Office of Environmental Health Hazard Assessment

Joan E. Denton, Ph.D., Director
Headquarters • 1001 I Street • Sacramento, California 95814
Mailing Address: P.O. Box 4010 • Sacramento, California 95812-4010
Oakland Office • Mailing Address: 1515 Clay Street, 16th Floor • Oakland, California 94612

Arnold Schwarzenegger
Governor

Agency Secretary

M E M O R A N D U M

TO: Garry Patterson, Ph.D.
Acting Assistant Director
Registration and Health Evaluation Division
830 K Street
Sacramento, California 95614-3510

FROM: Anna M. Fan, Ph.D., Chief
Pesticide and Environmental Toxicology Section

DATE: April 25, 2000

SUBJECT: COMMENTS ON THE DEPARTMENT OF PESTICIDE REGULATION'S DRAFT RISK CHARACTERIZATION DOCUMENT FOR THE ACTIVE INGREDIENT DELTAMETHRIN

We have completed our review of the draft risk characterization document (RCD) for 3-(2,2-dibromoethenyl)-2,2-dimethylcyclopropanecarboxylic acid cyano (3-phenoxyphenyl) methyl ester (deltamethrin) prepared by the Department of Pesticide Regulation. Deltamethrin is a synthetic pyrethroid insecticide. In California, the intended uses of deltamethrin include application in residential and institutional establishments, in non-food/feed areas of food/feed processing plants, in granaries, on ornamental plants and in the treatment of cotton. Other potential uses include residential, industrial, and institutional control of pests by professional pest control applicators.

The RCD package received by the Office of Environmental Health Hazard Assessment consisted of the draft RCD dated September 10, 1999, and an exposure assessment entitled "Estimation of Exposure of Persons in California to Pesticide Products that contain Deltamethrin" dated December 3, 1996. To assist in our review, we conducted an independent but brief review of the published literature on deltamethrin. In addition, we consulted our previous review comments on the draft RCD for tralomethrin, a structurally related pyrethroid for which a primary metabolite and degradation product is deltamethrin.

Based on our review, we feel that the draft RCD needs some revision before finalization. Certain portions of the draft RCD require additional scientific support, further clarification or corrections in key sections, or more detailed discussion in order to present a more comprehensive assessment of risks from exposures to deltamethrin. A summary of our major comments on the draft RCD for deltamethrin is provided below. For more detail on these comments, and for additional specific comments, please refer to the attachment.

1. We did not locate any information in the text or tables presenting reference exposure levels (RELs) for deltamethrin. The inclusion of RELs with observed exposure levels would be helpful in order to compare health-based exposure levels with measured air levels.

2. The choice of the no-observed-adverse-effect-levels (NOAELs) for risk assessment need to be further substantiated. The NOAELs selected for the acute and subchronic exposure risk assessment are equal to or lower than the NOAEL used in the chronic risk assessment. The biological and methodological implications of using a chronic NOAEL that is higher than NOAELs used for shorter-term exposures should be discussed and justified.

3. The exposure scenarios presented in the draft RCD and the corresponding margin of exposure (MOE) calculations refer to individual deltamethrin products under separate acute, seasonal, and chronic conditions. MOEs and RELs for the total exposure to deltamethrin should also be calculated.

4. We recommend that dermal sensitization be addressed in the main text of the RCD document.

5. We recommend using a value of 100 percent for absorption of deltamethrin via inhalation instead of the default value of 50 percent, which is not appropriate for this chemical. The occupational and residential inhalation risks should be re-calculated using the greater absorption rate.

6. The discussion of the oncogenic potential of deltamethrin should be expanded to include the studies published in the open literature, to address the significance of the positive genotoxic effects, and to discuss the structure-activity relationships for oncogenic activity among pyrethroids.

7. The draft RCD considers only one source of exposure to deltamethrin, those pesticide products containing deltamethrin as an active ingredient. Another source of exposure to deltamethrin is from the use of tralomethrin as an active ingredient, which rapidly undergoes debromination to form deltamethrin. We recommend that any additional risk associated with deltamethrin exposure from the use of tralomethrin be quantified or include a statement in the RCD that specifically states that secondary sources of deltamethrin exposure were not evaluated.

8. The toxicity of deltamethrin can also be increased by simultaneous action of organophosphate and carbamate pesticides. We recommend that a discussion on the interaction of organophosphate and carbamate pesticide exposures with deltamethrin be included in the RCD.

9. The tolerance assessment presented in the draft RCD does not completely evaluate the apparent greater sensitivity of children to deltamethrin exposure as compared to adults. There is significant potential for pre- and postnatal sensitivity, higher acute toxicity for weanling than for adult rats, endocrine disruptive activity for deltamethrin, as well as effects of cumulative exposure to other pyrethroids with the same mechanism of action as deltamethrin. It is also not clear whether degradation products were considered in the tolerance assessment for deltamethrin residues. We recommend that the draft RCD include more discussion on whether the MOE calculations sufficiently account for the greater susceptibility of children. You might also consider applying an additional uncertainty factor to the calculation of RELs.

10. The risk characterization does not include a complete discussion of uncertainties specific to the quality of the existing database of both toxicological and exposure data. The section is also deficient in discussing sensitive subpopulations.

11. According to the conclusions of the draft RCD, many scenarios for occupational exposure to deltamethrin result in MOEs less than 100 and in many cases less than ten. Residential use of deltamethrin result in even lower MOEs ranging from less than one to ten. All scenarios considered in the draft RCD are based on human expected exposures and NOAELs established in animal studies. It appears that mitigation measures for most if not all of the agricultural activities might be required.

Thank you for providing the document for our review. If you have any questions about our comments, please contact me or Dr. Michael DiBartolomeis at (510) 622-3170.

Attachment

cc: Joan E. Denton, Ph.D.
Director
Office of Environmental Health Hazard Assessment

Val F. Siebal
Chief Deputy Director
Office of Environmental Health Hazard Assessment

Michael J. DiBartolomeis, Ph.D., Chief
Pesticide and Food Toxicology Unit
Pesticide and Environmental Toxicology Section

Charles M. Andrews, Chief
Worker Health and Safety Branch
Department of Pesticide Regulation

bcc: George V. Alexeeff, Ph.D., DABT
Jolanta Bankowska, Ph.D.

ATTACHMENT

COMMENTS ON THE DRAFT RISK CHARACTERIZATION DOCUMENT FOR DELTAMETHRIN

As part of our review of the draft risk characterization document (RCD) for deltamethrin, we relied upon an independent, brief review of the published literature on deltamethrin and our previous review of the draft RCD for tralomethrin. Deltamethrin is a primary metabolite and degradation product of tralomethrin. Our comments are listed below according to the issues of concern, and are not necessarily in the order that they appear in the draft RCD.

Reference exposure levels

We did not locate any information in the text or tables presenting reference exposure levels (RELs) for deltamethrin. The use of margin of exposure (MOE) calculations does not provide a complete characterization of population risks. The inclusion of RELs with observed exposure levels would be helpful in order to compare health-based exposure levels with measured air levels.

Selection of toxicology endpoints for risk assessment

The value for no-observed-adverse-effect-levels (NOAELs) from acute, subchronic, and chronic toxicity studies selected as the basis for risk assessment usually is inversely correlated with the length of exposure (i.e., the longer the exposure, the lower the value). This is not the case for deltamethrin as presented in the draft RCD. In one set of calculations, a NOAEL of 0.06 mg/kg-day is selected for the evaluation of acute, subchronic, and chronic deltamethrin exposures. In another set of calculations, the NOAEL used for acute and subchronic exposure is actually lower (0.006 mg/kg-day) than the NOAEL used for chronic exposure assessment (0.06 mg/kg-day).

This dose-exposure relation raises some concern about the experimental design and validity of the toxicological data, the use of uncertainty factors, and/or the public health implications of basing risk on apparently inconsistent findings. From a toxicological perspective, RELs calculated for more serious effects such as peripheral neuropathies would generally be expected to be lower than doses estimated to protect against reversible acute effects such as diarrhea and vomiting. The presentation of MOEs without discussing whether a larger MOE might be justified for the more serious adverse health effects presents some concern.

We recommend that the selection of NOAELs for risk assessment be further substantiated in the RCD. The biological and methodological implications of using a chronic NOAEL that is higher than the NOAELs used for shorter-term exposures should be discussed and justified in the context of the validity of the risk assessment.

Exposure assessment

The draft RCD presents various occupational exposure scenarios for acute, seasonal, and chronic exposures to individual deltamethrin pesticide products. Corresponding MOEs were calculated

separately for the individual deltamethrin products, but it is not clear whether they were calculated for the total exposure to deltamethrin in all formulations under acute, seasonal, and chronic conditions. It seems plausible that agricultural workers such as mixer, loaders, applicators, and flaggers would be exposed not only to one, but also to various deltamethrin products during their regular activities under the acute, seasonal, and chronic conditions. We recommend that the RCD be revised to reflect these conditions and provide MOEs for the total exposures to deltamethrin as an active ingredient. It would also be more transparent to present a summary of the MOEs for the various exposure scenarios in a tabular form.

It would be useful to insert a discussion as to whether any adjustment is needed to account for the difference between administered and absorbed amounts of deltamethrin in human dietary exposure. More detailed summaries of dietary exposure estimates in tabular form would also be useful, as would the attachment of the computer printout of the acute and chronic dietary exposures.

Adjustments for absorption

For risk assessment purposes the draft RCD adjusted oral NOAELs identified from laboratory animal studies by applying a 60 percent absorption factor. However, it is not clear whether any adjustment for absorption was made for humans when oral dietary exposure analyses were performed. Considering the low residue values, the adjustment (resulting in less health protective values) would probably not significantly impact MOE or REL calculations. However, for the purpose of consistency, we recommend that this be clarified in the RCD.

The draft RCD uses a default value of 50 percent for inhalation absorption of deltamethrin (Appendix on exposure estimation, page 12). The publication by Raabe (1988) cited in support of this value refers to vapors of volatile organic solvents. The physical and chemical properties of deltamethrin, including very low volatility (vapor pressure of 1.5×10^{-8} mmHg at 25^{o}C), are uncharacteristic of a solvent. The expected value for inhalation absorption should be 70 to 100 percent depending on the size of the inhaled particles (Raabe, 1988). Therefore, we recommend that inhalation exposures be calculated assuming a pulmonary absorption value of 100 percent and that the occupational and residential inhalation risks be re-calculated using this greater absorption rate.

Oncogenicity

Based solely on the results of the studies in rats and mice presented in the draft RCD, it is reasonable to conclude that there is no oncogenic activity associated with deltamethrin (pages 24 to 28). However, studies published in the open literature provide some evidence for oncogenicity in rats (Cabral et al., 1986) and in mice (Goldenthal et al., 1980; Richter and Goldenthal, 1983). Furthermore, the potential for oncogenic activity of deltamethrin is supported by the positive genotoxicity results *in vivo* (e.g., chromosome aberrations and micronucleus test) and *in vitro* (sister-chromatid exchange in human lymphocytes). The weight-of-evidence for oncogenicity appears to be equivocal. We recommend that the RCD discussion on oncogenicity be expanded to include a summary of the studies we cite above. Furthermore,

we recommend that the discussion be expanded to include the structure-activity relationship for oncogenic potential among other pyrethroids.

Exposures to deltamethrin following the use of tralomethrin

The draft RCD for deltamethrin did not account for the use of another pyrethroid, tralomethrin, which is an active pesticide ingredient that undergoes rapid and essentially complete debromination to form deltamethrin under aerobic and anaerobic conditions in the environment. Tralomethrin is also formed in vivo once deltamethrin is absorbed after dermal contact, ingestion or inhalation. Although much of the tralomethrin database for environmental and toxicological information was used to support the assessment of risk for deltamethrin, the source of deltamethrin exposure from the use of tralomethrin as an active ingredient was not included in the draft RCD for deltamethrin. We recommend that the RCD for deltamethrin assess exposures from all sources of this chemical, including the use of pyrethroids that produce deltamethrin as a degradation product or metabolite. Alternatively, the RCD should include language that states that the RCD for deltamethrin pertains only to the use of deltamethrin as an active ingredient and does not consider exposures from secondary sources such as the use of tralomethrin.

Tolerance assessment

No information is provided in the draft RCD on the type of the deltamethrin residues considered for tolerance assessment (pages 6, 78 to 79). We recommend that a more specific description of the residues (e.g., parent chemical only, parent chemical and its metabolites) be included.

It would also be useful to provide a table with the estimates of the theoretical maximum residue contribution (calculated by using the tolerance level and a 100 percent crop treated assumption), the anticipated residue concentrations, and their representations as percentages of the acceptable daily intake or the reference dose, if available.

Sensitive populations

We conclude from our review of the draft RCD and the published literature that children are more susceptible to the toxicity of deltamethrin than adults. The following information supports this conclusion.

1. Deltamethrin caused prenatal toxicity in a developmental toxicity study in rats (Abd El-Khalik, et al ., 1993). Adverse effects such as early embryonic death, retardation of fetal growth, hypoplasia of the lungs, and dilation of the renal pelvis were observed at a lowest-observed-adverse-effect-level of 1 mg/kg-day (page 33 in draft RCD). There is no information provided on maternal toxicity or lack of it in the discussion of this study.

2. Deltamethrin has a strong potential for postnatal toxicity because of neurological effects (autonomic nervous system dysfunction) which may have higher impact on the not fully developed nervous system in the young. In adult humans, 10 mg/kg-day oral doses have been reported to cause seizures (Tippe, 1993) and an estimated dose of 2 mg/kg was

associated with short-term systemic effects in a child who ingested a deltamethrin product (O'Malley, 1997).

3. Deltamethrin was shown to be more acutely toxic in weanling rats compared to adults. The oral LD_{50} in adult rats was 81mg/kg and in weanling rats it was 51 mg/kg (Sheets et al., 1994).

It would be useful to add a discussion in the RCD on sensitive populations, including children and infants. Signs of developmental toxicity produced by deltamethrin may also indicate the potential for endocrine disruptive activity and this should be added to the discussion.

Risk characterization

The uncertainties inherent to the current methodology used in risk assessment are discussed in the risk characterization section of the draft RCD on pages 55 to 74. However, this section lacks discussion of uncertainties specific to the quality of the existing database of both toxicological and exposure data. It also lacks discussion on sensitive subpopulations (see comment above). We recommend expanding this section to include more information on these subjects.

Dermal sensitization

Dermal sensitization is addressed in a report entitled "Estimation of Exposure of Persons in California to Pesticides that Contain Deltamethrin" (Thongsinthusak, 1999). This report was submitted together with the draft RCD. The report concludes that "it is unlikely that deltamethrin is a dermal sensitizer." Dermal sensitization was not addressed in the text of the draft RCD. Therefore, it is not clear whether all results from the appropriate studies were negative, or whether only the negative results were used in the analysis and positive results not considered. We recommend that the RCD section on acute toxicity (page 17) be expanded to include a discussion on the potential for dermal sensitization with the positive and negative results of the relevant studies. The potential for deltamethrin to cause immunologically mediated allergic contact dermatitis in humans should also be addressed. This is important because deltamethrin has been shown to be immunotoxic. Cases of allergic reactions reported in humans included the following effects: anaphylaxis, bronchospasm, eosinophilia, fever, hypersensitivity pneumonia, pallor, pollinosis, sweating, sudden swelling of the face, eyelids, lips and mucous membranes, and tachycardia (Extoxnet, 1999).

Potentiation

According to Mueller-Beilschmidt (1990), the toxicity of deltamethrin can be increased by the simultaneous action of organophosphate carbamate pesticides that block esterases, enzymes that degrade pyrethroids by cleaving the molecule at the double bond between a carbon and an oxygen atom. Potentiation of toxic effects was shown when deltamethrin was applied together with azinphos ethyl, omethoate, and dichlorvos (WHO, 1990). We recommend that the RCD include a discussion about what is known about the potential for additive or synergistic effects of deltamethrin when combined with organophosphate and carbamate pesticides. Effects of

cumulative exposure to other pyrethroids with the same mechanism of action as deltamethrin should also be considered in the RCD.

Conclusions

According to the conclusions of the draft risk characterization document, various occupational exposures to deltamethrin products resulted in MOEs less than 100, frequently less than ten. According to the draft RCD, "when the NOEL for an adverse effect is derived from a laboratory study, a calculated MOE of 100 is generally considered adequate for protection against potential toxicity of a chemical."

For the residential use of deltamethrin, calculated MOEs ranged from less than one to ten for pest control operators, infants, and adult men. Acute dietary exposures and the combined acute occupational and dietary exposures to deltamethrin resulted in MOEs less than 100 for all population subgroups examined. Some seasonal occupational exposures and combined seasonal and occupational dietary exposures also resulted in MOEs of less than 100. On the basis of annual exposure estimates, calculated MOE for residential pest control operators was two. The lowest annual dietary MOEs were 64 and 80 for children of the ages of one to six and children of the ages of 7 to 12, respectively. The MOE for pest control operators under combined annual occupational and dietary exposure scenario was two.

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