³ World Health Organization (2000). Pesticide residues in food-1999. Joint FAO/WHO Meeting on Pesticide Residues, Geneva, Switzerland.

classification of “Suggestive” was supported. However, in accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment, the majority of the CRC classified permethrin as “Likely to be Carcinogenic to Humans” by the oral route based on the following weight-of-the-evidence considerations:

1. Two tumor types were seen in one species. Lung adenomas were seen in female CD-1 mice and hepatocellular adenomas were seen in both male and female CD-1 mice. These two tumor types were reproducible in two mouse studies
2. The lung tumors in female mice had an early onset (39 weeks) and were not reversible up to 104 weeks recovery period in the reversibility study. The liver tumors also were not reversible in this study.
3. The tumor findings in the Long Evans rat were considered equivocal.
4. Structure activity relationship indicated that Cypermethrin is a structural analogue of permethrin. Cypermethrin is classified as a Category “C” carcinogen (possible human carcinogen) with no Q₁* based on female mice lung tumors (adenomas and combined).”¹⁴

In summary, permethrin now comes for prioritization before the Committee with a history of at least seven previous reviews for carcinogenicity.¹⁵ In all of those previous reviews, each of the studies that are presented to the Committee now has been found not to present evidence that permethrin induces malignant tumors. Our analysis of these studies, like that of the agencies, committees and panels above, shows that they would not satisfy the criteria for listing under Proposition 65.

¹⁴ U.S. Environmental Protection Agency (US EPA, 2002), Permethrin: Report of the Cancer Assessment Review Committee (Third Evaluation), Cancer Assessment Review Committee, Health Effects Division, Office of Pesticide Programs, October 23, 2002, at 15-16.

¹⁵ Indeed, California’s Department of Pesticide Regulation also has reviewed the data for permethrin. The DPR review is addressed in Section III.

III. Permethrin Does Not Satisfy The Proposition 65 Criteria For Listing Or The Committee's Criteria Under The Prioritization Process For Advancement To The Next Stage Of The Listing Process

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 . . .*"¹⁶ The test is whether "the *weight of scientific evidence clearly shows that [permethrin] 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)."¹⁷

"Scientifically valid studies of carcinogenesis" include "[e]pidemiological studies of carcinogenesis in humans," and "[s]tudies of carcinogenesis in animals."¹⁸¹⁹ The "weight of evidence depends upon the degree to which [various factors] can be verified or rejected with respect to *malignancies or tumors of malignant potential*."²⁰

The Prioritization Process is intended to identify chemicals for which existing human data or animal toxicology data will at least potentially satisfy the foregoing listing criteria, and OEHHA's March 2009 proposal of thirty-eight chemicals, including permethrin, accordingly recites that the agency conducted "screening level literature searches" to (1) identify such human studies showing "a positive finding of cancer associated with exposure to the chemical" and (2) "positive animal chemical bioassays," *i.e.*, studies "in which a treatment-related increase in the incidence of *malignant* or *combined malignant and benign tumors* is observed"²¹

¹⁶ California Health & Safety Code § 25249.8(b) (emphasis added).

¹⁷ Guidance Criteria for Identifying Chemicals for Listing as "Known to the State to Cause Cancer" (OEHHA March 2001), at 1 (emphasis added).

¹⁸ *Id.* at Section 2.A, B.

¹⁹ 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).

²⁰ Guidance Criteria for Identifying Chemicals for Listing as "Known to the State to Cause Cancer" (OEHHA March 2001) at Section 2.B.(ii).

²¹ OEHHA, March 2009, at pp. 1 – 3 (emphasis added).

In the absence of epidemiology data, any proposal to advance permethrin for priority consideration by this Committee is based entirely on animal data. OEHHA states that “Permethrin passed the animal data screen, underwent a preliminary toxicological evaluation, and is being brought to the Carcinogen Identification Committee for consultation.” OEHHA lists several long-term diet studies in the rat and mouse as the “animal carcinogenicity data” identified during its preliminary evaluation. The Agency also lists several genotoxicity studies and reviews, and “structure activity considerations,” as “other relevant data” identified in its preliminary evaluation. From these statements and lists of studies, we infer that OEHHA is asserting that the cited animal studies show increased incidence of malignant tumors or combined malignant and benign tumors in one or more species, and that this evidence of carcinogenicity is supported by the results of the genotoxicity studies and by permethrin’s “structural similarity” to certain other pyrethroids.

These assertions, both explicit and implicit, are incorrect, for the reasons that follow. First, and crucially, none of the animal studies on permethrin listed in the March 2009 notice in fact show any increase in malignant tumors in any species. Second, none of the listed genotoxicity studies demonstrate genotoxicity except at exposure levels that also cause cytotoxicity. Finally, new research calls into question the relevance to humans of the mechanism or mechanisms by which permethrin and other pyrethroids induce increases in tumors in rodents. Therefore, permethrin does not satisfy the criteria either for ultimate listing by this Committee as a carcinogen or for selection in the Prioritization Process for expedited listing consideration.

A. The Animal Data Would Not Support Listing And Do Not Support Prioritization For Review

OEHHA’s March 2009 Notice identifies three relevant studies in the rat and five in the mouse. FMC agrees that this is the universe of the relevant animal studies. For the convenience of the Committee, we have summarized each of these studies, based in significant part on summaries that appear in a “Risk Characterization Document” for permethrin prepared by the California Department of Pesticide Regulation.²² We have included with each summary the conclusions drawn from the studies by US EPA and California DPR.

As the summary below demonstrates, the agencies that have reviewed these data have concluded that certain of the studies show increased incidences of benign lung and liver tumors in the mouse, and that none of the studies shows an increased incidence of malignant tumors.

²² California Department of Pesticide Regulation (CDPR, 1994), Permethrin Risk Characterization Document (Revised). Medical Toxicology and Worker Health and Safety Branches, California Environmental Protection Agency.

None of these studies would support the designation of permethrin as a carcinogen under the Proposition 65 listing criteria, and none satisfy the requirement of the Prioritization Process for “positive animal chemical bioassays.”

1. The Rat Data Are Negative For Carcinogenicity

The March 2009 Notice identifies three long-term dietary studies in rats. As discussed below, none of these studies presents evidence of carcinogenicity. Two studies in the Wistar rat showed no carcinogenic effects and the third study, in the Long-Evan rat, is considered negative or equivocal.^{23, 24}

a. Two-year studies in male and female ALpk:AP (Wistar-derived) rats: Ishmael and Litchfield (1988)/ICI (1977)

In this study, sixty Wistar rats per sex per group were administered permethrin in their diet at 0, 500, 1000 or 2500 parts per million (“ppm”) (0, 25, 50 or 125 mg/kg/day) for two years. Non-neoplastic liver effects (increased liver-to-body weight ratios and histological changes in centrilobular cells were seen at the mid-and high-dose level. The No Observable Effect Level (“NOEL”) for these liver effects was 500 ppm (25/mg/kg/day) and the Lowest Observable Effect Level (“LOEL”) was 1000 ppm (50 mg/kg/day). This study did not show a carcinogenic response at any site.²⁵

b. Two-year studies in male and female Long-Evan rats: Braun and Rinehart (1977) / Bio/dynamics (1977)

Sixty Long-Evan rats per sex per group were fed permethrin in their diet at 0, 20, 100 or 500 ppm (0, 1, 5, or 25 mg/kg/day). The initial examination of the lung tissue from the male rats suggested a dose-related increase in lung tumors. The lung tissue for all males was reexamined

²³ U.S. Environmental Protection Agency (US EPA, 2002), Permethrin: Report of the Cancer Assessment Review Committee (Third Evaluation), Cancer Assessment Review Committee, Health Effects Division, Office of Pesticide Programs, October 23, 2002, at 14-15.

²⁴ California Department of Pesticide Regulation (CDPR, 1994), Permethrin Risk Characterization Document (Revised). Medical Toxicology and Worker Health and Safety Branches, California Environmental Protection Agency, at 21.

²⁵ *Id.*

after step-sectioning at 250 micron intervals. The incidence from the second reading (8/60, 5/55, 9/60 and 9/59 at 0, 20, 100 and 500 ppm, respectively) was not statistically significant. No increase in tumors was observed at any other site in this study. The response in the lung was considered to be equivocal.²⁶

**c. 103-week studies in male and female Wistar rats:
McSheehy, *et al.* (1980 / Wellcome (1980)**

Seventy-five Wistar rats per sex per group were given permethrin in their diets at 0, 10, 50 or 250 mg/kg/day for 103 weeks. Hepatocytic hypertrophy was observed histopathologically in both sexes and the mid- and high-dose levels. There also was a significant increase in the incidence of focal disturbances in the grown pattern of follicular cells in the thyroid in high-dose males that died during weeks 53 to 103. The NOEL and LOEL were 10 and 50 mg/kg/day, respectively, based on liver hypertrophy. There was no increase in carcinogenic response at any site.²⁷

**2. The Mouse Data Do Not Show An Increase In The Incidence Of
Malignant Tumors At Any Site**

The March 2009 Notice identifies five studies in mice. Collectively, these studies showed increases in benign (bronchiolar-alveolar) lung tumors in female mice and an increased incidence of benign hepatocellular tumors in males and females. No other types of tumors were observed to be treatment-related in any of the studies. The data in these five studies show no statistically significant increase in malignant lung or liver tumors in male or female mice.²⁸

**a. Two-year studies in male and female CD-1 mice:
Hogan and Rinehart (1977) / Biodynamics Mouse I (1977)**

In this study, groups of seventy-five CD-1 mice per sex per group were fed permethrin in their diets at 0, 20, 500 or 4000 ppm (0, 3, 75 or 600 mg/kg/day) for two years. The highest dose

²⁶ *Id.*

²⁷ *Id.* at 21-22.

²⁸ U.S. Environmental Protection Agency (US EPA, 2002), Permethrin: Report of the Cancer Assessment Review Committee (Third Evaluation), Cancer Assessment Review Committee, Health Effects Division, Office of Pesticide Programs, October 23, 2002, at 13-14.

level was changed from 100 to 4000 ppm (15 to 600 mg/kg/day) at week 21. There was no evidence of an oncogenic effect in this study.²⁹

**b. 98-week studies in male and female Alderley Park
(Swiss-derived) mice: Ishmael & Litchfield (1988) / ICI (1977)**

Seventy Alderley Park mice per sex per group were fed permethrin in their diets at 0, 250, 1000 or 2500 ppm (0, 37.5, 150, or 375 mg/kg/day). The incidence of benign lung tumors in the male exhibited a dose-related trend. The incidence of malignant lung tumors was not significantly greater than the controls in either sex. The study was considered to be negative for oncogenic effects.³⁰

**c. Two-year studies in male and female CD-1 mice:
Tierney and Rinehart (1979) / Biodynamics Mouse II (1979)**

Seventy-five CD-1 mice per sex per group were fed permethrin in their diets at 0, 20, 2500 or 5000 ppm (0, 3, 375, or 750 mg/kg/day) for females and 0, 20, 500 or 2000 ppm (0, 3, 75 or 300 mg/kg/day) for males for 104 weeks. There was a significant increase in the incidence of alveolar cell adenomas in females, a significant increase in hepatocellular adenomas in females, and an increase in the incidence of hepatocellular adenomas.

The incidences of benign lung and liver tumors in female mice are shown in the following table:

BENIGN LIVER & LUNG TUMOR INCIDENCE IN FEMALE MICE (FMC MOUSE II STUDY)		
<i>Dose Level (ppm)</i>	<i>Lung Adenoma</i>	<i>Hepatocellular Adenoma</i>
0	11/74 (15%)	2/66 (3%)
20	20/76 (26%)	4/62 (6%)
2500	27/76 (36%)*	22/63 (35%)*

²⁹ California Department of Pesticide Regulation (CDPR, 1994), Permethrin Risk Characterization Document (Revised). Medical Toxicology and Worker Health and Safety Branches, California Environmental Protection Agency, at 15.

³⁰ *Id.* at 15.

BENIGN LIVER & LUNG TUMOR INCIDENCE IN FEMALE MICE (FMC MOUSE II STUDY)		
<i>Dose Level (ppm)</i>	<i>Lung Adenoma</i>	<i>Hepatocellular Adenoma</i>
5000	34/75 (45%)*	28/65 (43%)*

* $p < 0.01$, pairwise comparison with control.

This study also reported an increase in benign liver tumors in male mice (6/66, 17/63, 15/63 and 17/57 for the control, 20, 500 and 2000 ppm dose levels³¹). These increases were outside of the historical control ranges for this laboratory.³²

**d. 91-week studies in male and female CFLP mice:
James (1980) / Wellcome (1980)**

Seventy-five CFLP mice per sex per group were fed permethrin in their diets at 0, 10, 50, or 250 mg/kg/day for ninety-one weeks. The incidence of benign lung tumors in female mice was significant by pair-wise comparison with controls at the high dose level. The incidence of lung tumors, even at the high-dose level, was within the normal range (10-30%) for this strain based on the historical control data, and the incidence in the controls was unusually low. This study showed no increase in malignant tumors.³³

**e. FMC 100-week carcinogenicity/reversibility studies in female
CD-1 mice: Barton, *et al.* (2000)**

This study was conducted to examine the reversibility of the liver and lung lesions in mice. Groups of 50, 75 or 100 female CD-1 mice were fed permethrin in their diets at a single dietary concentration of 5000 ppm (250 mg/kg/day) for various periods of time ranging from 40 to 78 weeks. Groups were sacrificed after dosing with some groups being allowed recovery times of up to 63 weeks. Increases in lung tumors were observed after dosing periods of 39, 52, 65 and 78 weeks. Results confirmed that the lung adenomas were benign and showed negligible potential to progress to malignancy. A small but statistically significant increase in eosinophilic

³¹ Dietary concentrations for males were lowered to 20, 500 and 2000 ppm during month three of study.

³² *Id.* at 15-19.

³³ *Id.* at 19-20.

hepatocellular adenomas was observed in mice treated for 78 weeks. The results of the study showed no increase in the incidence of liver carcinomas for any dosing period.³⁴

B. The “Other Relevant Data” Would Not Support Listing Or Prioritization

1. Permethrin Is Not Genotoxic

As noted above, OEHHA’s list of relevant studies on permethrin includes, under “other relevant data,” reference to several genotoxicity studies. The implication of this listing is that the studies in question demonstrate that permethrin is genotoxic, but this is not in fact the case. There appears to be a scientific consensus that permethrin is not genotoxic:

“The acceptable genetic toxicology studies on permethrin indicate that the compound is not mutagenic in the *Salmonella typhimurium*/mammalian activation gene mutation and the mouse lymphoma assays. Permethrin is also negative for clastogenicity in a mouse bone marrow micronucleus assay and does not cause unscheduled DNA synthesis in primary rat hepatocytes. There is no evidence of increased dominant lethal mutations in the germinal cells of male mice.”³⁵

The specific genotoxicity studies listed by OEHHA are addressed below.

a. *Salmonella typhimurium* reverse mutation assays: Pednekar *et al.* (1987); Herrera and Laborda (1988)

Pednekar *et al.* reported that permethrin was not mutagenic in 3 strains of *Salmonella typhimurium*, with or without S9 mix (rat liver microsomal activation system). Results were negative for mutagenicity at both cytotoxic and non-cytotoxic concentrations. Herrera and Laborda concluded that permethrin was not mutagenic in seven strains of *Salmonella typhimurium*, with or without S9 mix.

³⁴ Barton SJ, S Robinson and T Martin. Permethrin Technical: 100 week carcinogenicity/reversibility study in mice with administration by diet. Inveresk Project Number 452695. FMC Report A95-4264. May 24, 2000.

³⁵ U.S. Environmental Protection Agency (US EPA, 2002). Memorandum: Permethrin: Report of the Cancer Assessment Review Committee (Third Evaluation), at 15. Cancer Assessment Review Committee, Health Effects Division, Office of Pesticide Programs, October 23, 2002.

b. Chromosomal aberration assay in human lymphocyte cultures: Barrueco *et al.* (1994); Chromosomal aberration assay in Chinese hamster ovary cells: Barrueco *et al.* (1994)

Chromosome aberrations were recorded in human lymphocytes and Chinese hamster ovary (“CHO”) cells after dosing *in vitro* at 50 to 200 µg/ml in lymphocytes and 20, 50 and 100 µg/ml in CHO cells. Assays were also conducted in the presence of S9 mix. The authors recognized, however, that the top concentration used was cytotoxic to lymphocytes and was only just below the solubility limit of permethrin (250 µg/ml). In CHO cells, the mitotic index was reported as a measure of cytotoxicity. A significant increase of chromosomal aberrations was observed only at concentrations causing a significant fall in the mitotic index, at 50 and 100 µg/ml. Therefore, it can be concluded that genotoxicity in this study likely was a result of cytotoxicity. No positive controls were run and no cytotoxicity data were reported for human lymphocytes.

c. Micronucleus assay in human whole blood lymphocyte cultures: Surralles *et al.* (1995)

In this study, the induction of micronuclei in lymphocytes exposed to permethrin *in vitro* was measured in blood from 3 healthy adult donors. Cytotoxicity was measured and reported relative to control. In one of these donors, there was a slight increase in the formation of micronuclei, but only at 100 µg/ml. At 200 µg/ml, 100% cytotoxicity was reported and in one of the other donors, both 100 and 200 µg/ml caused 100% cytotoxicity. As the study authors noted, the genotoxic effects of permethrin “can be considered marginal.”

2. Mode Of Action Information Does Not Support Listing Or Prioritization

Further evidence against assigning a high priority for listing arises from mode of action information for the induction of the tumor types associated with permethrin exposure. Subsequent to conduct of the mouse oncogenicity studies, mechanistic information has become available to show that rodent tumors associated with the induction of the microsomal enzyme CYP 2B are not predictive of a carcinogenic response in humans.³⁶ Both the lung and liver tumors induced by permethrin are likely to result from the P450 induction mode of action based upon increased liver weights and hypertrophy seen at dose levels associated with tumor

³⁶ (Holsapple *et al.*, 2006) Mode of action in relevance of rodent liver tumors to human cancer risk. *Toxicol Sci* 89:51-56.

induction and preliminary data indicating the liver weight increases are associated with P450 induction and specifically, CYP 2B and CYP 4A, following permethrin dosing in the female mouse.

Phenobarbital, the best studied of CYP 2B enzyme inducers, produces liver tumors in rodents but there is no evidence of a carcinogenic effect in patients receiving phenobarbital for many years at plasma concentrations similar to those that produce a carcinogenic effect in rodents.³⁷ Most recently, it has been shown that human hepatocytes, unlike those in the rat, are refractory to the proliferative effects of phenobarbital.³⁸ Phenobarbital-like microsomal CYP 2B inducers therefore appear to be rodent but not human carcinogens.

Application of the International Programme on Chemical Safety “Human Relevance Framework” to metofluthrin, a structurally similar compound that induces rodent tumors by this mode of action, resulted in the following determination: “It is reasonable to conclude that Metofluthrin will not have any hepatocarcinogenic activity in humans.”³⁹ Based upon some of this new mode of action data available for metofluthrin, on July 26, 2007 the US EPA CARC revisited the carcinogenicity classification that was referenced by OEHHA. The new US EPA CARC conclusion regarding metofluthrin is as follows: “Not likely to be carcinogenic to humans at doses that do not result in a mitogenic response.” A similar conclusion was reached by EPA concerning liver and thyroid tumors associated with dosing rats with pyrethrins.⁴⁰

In order to facilitate further consideration, FMC is generating mode of action data for permethrin to test the hypothesis that permethrin causes tumors by a rodent-specific mode of action. This will include examining the induction liver P450 isoforms, such as CYP 2B or CYP 4A (PPAR α , an indicator of peroxisome proliferation). FMC is working with a test laboratory

³⁷ (IARC 2001, cited in Holsapple *et al.*, 2006) Mode of action in relevance of rodent liver tumors to human cancer risk. *Toxicol Sci* 89:51-56.

³⁸ (Hirose *et al.*, 2009) Comparison of the effects of the synthetic pyrethroid metofluthrin and penobarbital on CYP 2B form induction and replicative DNA synthesis in cultured rat and human hepatocytes. *Toxicology* doi.10.1016/j.tox.2009.01.007.

³⁹ (Yamada *et al.*, 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.

⁴⁰ Finch *et al.*, (2006). A mode of action for induction of thyroid gland tumors by Pyrethrins in the rat. *Toxicol Appl Pharmacol* 214:253-262.

Price *et al.*, (2007). A mode of action for induction of liver tumors by Pyrethrins. *Toxicol Appl Pharmacol* 218:186-195.

and a leading researcher in the field of liver toxicology to determine more precisely the dose relationship between exposure to permethrin, cell proliferation and P450 isoform induction, and to examine reversibility of enzyme induction and cell proliferation as a result of discontinuation of dosing. The company expects that US EPA will reach the same conclusion for permethrin that it reached for pyrethrins and metofluthrin when the Agency evaluates those studies.

C. The Weight Of Evidence Would Not Support Listing

As noted previously, none of the studies summarized above showed an increase in malignant tumors of any type. Furthermore, eosinophilic hepatocellular adenomas, the predominant liver tumor associated with permethrin exposure, are similar in histological appearance and growth behavior to normal hepatocytes and are different in nature from spontaneous tumors or tumors induced by genotoxic agents.⁴¹ This tumor type has a negligible potential to progress to malignancy and questions have been raised as to whether this histological change represents a neoplastic transformation or whether it should more accurately be called reactive or adaptive response.⁴² Both the lung and liver tumors associated with permethrin exposure are commonly occurring tumors and occur only at relatively high dietary exposure concentrations.

IV. Permethrin Should Not Be Advanced to the Next Stage in the Listing Process or Should Be Assigned a Low Priority for Review

We recognize that the issue before the Committee is not whether permethrin should be listed under Proposition 65, but whether the chemical should be advanced to the next stage of the listing process and/or what priority should be assigned to permethrin for further review. It is not possible to consider the latter questions, however, without considering whether permethrin is a good candidate for listing.

If the Committee were to review the studies in detail, the data discussed above should compel the conclusion that permethrin presents no evidence of induction of malignant tumors, and only weak evidence of benign tumor induction and is not genotoxic. We thus believe the

⁴¹ (Pedrick *et al.*, 1994) Growth characteristics and Ha-ras mutations of cell cultures isolated from chemically induced mouse liver tumors. *Carcinogenesis* 15():1847-1852.

⁴² (Butler, 1996). A review of the hepatic tumors related to mixed-function oxidase induction in the mouse. *Toxicol Pathol* 24(4)484-492.

Committee would conclude, like the US EPA CPRC, the FIFRA SAP, the WHO and IARC, that there is little or no evidence of carcinogenic potential in humans.

The US EPA CARC's classification of permethrin as "Likely to Cause Cancer to Humans" under the Guidelines for Carcinogen Assessment Risk Assessment is not in itself a cause for listing. Rather, the data must govern, and the data would not support listing under the Proposition 65 standards articulated in the statute,⁴³ the implementing regulations,⁴⁴ and the Committee's own Guidance Criteria.⁴⁵ Nor is that classification a good reason to assign the chemical a high priority for review. In this regard, we believe that the US EPA classification reflects the developing appreciation for mechanistic data in the study of carcinogenesis, and the difficulty in applying the US EPA Guidelines to chemicals for which the mechanistic data are not complete. As noted above, FMC is in the process of generating such data in order that reviewing bodies such as this one may determine whether the mode of action for permethrin is relevant to humans, and expects, as in the case of phenobarbital, pyrethrins and metofluthrin, the data will show that permethrin does not present a significant risk of cancer to humans.

Because the issue is prioritization, and not listing, this is a compelling reason for OEHHA and the Committee to move at a deliberate pace. In a word, it would be appropriate to allow the data to catch up with the US EPA Guidelines for Carcinogen Risk Assessment. The alternative would be to initiate review prematurely, on the basis of inadequate or incomplete data, and to risk depriving Californians of a product that is vital to the agricultural economy, the food supply, and to maintaining public health.

⁴³ Cal. Health & Safety Code § 25249.8(b) (requiring listing for chemicals "*clearly shown*, through scientifically valid testing according to generally accepted principles, *to cause cancer* . . .").

⁴⁴ Cal. Code Regs., tit. 22, § 25305(a)(1) (requiring Committee to identify chemicals "*clearly shown*, through scientifically valid testing according to generally accepted principles, *to cause cancer* . . .").

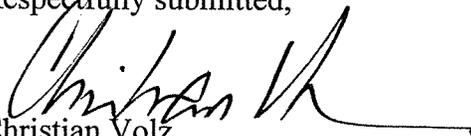
⁴⁵ Guidance Criteria for Identifying Chemicals for Listing as "Known to the State to Cause Cancer" (OEHHA March 2001) (indicating that "weight of evidence depends upon the degree to which [various factors] can be verified or rejected with respect to *malignancies or tumors of malignant potential*").

Thomas M. Mack, M.D., M.P.H., *Chairperson*
Committee Members
May 5, 2009
Page 20

Conclusion

For all the foregoing reasons, we respectfully submit that this Committee should recommend against advancing permethrin to the next stage of the listing process under Proposition 65. Alternatively, we request that permethrin be assigned a low priority for review.

Respectfully submitted,


Christian Volz
Counsel for FMC CORPORATION

cc: Joan Denton, Ph.D., *Director*, OEHHA
George Alexeeff, Ph.D., *Deputy Director*, OEHHA
Carol Monahan-Cummings, *Chief Counsel*, OEHHA