Comments on Behalf of the Permethrin Data Group II Steering Committee/Joint Venture

The Permethrin Data Group II Steering Committee/Joint Venture (PDGII), operating under the auspices of the Consumer Specialty Products Association, Inc., respectfully submit these comments to the Office of Environmental Health Hazard Assessment's Prioritization 2016: Chemicals for Consultation by the Carcinogen Identification Committee. Members of the PDGII include AMVAC, Bayer CropScience, FMC, Gharda Chemicals Ltd., LG Life Sciences, Meghmani Organics Ltd., MGK Co. and UPI.

Summary

A scientifically robust assessment of the potential carcinogenicity of permethrin requires a careful review of all of the available relevant information. A large body of highly relevant information on permethrin has been developed in the past five years. Most of this is presently not yet published and will not be located with computerized literature searches. As the deliberations of the CIC move ahead, the PDGII will work with OEHHA to be sure that the latest information is included in their review of the potential carcinogenicity of permethrin. This information indicates that permethrin is not likely to be carcinogenic to humans.

Background

These comments discuss the basis for the grouping of the Type I pyrethroids for the purpose of consideration of potential carcinogenicity and to make OEHHA aware of the extensive information base on the carcinogenicity of permethrin that goes far beyond what is listed in the OEHHA document on the Type I pyrethroids.

Grouping of the Type I Pyrethroids

We are puzzled by the use of the Type I criteria for grouping of the pyrethroids respect to potential carcinogenicity. The Type I, Type II designations are based on collection neurologic signs exhibited in mammals following acute intoxication. These are a result of the interaction of the chemical with a complex array of voltage-gated sodium channels in nerves. The is not related to the potential to be carcinogenic to the nervous system or various non-neural tissues (such as lung and liver) following chronic administration in rodents. Recognizing this, each of the pyrethroids should evaluated individually.

Additional Data for Permethrin

A large body of data on the carcinogenic potential of potential has recently been developed and should be considered when evaluating the merits of listing permethrin under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65). It is beyond the scope of these comments to discuss this information in detail, but the PDGII will work with the State as needed to make this information available. The consideration of this information is essential to a

complete and robust assessment of permethrin prior to making decisions about the priority for a future CIC review.

The additional information fits into each of the three categories that OEHHA has used to organize its evaluations: epidemiological data, animal carcinogenicity data, and endocrine disruption data.

Epidemiological Data

Several epidemiology studies have reported results on exposure to permethrin, both in the workplace and in the household, and risk of different cancers (multiple myeloma in particular), but a systematic review and critical analysis of those studies has not been published. The PDGII will is considering sponsoring such an independent review.

The interpretation of the results of the epidemiologic studies is not straightforward. A robust review should include:

- Identification of all relevant results, including those not captured by traditional searching strategies;
- Interpretation of strength and consistency of the available evidence;
- Consideration to potential sources of bias, their plausible impact in terms of likelihood, direction and magnitude of the effect;
- Quantitative assessment of the combined evidence, through a meta-analysis of available results.

Established guidelines for reporting and reviewing epidemiologic studies and for meta-analyses need to be followed. Each study needs to be reviewed using a standardized approach, the key aspects of the study design and the results summarized in one or more tables, which would be organized by cancer site. The review should include a general section on methodological issues in the design, conduct, analysis and interpretation of epidemiologic studies of insecticides and cancer. The results of the studies on permethrin exposure need to be interpreted within this broader framework.

Animal Carcinogenicity Data

Although no new carcinogenicity studies have been undertaken recently, a tremendous amount of research into the Mode of Action (MOA) for the elicitation of the liver tumors (male mice) and lung tumors (female mice) observed in a mouse carcinogenicity study has been conducted. These data were submitted to the U.S. EPA in 2014. A list of the studies sponsored by Sumitomo Chemical Company Ltd. that were submitted to the U.S. EPA is attached as Appendix 1.

Along with the study reports, a comprehensive overview document sponsored by the PDGII discussing and interpreting the data was also submitted to U.S. EPA (An Evaluation of the Human Relevance of the Liver and Lung Tumors Observed in Mice Treated with Permethrin

Based on Mode of Action, July 11, 2014, MRID 49444101).

This analysis was conducted using the Human Relevance Framework developed by the WHO's International Program on Chemical Safety (IPCS). Based on the data from the studies listed in Appendix 1, plausible MOAs have been established for permethrin-induced liver tumor formation in male and female mice and for permethrin-induced lung tumor formation in female mice. The proposed MOAs for permethrin-induced mouse liver and lung tumor formation were then evaluated using the IPCS framework. Both the proposed liver tumor MOA and the proposed lung tumor MOA were found to satisfy the conditions of dose and temporal concordance, biological plausibility, coherence, strength, consistency and specificity as described in the IPCS framework. Alternative MOAs for both permethrin-induced liver and lung tumor formation were excluded.

For liver tumors, it was concluded that the proposed MOA could not qualitatively operate in humans. The proposed MOA for permethrin-induced liver tumor formation is similar to that established for some other PPARα agonists, known not to be relevant to humans. For lung tumors, although the postulated MOA could potentially operate qualitatively in humans, marked quantitative species differences in lung anatomy, physiology, and susceptibility to tumor formation make this highly unlikely. Furthermore, there is a marked quantitative difference in the level of human exposure to permethrin compared to the doses required to produce lung tumors in mice. Therefore, even though liver and lung tumors were increased in a single permethrin mouse 2-year study, the conclusion of this MOA analysis is that permethrin does not pose a tumorigenic hazard to humans.

Four manuscripts presenting these data and the MOA analysis are in preparation and will be submitted for publication by early 2017, the titles of which are listed below:

- An evaluation of the human relevance of the liver tumors observed in mice treated with permethrin based on mode of action: I. Peroxisome proliferator-activated receptor-alpha activation and mitogenicity of hepatocytes;
- An evaluation of the human relevance of the liver tumors observed in female mice treated with permethrin based on mode of action: II. Human relevance using the IPCS framework.
- An evaluation of the human relevance of the lung tumors observed in mice treated with permethrin based on mode of action: I. Mitogenicity of lung Club cells.
- An evaluation of the human relevance of the lung tumors observed in mice treated with permethrin based on mode of action: II. Human relevance using the IPCS framework.

Other Information – Endocrine Disruption

Endocrine disruption is one of the widely accepted Modes of Action by which chemicals can be tumorigenic. The State cited a small number of published studies on permethrin in their recent document on the Type I pyrethroids. However, as a result of the U.S. EPA's Endocrine Disruptor

Screening Program (EDSP), and extensive data base on permethrin using validated endocrine screening assays is now available. The PDGII performed the following EDSP Tier 1 assays to satisfy the EDSP Test Orders:

- Amphibian Metamorphosis
- Aromatase
- Fish Short Term Reproduction
- Female Pubertal
- Hershberger
- Male Pubertal
- Steroidogenesis

Although the voluminous study reports are not included with this submission, their titles are listed in Appendix 2. In addition, the PDGII has prepared a Weight of Evidence (WOE) document to summarize and assess the results of Endocrine Disruptor Screening Program (EDSP) Tier 1 Screening for permethrin. (Weight of Evidence Evaluation for EDSP Tier 1 Screening of Permethrin, July 29, 2013, MRID 49187001).

This review contains a:

- Summary of the results of the 11 EDSP Tier 1 assays, or their functional equivalent, conducted for permethrin (Table 1);
- Examination of the overall results related to potential estrogen, androgen and thyroid effects;
- Review of Other Scientifically Relevant Information (OSRI) for permethrin to determine its consistency with the Tier 1 findings.

As discussed and supported in detail in the WOE document, and based on the data developed in the EDSP Tier 1 screening program, it is clear that permethrin does not interact with estrogenic, androgenic, and thyroid components of the endocrine system. Because of the lack of observed effects on the endocrine system from the Tier 1 screening battery, considered along with the appropriate OSRI, it was concluded that it was not necessary to undertake EDSP Tier 2 testing for permethrin.

Similarly, the U.S. EPA reviewed all of the available data to determine whether permethrin interacts with estrogen, androgen, or thyroid hormone pathways. This include a close look at all available studies with respect to the number and type of effects induced, the magnitude and pattern of responses observed across studies, taxa, and sexes. Additionally, the conditions under which effects occur were considered, in particular, whether or not endocrine-related responses were only observed at levels at which general toxicity was also evident. Based on these considerations, the U.S. EPA agreed that Tier 2 testing was not required for permethrin. (U.S. EPA, EDSP Weight of Evidence Conclusions on the Tier 1 Screening Assays for the List 1 Chemicals, Permethrin, June 29, 2015).

Appendix 1

Animal Carcinogenicity Data Sponsored by Sumitomo Chemical Company, Ltd.

U.S. EPA MRID	Studies*
49322801	Study for Mode of Action Analysis for Mouse Lung and Liver Tumors by Permethrin – Time Course Analysis 1 – (Study No. S1437)
49322802	Study for Mode of Action Analysis for Mouse Lung and Liver Tumors by Permethrin – Time Course Analysis 2 – (Study No. S1460)
49322803	Study for Mode of Action Analysis for Mouse Lung and Liver Tumors by Permethrin – Dose Response and Reversibility – (Study No. S1488)
49322804	Study for Mode of Action Analysis for Mouse Lung Tumors by Permethrin – Strain Difference on Clara Cell Proliferation 1 – (Study No. S1492)
49322805	Study for Mode of Action Analysis for Mouse Lung Tumors by Permethrin – Strain Difference on Clara Cell Proliferation 2 – (Study No. S1520)
49322806	Study for Mode of Action Analysis for Mouse Lung and Liver Tumors by Permethrin – Species Difference – (Study No. S1490)
49322807	Gene Expression Profiling Analysis at Early Phase of Treatment in the Liver from Permethrin-treated Mice – (Study No. S1566)
49322808	Gene Expression Profiling Analysis of Lung at Early Phase of Treatment from Permethrin-treated Mice – (Study No. S1617)
49322809	Study for Mode of Action Analysis for Mouse Liver and Lung Tumors by Permethrin – Effects of Selected Metabolites – (Study No. S1619)
49322810	Study for Mode of Action Analysis for Mouse Liver and Lung Tumors by Permethrin – Evaluation in PPAR*α* Knockout Mice – (Study No. S1634)
49322811	Study for Mode of Action Analysis for Mouse Lung Tumors by Permethrin – Evaluation for Cytotoxicity in Female Mouse Lung following Acute Treatment with Permethrin – (Study No. S1644)
49322812	Study for Mode of Action Analysis for Mouse Liver Tumor by Permethrin – the Effects of Permethrin and its Major Metabolites on CYP Enzyme Induction and Replicative DNA Synthesis in Cultured Mouse, Rat and Human Hepatocytes – (Study No. S1536)
49322813	Plasma Concentration of Permethrin and its Main Metabolites in Mice and Rates Treated with Permethrin at 5000 ppm in diet for 7 Days – (Study No. S1620)
49322814	Pharmacokinetics of Permethrin in Female Rats and Mice after Single Oral Administration at Dose Rate of 150 mg/kg – (Study No. X0219)

*None of these studies follow a specific OCSPP guideline.

Appendix 2

EDSP Data Sponsored by the Permethrin Data Group II Steering Committee/Joint Venture

U.S. EPA MRID	Studies
48102301	Permethrin: Fish Short-Term Reproduction Assay with the Fathead Minnow (*Pimephales promelas*)
48618601	Permethrin: Human Recombinant Aromatase Assay
48618602	The Hershberger Bioassay for Permethrin
48618603	Permethrin: H29R Steroidogenesis Assay
48672901	Pubertal Development & Thyroid Function in Intact Juvenile/Peripubertal Female Rats; Permethrin
48687101	Pubertal Development & Thyroid Function in Intact Juvenile/Peripubertal Male Rats with Permethrin
48988601	Permethrin: Amphibian Metamorphosis Assay for the Detection of Thyroid Active Substances
49187002	Range Finder Study for *In Vivo* Mammlian Assays for Permethrin