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OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT
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M E M O R A N D U M

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FROM: Richard J. Jackson, M.D., M.P.H., Chief
Hazard Identification and
Risk Assessment Branch

12/23/91

DATE: December 23, 1991

RE: Review of Draft Permethrin (Permanone) Risk Characterization Document

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Thank you for sending us the draft SB 950 risk characterization document for permethrin (Permanone Tick Repellant). Please find attached the Office of Environmental Health Hazard Assessment's (OEHHA) comments on this report.

In general, the document is well-written and logical in its presentation. OEHHA concurs with the conclusion that the potential for dermal irritancy promoted by permethrin and the formulated end-product is incompatible with its proposed uses. With respect to the potential for adverse health effects, however, OEHHA questions the extent of potential exposures. In view of the tenacity of permethrin to bind to clothing, it may not be possible to predict exposures using the model presented by the California Department of Pesticide Registration (CDPR). In fact, it is possible, given the information presented herein that exposures to workers are underestimated, as workers will be exposed to permethrin year-round through wearing treated clothing rather than six months as assumed in the "worst-case" exposure scenario.

OEHHA is also concerned about the projected higher-than-acceptable risks of cancer (over one in one million) to the general and worker populations who would be using this product. Furthermore, if the projected exposures are underestimated, these potential risks would be of greater concern.

In summary, based on the dermal irritancy of Permanone and the sensitization effects of permethrin, and the potential for significant cancer risks, OEHHA agrees with CDPR that the registration of Permanone for use on human clothing should be denied as currently proposed. On the other hand, OEHHA understands that permethrin may offer public health benefits in the prevention of tick-borne Lyme disease. OEHHA believes that mitigation

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measures may be devised and successfully implemented (see attached comments) if the public health benefit warrants the potential use of this product. Therefore, OEHHA recommends that CDPR include a risk mitigation analysis in the revised document or propose a course of action that may be of use for the registrant to make such proposals.

We have several other concerns which are included in the attached comments. If you have any questions concerning this review, please contact me or Dr. Michael DiBartolomeis at 8/571-3063.

Attachment

cc: Steven A. Book, Ph.D.
Michael DiBartolomeis, Ph.D.
Anna M. Fan, Ph.D.
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James W. Stratton, M.D, M.P.H.

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT'S REVIEW OF THE DEPARTMENT OF PESTICIDE REGULATION'S DRAFT RISK CHARACTERIZATION DOCUMENT FOR PERMETHRIN

1.0 GENERAL COMMENTS

Permethrin is a pyrethroid repellant/insecticide under evaluation for a special local need registration (Section 24(c)) as a tick repellent to be used on human clothing (Permanone Tick Repellent). The Office of Environmental Health Hazard Assessment (OEHHA) has reviewed the draft risk characterization document for permethrin prepared by the California Department of Pesticide Registration (CDPR) and has the following general comments.

The document is well-written and logical in its presentation. OEHHA concurs with the conclusion that the potential for dermal irritancy promoted by permethrin is incompatible with its proposed uses. Based on the dermal irritancy of Permanone and sensitization effects of permethrin, CDPR concluded that registration for use on human clothing should be denied. However, it was suggested, considering the hazards of Lyme disease, that the benefits of utilization should be considered. Furthermore, it was stated that apart from the dermal effects, the risks of cancer would be acceptable for the workers but not the public, assuming the public would not comply with the strict usage requirements. There were adequate margins of safety for noncancer adverse health effects to both worker and general populations.

With respect to the potential for adverse health effects, OEHHA has serious doubts regarding the extent of potential exposures. In view of the tenacity of permethrin to bind to clothing, it may not be possible to predict exposures using the model presented by CDPR. In fact it is quite possible, given the information presented herein, that exposures to workers are underestimated as workers will be exposed to permethrin year-round through wearing treated clothing rather than six months as assumed in the worst-case exposure scenario.

OEHHA is also concerned about the projected higher-than-acceptable risks of cancer (over one in one million) to the general and worker populations who would be using this product. Furthermore, if the projected exposures are underestimated, these potential risks would be of greater concern.

2.0 ADEQUACY OF THE DATA PACKAGE

According to CDPR's review, the data package for permethrin is complete and adequate to appraise the toxicity of this pesticide under the potential use conditions. However, upon review of the toxicology summary (Appendix A of the risk characterization document), it appears that the data for genetic toxicity is lacking. Although these data are not critical to the evaluation of the toxicity of permethrin, CDPR does refer to the existing data as evidence for a possible nongenotoxic mechanism for carcinogenicity. Of the 24 available studies listed in Appendix A under the categories of genetic toxicity, only eight evaluate permethrin, and only three of these studies were considered

acceptable by CDPR. Although these studies were reported to be supportive evidence for nongenotoxicity, the main text refers to two published articles that suggest a clastogenic effect of permethrin. OEHHA recommends further testing in order to provide adequate evidence to support the claim that permethrin is nongenotoxic.

OEHHA is also concerned that CDPR considers the database for mouse oncogenicity studies to be complete. This concern is discussed in more detail in Section 3.2 of these comments.

3.0 TOXICOLOGICAL EVALUATION

3.1 Subchronic/Chronic Effects

The predominant toxic effect observed in chronic studies with several species was liver hypertrophy, although this was thought to be an adaptive response to permethrin resulting in the induction of liver metabolic enzymes and increased proliferation of the smooth endoplasmic reticulum. The lowest No-Observed-Effect-Level (NOEL) of 5 mg/kg-day was identified from a one-year dog study based on effects on the liver noted at the higher dose levels (Kalinowski 1982). In this study, permethrin was given to six beagle dogs per sex per group in capsules with corn oil in doses of 0, 5, 100 or 1000 mg/kg-day. At the 100 and 1000 mg/kg-day dose levels, liver hypertrophy, adrenal alterations and decreased weight gain were observed. Therefore, 100 mg/kg-day was designated by CDPR as the Lowest-Observed-Effect-Level (LOEL).

An *estimated* NOEL of 2.5 mg/kg-day was proposed by CDPR based on the effects on weanling rats in a three generation reproduction study (Hodge 1977). In this study, 12 male and 24 female Wistar-derived rats were administered permethrin in the feed at 0, 500, 1000 or 2500 ppm for three generations with two litters per generation. Since liver hypertrophy was observed at all dose levels, 500 ppm (25 mg/kg-day) was determined to be the LOEL. CDPR derived an estimated NOEL of 2.5 mg/kg-day by dividing the LOEL by an uncertainty factor of 10.

OEHHA agrees that the selection and the consideration of liver hypertrophy as an undesirable toxic endpoint is appropriate even though it could be argued that this effect may be reversible. The method used to derive an estimated NOEL from a LOEL could be considered consistent with the standard approach to calculate a reference exposure level from a LOEL, using an uncertainty factor of 10. The estimated NOEL of 2.5 mg/kg-day is comparable to the NOEL of 5 mg/kg-day derived from the dog study.

3.2 Oncogenic Effects

Several chronic/oncogenicity studies have been reviewed by CDPR for potential oncogenic effects, including four in mice, three in rats and one in dogs. Evidence of oncogenic effects was seen in three of the four mouse studies.

In the ICI study (Ishmael 1988), 70 Alderley Park (Swiss-derived) mice per sex per group were administered permethrin in the diet at levels of 0, 250, 1000, or 2500 ppm. There was a positive trend in the incidence of benign lung tumors in males and malignant lung tumors in females. However, the incidence was not significant when compared pair-wise.

In the Wellcome study (Ishmael 1988), 75 CFLP mice per sex per dose were fed permethrin in the diet at 0, 10, 50, 250 mg/kg-day for 91 weeks. The incidence of benign lung tumors in female mice was significant by both the trend and pair-wise comparison with controls at the 250 mg/kg-day dose level. The incidence of malignant lung tumors in females was also significant by trend analysis. When benign and malignant lung tumors were combined, the results were highly significant.

The most convincing evidence for carcinogenicity, however, is from the Bio/dynamics Mouse II study which showed significant incidences of benign and malignant lung and liver tumors in females and benign liver tumors in males (Tierney 1977). Permethrin was administered in the feed to 75 CD-1 mice per sex per group at 0, 20, 2500, or 5000 ppm for females and 0, 20, 500 or 2000 ppm for males for 104 weeks. A highly significant occurrence of alveolar cell adenomas in females with a dose-related trend was observed. There was a highly significant occurrence of hepatocellular adenomas with a dose-related trend in both sexes. Only in females was there a significant occurrence of hepatocellular carcinomas.

The rat and dog studies were essentially negative. Three studies were conducted in the rats. In the ICI rat study (Ishmael 1988) 60 Wistar-derived rats/sex/group were administered permethrin in the feed at 0, 500, 1000 or 2500 ppm for 2 years. Nonneoplastic liver effects were noted in the mid- and high-level dose. In the Bio/dynamics rat study (Braun 1977), 60 Long-Evans rats/sex/group were fed permethrin for two years. Initial evidence suggested a dose-related increase in male lung tumors, however, it was found to be only marginal. In the third rat study, 75 Wistar rats per sex per group were administered 0, 10, 50, 250 mg/kg-day of permethrin for 103 weeks in the diet (McSheehy 1980). Hepatocytic hypertrophy was the only toxic effect observed in the study. There were no signs of carcinogenicity in the one-year chronic study conducted in dogs.

The U.S. Environmental Protection Agency (USEPA) has previously classified permethrin as a possible human carcinogen (Category C) and derived a cancer potency from the available data. However, this status is under reevaluation (IRIS 1991). A structurally similar pyrethroid, cypermethrin, also produces lung tumors in female Swiss mice. CDPR notes that the evidence for oncogenicity of permethrin is limited for several reasons including that the tumor sites observed for permethrin were of the type commonly seen in the Swiss-strain of mice used in these experiments, and that the conduct of these studies is questionable according to Federal Insecticide, Fungicide and Rodenticide Act's good laboratory practices. Nevertheless, CDPR concluded that there was adequate evidence from the three mouse studies to calculate a cancer potency.

Cancer potency values were derived by CDPR from the results of the Bio/dynamics II study using the linearized multistage model (Global 82) and the multistage Weibull time-to-tumor model. Animal doses were converted to equivalent human doses by using a scaling factor of body weight to the 3/4 power. OEHHA considers these methods reasonable. The highest cancer potency of 2.4×10^{-2} $(mg/kg\text{-}day)^{-1}$ (95% upper-bound) was derived from combining liver tumors in male mice using the time-to-tumor model to compensate for early mortality. However, CDPR argues that this potency value should not be used because of the poor survival of treated males and because liver tumors were only observed in one experiment (out of four) in mice. Therefore, CDPR used the cancer potency of 7.8×10^{-3} $(mg/kg\text{-}day)^{-1}$ (95% upper-bound) in its risk characterization which was derived from the data on combined lung tumors (adenomas and carcinomas) in female mice.

OEHHA is moderately concerned that CDPR considers the database for mouse oncogenicity studies to be complete in its data gap status for permethrin. In fact, CDPR states in Appendix A that "a definitive replacement mouse study is strongly recommended...to address the shortcomings of those studies on file." OEHHA understands that the combined evidence from four "unacceptable" studies may be used as a preliminary evaluation of the oncogenic properties of permethrin. However, it seems reasonable to *require* (rather than recommend) a definitive mouse oncogenicity study from the registrants and declare that a data gap exists for this information in the interim.

In reference to the database, OEHHA believes that the cancer potency for combined liver tumors should be used instead of, or in addition to, the cancer potency estimate for combined lung tumors in assessing cancer risk. There are several arguments that can be made to support the use of the liver results:

- the database is currently incomplete and a new study may confirm the increases in liver tumors seen in one mouse study;
- typically, the most sensitive site of toxicity should be considered as the endpoint of concern, in this case it would be liver; and
- noncancer effects have been observed in the liver providing other evidence of an effect on that organ.

OEHHA recommends that the revised document include cancer risk estimates for workers and the general public using the cancer potency derived from the liver tumor data.

3.3 Developmental/Reproductive Effects

CDPR concludes that permethrin could be a possible developmental toxicant based on the occurrence of buphthalmos in weanling rats reported in the three generation permethrin developmental study described above in Section 3.1 (Hodge 1977). Buphthalmos is clinically described as a red eye. This effect was observed in the absence of maternal toxicity. Buphthalmos was not detected in the teratological studies, but the reason may have been that such a deformity could not be detected in fetuses because of constraints in the

methodology. An *estimated* NOEL of 2.5 mg/kg-day was derived by CDPR for this endpoint by dividing the observed LOEL of 25 mg/kg-day by the uncertainty factor of 10.

3.4 Dermal Effects

Permethrin has been tested for irritancy and sensitization in both animals and humans. The consumer product (Permanone) was determined to be a category II, severe irritant, probably as the result of the inert ingredients in the formulation. Technical grade permethrin is category III, a moderate irritant. CDPR concludes that since the labeling for category II requires a warning against contact with the skin, the warning would be incompatible with the designated use of the formulated product. OEHHA therefore recommends that CDPR should, if appropriate, work with the registrant to identify the ingredients in the formulation that potentiate this effect.

The patch test used on humans failed to demonstrate a sensitization effect, however, a guinea pig maximization test provided evidence for potential sensitization. The patch test was conducted with 184 volunteers of both sexes that ranged from age 18 to 80 and represented three races (Caucasian, Black and Asian) (Snodgrass 1986). The subjects had 0.2 ml of a 40% permethrin solution applied to the upper arm or back three times weekly for a total of three weeks. Two weeks later, a challenge dose was applied and then the skin was scored after 72 hours. There was no evidence of sensitization, however, the treatment did cause a transient burning, stinging or itching.

The guinea pig maximization test was given more credence by CDPR since it is more sensitive than the patch test. Although the tick repellant formula (Permanone) has not been found as a sensitizer, CDPR concludes that permethrin is a probable sensitizer. Therefore, CDPR believes the possibility exists that with repeated application, some sensitive individual will develop allergic dermatitis. OEHHA agrees that this is a concern.

3.5 Other Effects

Like other pyrethroids, permethrin causes a variety of neurological effects in experimental animals including: tremors, salivation, paresthesias, splayed gait, tail erection, and depressed reflexes. At higher doses, reversible axonal damage has been reported. From a rat acute inhalation study, CDPR derived an *estimated* NOEL of 3.8 mg/kg-day by dividing the LOEL for the acute neurological signs of 38 mg/kg-day by an uncertainty factor of 10.

4.0 EXPOSURE ASSESSMENT

4.1 Methodology

In estimating human doses from permethrin exposure during application or wearing clothing, CDPR made corrections for absorption of permethrin through the skin, intestines and lungs. The correction factor for dermal uptake was

well-documented in the risk characterization and CDPR utilized a health-conservative approach.

However, corrections for intestinal and pulmonary uptake were not as well substantiated. For example, CDPR cites two articles when supporting a correction factor of 50% for absorption of permethrin following inhalation. One of these articles was available for OEHHA to review (Raabe 1988). From this article, it is difficult to see how CDPR arrived at its conclusion since there were no data directly relevant to permethrin exposure nor were the conclusions of this study supportive of a 50% absorption rate. In fact, Raabe concluded that the expected uptake in humans of chemicals that are highly blood soluble should "readily exceed 60% even if there were no upper respiratory tract absorption, and should approach 80% with modest upper tract absorption".

More importantly, CDPR did not provide comparative data in animals and humans to support that a correction factor would be appropriate for oral or inhalation exposures. Data such as were presented for dermal uptake would be required. Therefore, OEHHA recommends that the exposure assessment be revised to include dose estimates assuming 100% absorption for inhalation and oral exposures.

Other methodological concerns are described below.

4.2 Occupational

In characterizing occupational health risks from exposure to the formulated product, CDPR assumes that park and forestry workers will apply Permanone to their field clothes. In CDPR's exposure scenario, workers are expected to wear five sets of clothes per week on which they will spray Permanone. The re-treatment would occur on a schedule of once every two weeks, for a six month season, for a working lifetime of 40 years. Each set will be laundered once every week. Potential routes of human exposure would consist of inhalation of permethrin during application, and dermal absorption from treated garments. In retrospect, there may be some oral exposure from transfer of permethrin from hands to mouth, especially during initial application. However, oral exposure is likely to be small relative to dermal and inhalation exposures.

CDPR's exposure estimations are based on the treatment schedule developed by the registrant, the purpose of which is to assure that an effective concentration of the active ingredient is maintained on the garment. However, this schedule assumes that at the end of the second week, essentially all of the permethrin would be removed before the next application. According to the technical information provided in the document regarding the permanency of permethrin on clothes, 20% is lost in the first laundering, 6% in the second, and only 2-3% is lost subsequently. These data indicate the high sorptive potential for permethrin on clothing (Snodgrass 1988).

CDPR assumes that saturation of the clothing can occur to a point where the total amount of permethrin capable of binding to the clothing would be

limited. However there is no evidence provided in the risk characterization document on what that limit might be. Instead, evidence is provided on the permanency of permethrin on clothes. By incorporating permanency information into the CDPR exposure scenario, the permethrin content of recycled treated clothes at the end of five weeks can be estimated (Table A).

Table A. Amount of Permethrin on Treated Clothes

Week	Lost (%)	Applied	Left
1st		75 g	75 g
2nd	-20%		60 g
3rd	-6%	75 g	131 g
4th	-20%		104 g
5th	-6%	75 g	173 g

Thus, at the end of five weeks, the clothing would have about 2.5 times more permethrin bound than the amount of permethrin originally applied.

It is believed that at some point saturation of the available binding sites on clothes for permethrin will be reached. Nevertheless, permethrin binding to clothing may increase on each subsequent application and whatever does not bind is available to be absorbed by the skin or leached into the wash water, and presumably other clothes will be contaminated in the process. Even after treatment has been stopped, only 3% percent of the clothing permethrin concentration is predicted to be lost on each subsequent washing. In the example above, if further treatment is terminated, after 10 weeks approximately 147 grams would remain on the clothing and after another 10 weeks, approximately 108 grams would remain. It is possible that a continuous yearly exposure to permethrin could be maintained by using the same clothing in the field.

A portion of the permethrin bound to the clothing should be considered available for human dermal exposure after laundering. A study conducted in rabbits showed 1.8% of the original dose of permethrin absorbed by the animals from laundered garments (Snodgrass 1988). With more permethrin retained on the garments after subsequent treatments, it is possible that more permethrin will be available for dermal absorption.

OEHHA is concerned that a reasonable or worse-case exposure to permethrin from treated clothes cannot be estimated by the CDPR method. OEHHA agrees with CDPR that the potential exposure under any continuous usage conditions will be limited by the permethrin-binding capacity of the clothing. It is reasonable to recommend that studies be conducted on the maximum binding capacity of permethrin to various fabrics. Subsequently, a more refined exposure estimate can be made and the re-treatment schedule revised accordingly. OEHHA requests that CDPR follow up with the registrant, if appropriate, on the possibility for further testing.

4.2 Non Occupational

To address the exposure to the general public, CDPR assumes either an upper-bound continuous exposure (seven days per week) for six months, or a more likely exposure of two weeks of uninterrupted exposure per year, including all weekends in an exposure season.

The same concerns expressed above for occupational exposure, the accumulation of the dose, and the potential for cross-contamination of other clothes, are relevant for general public exposure scenarios. In all likelihood, there exists the potential for higher exposures than those estimated under these scenarios. OEHHA shares the concern of CDPR whether the general public will be diligent in following the directions for treatment which may result in an increased health risk from higher exposures.

5.0 RISK CHARACTERIZATION

5.1 Acute Toxicity

Based on the estimated acute NOEL for neurological effects, the calculated margin of safety (MOS) was 237 with the substantial portion being contributed from inhalation of the airborne permethrin during application. CDPR estimated that the acute dose from the dermal route is highest after the first application. However, as was suggested herein, potentially higher doses may be achieved on each successive treatment of clothing with permethrin. The acute dose may be dependant on the maximum amount of permethrin bound to the clothes.

5.2 Subchronic and Chronic Exposure

The chronic NOEL of 2.5 mg/kg-day, derived on the basis on the observations of liver hypertrophy and buphthalmos was used to determine an MOS for workers of 581. These toxic endpoints appear to be the most sensitive endpoints for use in determining the hazards to the general public. The MOS were 409 and 782, based on the extreme and more likely exposure scenarios, respectively.

5.3 Cancer Risk

The theoretical excess individual cancer risks calculated by CDPR for the general public were 2.4×10^{-5} (95% UB) for the extreme exposure, and 1.3 x

10^{-5} for the more reasonable scenario. For workers, the risk was 9.9×10^{-6} (95% UB). As CDPR points out, these risk values are higher than what are generally recognized as acceptable risks (less than one in one million). In addition, there is the likelihood for exposures to be underestimated if the retention of permethrin to clothing is considered. Regardless, the cancer risks are a public health concern. OEHHA also requests that cancer risks be calculated using the cancer potency values derived from the liver tumor data for comparison.

6.0 LABELING/MITIGATION MEASURES

No mitigative measures are proposed by CDPR. Proposals seem reasonable for either a re-labeling of the product to be commensurate with the effects, or for reformulating the product to prevent dermatitis produced primarily by the vehicle. Information is lacking as to why the registrant is recommending a higher than efficacious amount of permethrin to be reapplied on a schedule of once every two weeks when other information shows a strong tenacity of permethrin for clothing fibers. The registrant should anticipate the maximum loading capacity of permethrin on particular clothing fibers and accordingly provide a revised treatment schedule.

OEHHA proposes that to limit inhalation exposure, it may be more prudent to treat clothing by dipping them into a permethrin bath (wearing appropriate protection). Furthermore, treated clothes should be washed separately from other garments, otherwise cross-contamination will occur. These modifications to the stated procedures should eliminate inhalation exposure, limit dermal exposures, while more effectively and evenly distributing the pesticide throughout the clothing. OEHHA asks that CDPR pursue these issues with the registrant as appropriate.

7.0 SPECIFIC COMMENTS

7.1 Executive Summary

Assumptions regarding exposure were not addressed in the Executive Summary, including how the product would be used by the two defined exposed populations, workers and general public. Since exposure assessment is an integral part of any risk assessment, a summary of the procedures should have been included.

7.2 Acknowledgements

Change "Hazard Evaluation Section" to "Pesticide and Environmental Toxicology Section".

7.3 Summary

The methods and results of the exposure assessment are not summarized. For instance, what is the difference between the extreme and most likely exposure scenario for the general public?

Second and eighth paragraphs, include a summary of the differences between permethrin technical and the Permanone formulation in terms of sensitization and dermal irritancy. This is a key toxicological problem that needs to be addressed in the summary.

In several paragraphs in the summary, CDPR refers to adjustments for absorption. OEHHA agrees that a correction for human dermal absorption is justified from the available data but that adjustment for inhalation or oral exposures has not been adequately justified in the risk characterization.

The summary (and other portions of the report) includes some risk management decisions with regard to the cancer risk assessment (last paragraph). OEHHA understands that it is useful to offer some perspective on the meaning of these results for risk managers. However, CDPR must be aware that as long as such discussion is provided in the risk characterization documents, OEHHA may be compelled to comment. In this case, the significance of *de minimis* cancer risk is debatable given the equivocal nature of the evidence for the carcinogenicity of permethrin. Therefore, OEHHA recommends that a discussion on the significance of this risk be deleted in the summary and in other parts of the document. A factual representation of the results and cancer risks and a list of uncertainties associated with the methodology should be adequate for risk managers.

7.4 Toxicology Profile

Page 6, the reference to 70% oral absorption estimate. This estimate was based on studies in experimental animals. What evidence exists for a different absorption rate in humans? If no data exist, what would be the rationale for using this correction factor to account for species differences in the absorption of an applied dose?

The guinea pig maximization test should be described and discussed in this report since it is the basis for CDPR's conclusion that permethrin is a possible sensitizer.

The acute inhalation study performed in rats, the basis for the acute NOEL, should also be described in the text.

Although a NOEL can not be established for dermal irritancy in the typical manner, the information from the human study conducted on 184 subjects should be utilized even for comparative purposes. One dose caused some signs of dermal irritancy and possible local neural effects in a few individuals. The applied dose per unit area could be estimated from the study protocol and then used to compare with the extrapolated skin loading of permethrin from wearing treated clothes.

Lethality from a chronic study (Bio/dynamics I) cannot be a suitable basis for a NOEL. If the death is compound related, there must have been preceding clinical or subclinical effects with the same dose or at lower doses. If so, OEHHA would be concerned that there is an insufficient margin of safety between the observed effect (death) and the no observed effect. Were chemical and subclinical changes considered such as weight changes, food and water consumption patterns?

Pages 11 to 18. The discussion of the chronic/oncogenicity studies appears to be complete. However, the presentation is difficult to follow. Some suggestions to improve on this section might be to include: 1) a table of the relevant oncogenicity studies with some general information on the design of the studies; and 2) a table presenting the results of the Bio/dynamics Mouse II Study (1979) from the original pathology analysis (the results are difficult to follow when integrated into the text).

Page 19, first sentence, change "Several..." to "Three...". CDPR should emphasize that only two of the four gene mutation studies submitted for registration were acceptable. The available database on genetic toxicity is marginal at best. Based on CDPR's evaluation of the original studies in Appendix A, OEHHA would conclude that there may still be a data gap for the required studies.

Page 21, substitute in line 7 "litters" for "liters".

7.5 Risk Assessment and Appraisal

Pages 26 and 37, when referring to the Permanone formulation please use "inert ingredients" rather than just the word "inerts".

Page 27, Table 7. There appears to be some discrepancies between the NOEL/LOEL values in the text and those presented in the table. Perhaps the units of mg/kg-day should be checked as some of these values may be presented in units of ppm. Otherwise, some data were omitted from the table (e.g., page 14, NOEL of 3 mg/kg-day, Bio/dynamics Mouse II).

Page 29, third paragraph. OEHHA welcomes discussion on the potential mechanism of action of carcinogens. However, for permethrin, the available studies are unacceptable on which to base even speculation that the chemical may be a mutagen. Furthermore, CDPR apparently reviewed some data that indicate a marginal clastogenic effects of this compound. OEHHA's conclusion is that more data are required on which to make an adequate determination of the genotoxic potential of permethrin.

Page 31, third paragraph, see discussion on oncogenicity in Section in 3.2 of these comments.

Page 33, second paragraph. When describing the derivation of absorbed daily dose, please include a description of which factors are based on measurements and which are assumptions.

Page 34, calculation of MOS. CDPR should consider whether it is appropriate to base an MOS on an internalized dose of permethrin from inhalation when comparing to toxicological data obtained from applied doses in animals, without adequate pharmacokinetic data. If CDPR believes that this correction is justified, OEHHA would request an oral presentation from the Worker Health and Safety Branch of the data, calculations and conclusions related to this exposure analysis. Also, is it "adsorption" or "absorption"?

Page 35, first paragraph. It is not clear from the discussion what the oral absorption correction factor was used for, to correct for external versus internal dose, or to correct for oral versus inhalation and dermal exposures. If the reason is the former, the previous comments on applied versus internal dose apply here. If the latter, a more detailed explanation is required in the revised document.

Page 36, with reference to oncogenic effects and the risk management discussion, see Section 7.3 of these comments.

Page 37, USEPA cancer potency estimate. OEHHA checked IRIS (11/91, but only updated as of 3/90) and the cancer potency estimate for permethrin is under reevaluation (i.e., no cancer potency given). CDPR should revise document accordingly.

In the Exposure Assessment Appraisal section, CDPR addresses as an uncertainty the accumulation of permethrin residues on clothes. This is a major reservation of OEHHA regarding the exposure assessment, namely that this uncertainty casts doubt on the validity of the exposure estimation which CDPR is employing. The statement that "the binding of permethrin to the fibers may also make it less available for absorption" needs to be supported, since animals were able to absorb permethrin from washed clothes (Snodgrass 1988). It is not clear from the citation if more than one absorption per washing was studied.

Additional uncertainties not addressed may include the amount of permethrin bound after other washing-related activities, including bleaching and ironing.

7.6 Risk Mitigation

CDPR should include mitigation measures with regard to labeling as discussed with OEHHA at the meeting on September 20, 1991. Other mitigation measures may include: different treatment procedures both in the manner of application and formulation, as well as a revised schedule of treatments. See comments above for more details.

7.7 Appendices

Appendix B

On page 5, sentence beginning "Conversely, it is clear that under conditions of washing, which are very likely more leaching than any environment in which the clothes are worn, little (2-3 percent in third to tenth laundering) could be removed". This sentence is awkward and should be rewritten. Is washing the optimum method to remove or deactivate permethrin residues? What about heat or sweat?

8.0 RECOMMENDATIONS AND CONCLUSIONS

- The exposure assessment should be revised to take into account the information on the tenacity of permethrin to clothing. Data demonstrating the maximum loading of permethrin on the garments would be useful. OEHHA recommends that the registrant provide evidence for an effective concentration in clothing and a revised schedule to maintain that effectiveness.

- OEHHA recommends that the exposure assessment be revised to include dose estimates assuming 100% absorption for inhalation and oral exposures. If CDPR can justify the use of the correction factors used in the report, the revised risk characterization document should include a detailed explanation. Perhaps also an oral presentation by Worker Health and Safety would be appropriate.

- It seems reasonable to *require*, rather than recommend, a definitive mouse oncogenicity study from the registrants and declare that a data gap exists for this information in the interim.

- In reference to the database, OEHHA recommends that the cancer potency for combined liver tumors be used to derive cancer risks to compare with the risks obtained by using the cancer potency estimate for combined lung tumors in assessing cancer risk.

- OEHHA recommends further testing in order to provide adequate evidence to support the claim that permethrin is nongenotoxic.

- CDPR should, if appropriate, work with the registrant to identify the ingredients in the Permanone formulation that potentiate the dermal irritant effects of permethrin.

- OEHHA believes that mitigation measures may be devised and successfully implemented if the public health benefit warrants the potential use of this product. Include a more detailed risk mitigation analysis in the revised document or propose a course of action that may be of use for the registrant to make such proposals.

- The label should also caution the potential user of washing non work-related clothing with the treated clothing.

- In addition, other comments should be addressed as indicated.

9.0 REFERENCES

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