California Environmental Protection Agency
James M. Strock, *Secretary for Environmental Protection*

State of California
Pete Wilson, *Governor*

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT
Steven A. Book, *Interim Director*

MEMORANDUM

TO: Larry L. Nelson, Ph.D., Chief
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FROM: Richard J. Jackson, M.D., M.P.H. for RJ Jackson
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DATE: July 24, 1992

SUBJECT: Review of the California Department of Pesticide Regulation's Risk Characterization Document for Avert (Abamectin)

Thank you for the opportunity to review the risk characterization document entitled "Abamectin: Avert Prescription Treatment 310 (Section 3 Registration)". The Hazard Identification and Risk Assessment Branch (HIRAB) reviewed this document and our comment report is attached. In reviewing the risk characterization we considered it an additional source of information to be combined with previous risk characterization and exposure assessment documents for abamectin as an active ingredient.

HIRAB's primary concern over abamectin-containing formulations is that despite the potential for serious adverse effects (i.e., tremors and death following acute exposure) and the uncertainties surrounding the potential for long-term neurotoxicity (that presently can not be adequately assessed), abamectin use in California is being expanded. We have previously, on numerous occasions, stated our concern about the expanding use of abamectin in California, and it was our impression that you shared our concern.

The registration of this new product for indoor home use will increase the potential for acute exposure to abamectin by several fold. This is especially disturbing since young children who incur the highest exposures to abamectin may also be the most sensitive to its neurological and lethal effects.

The severity of toxic effects in animals and the resulting narrow margins of safety calculated in the risk characterization raise issue

that this product cannot be used indoors with adequate protection for children and infants. In calculating a reference dose for long-term exposures, the U.S. Environmental Protection Agency included an additional three-fold uncertainty factor to account for severity of effects. We consider the potential acute effects severe, and a similar approach should be adopted for short-term exposures. Applying this public health protective assumption to the margin of safety allowed by the Department of Pesticide Regulation (100) would result in a minimum margin of safety of 300. The margins of safety for children and infant exposures calculated in the risk characterization are less than 300.

In addition to the narrow margins of safety, there is a lack of information on mechanism of action in mammals, indoor fate, and human response to abamectin.

Based on these concerns, we would like to meet with you to discuss the possible options regarding the registration of Avert, and to discuss our concerns over the expanding use of abamectin formulations in California.

At your convenience, please contact me or Dr. Michael DiBartolomeis at (510) 540-3063 to arrange a time to meet to discuss the risk characterization of abamectin.

Attachment

cc: Jolanta Bankowska, Ph.D.
Steven A. Book, Ph.D.
Michael J. DiBartolomeis, Ph.D.
Anna M. Fan, Ph.D.
Ephraim Kahn, M.D.

COMMENTS ON THE DEPARTMENT OF PESTICIDE REGULATION'S DRAFT RISK CHARACTERIZATION DOCUMENT FOR ABAMECTIN: AVERT PRESCRIPTION TREATMENT 310

Hazard Identification and Risk Assessment Branch
Office of Environmental Health Hazard Assessment
July 24, 1992

1.0 INTRODUCTION

The primary objective of this comment report is to review the risk characterization document for the new abamectin product. However, the risk characterization may also be used as an additional source of information for comments on the general health risks from abamectin exposure. Therefore, our comments apply to abamectin as an active ingredient for all of its current uses in California. The comment report only briefly addresses the issues which have been previously raised by the Hazard Identification and Risk Assessment Branch (HIRAB) in several reports, memoranda, and meetings with the Department of Pesticide Regulation (DPR).

2.0 BACKGROUND INFORMATION

The subject document submitted by DPR is the second risk characterization document for abamectin. The risk characterization document was prepared in support of the full registration (Section 3) of abamectin for use as a crack and crevice bait formulation, Avert Prescription Treatment 310 (Avert), to control cockroaches in residential, commercial, or industrial buildings and transportation facilities. Avert contains 0.05% abamectin B_1, as a dust formulation.

Abamectin has already been granted full registration on cotton seed, and Emergency Exemption (Section 18) registration on strawberries, pears, celery, and head lettuce. Registration of Avert would expand abamectin uses in California by including indoor applications.

HIRAB had an opportunity to comment on the previous risk characterization of abamectin in support of the Section 3 registration in cotton seed. Also, HIRAB provided comments on four dietary risk assessment documents prepared by DPR, the most recent of which related to the Revised Section 18 Emergency Exemption for abamectin on celery.

3.0 GENERAL COMMENTS

In summary, HIRAB is primarily concerned about: abamectin's constantly expanding uses, its potential for long-term neurotoxicity (that presently can not be adequately assessed), its very high acute toxicity, the potential that indoor exposures are underestimated, and the questionable "protectiveness" of the margin of safety (MOS).

The calculated MOS of 100 is currently assumed by DPR to be adequate for even the most severe acute toxicological responses produced, including death. Serious consideration should be given to restricting the uses of abamectin and increasing the currently acceptable MOS of 100 for effects such as lethality or other severe acute effects.

The risk characterization document for Avert does not alleviate these concerns. By introducing the new abamectin product for indoor use, potential exposure to small children, which constitute the most vulnerable population, is greatly increased. Indoor use of abamectin contributes to 80% of the total, acute combined (with dietary) infants' exposure to this chemical. In addition, children's health risk for neurotoxic effects and mortality are increased.

It can be expected that additional registrations for abamectin uses in California will be granted in the future. These are likely to include tomatoes, almonds, and walnuts. This prediction is based on the information provided in the current DPR risk characterization document that the above listed commodities are awaiting tolerance approval from the U.S. Environmental Protection Agency (U.S. EPA) (see the bottom paragraph on page four of the subject document). Tolerance approval by U.S. EPA often precedes subsequent Section 18 Emergency Exemption registrations granted for particular uses in California.

4.0 SPECIFIC COMMENTS

4.1 Data Package

The submitted "final" draft risk characterization document for a Section 3 registration of Avert consists of a summary, an introduction, a toxicology profile, a risk assessment, a risk appraisal, references, and four appendices. The appendices include toxicology summaries, exposure assessment, product label information, and dietary assessment. According to the "Summary of Toxicology Data" of March 14, 1990, by the Medical Toxicology Branch in DPR, there are no toxicological data gaps for abamectin (avermectin B_1). All tests required by the SB 950 program are currently available.

4.2 Chemical Identification

Abamectin, also known as avermectin B_1, is derived from the soil microorganism, *Streptomyces avermitilis*. Its pesticidal activity and toxicity are due to the interaction with the nerve transmitter, gamma aminobutyric acid (GABA). This mechanism of action is not yet fully understood. A breakdown product of abamectin, a delta 8,9-isomer that is formed in plants by a reaction with sunlight, has comparable toxicological properties to abamectin. The majority of the currently available chemical data relate to abamectin, with some data on its isomer.

On page three of the risk characterization document, DPR describes abamectin's mode of action as a GABA release stimulant in nematodes and arthropods. The abamectin-GABA interaction in mammals should also be addressed.

4.3 Technical and Product Formulations

Abamectin as an active ingredient has been granted full registration (Section 3) in California in two products: Avid 0.15 EC, for use in fields, shadehouses, and greenhouses on flowers, foliage plants, and other non-woody ornamentals; and Zephyr 0.15 EC, Section 3 registration on cotton. The risk characterization document for Avert (0.05% abamectin dust formulation) was prepared in support of the Section 3 registration for residential uses.

Ivermectin, a synthetic derivative of abamectin (22, 23-dihydroavermectin B_1) has toxicological properties similar to those of abamectin. This compound is used in veterinary medicine to control endo- and ecto-parasites in cattle, sheep, swine, horses, and dogs. It is also currently being evaluated as a treatment for *Onchocera volvulus* (river blindness) in humans. Abamectin is used in Australia under the trade name Avomec as a cattle anthelminthic and ectoparasiticide in 1% injectable solution.

Based on the current veterinary uses and potential applications of abamectin and its derivatives in human medicine, it can be assumed that there is more information that might be useful and pertinent to abamectin's risk characterization. These data may not have been submitted by the registrants, however, and the general literature should be searched. Of special value would be data on human effects. These data should be evaluated and discussed in a revised risk characterization document.

4.4 Environmental Fate

According to the label, Avert can be used both indoors and outdoors. The section on environmental fate addresses persistence and distribution of abamectin and the delta 8,9-photoisomer in soil and water.

The risk characterization states that the environmental degradation of abamectin occurs mainly by photolysis and aerobic microbial soil metabolism. Hydrolysis reportedly plays an insignificant role in the environmental breakdown of abamectin. The half-life of avermectin B_1a [a major (80%) component of abamectin] in aqueous solutions and on soil surfaces ranged from 3.5 to 21 hours depending on the conditions of the experiments. The risk characterization does not specify a mechanism for breakdown in aqueous solution, however, and it should. The degradation in water and soil was enhanced by sunlight. Microbial degradation of avermectin B_1a in soil under aerobic conditions was shown to range from 14 days to 8 weeks, depending on the type of soil and concentrations of the chemical used in the experiments.

Avermectin B_1a was determined to have a low leaching potential in different kinds of soils. The DPR risk characterization states that avermectin used under field conditions would result in only minimal contamination of the aquatic ecosystem. The half-life of avermectin was said to be four days in water and two to four weeks in sediment.

The discussion of the distribution and persistence of abamectin is followed by a section on plant residues. Issues such as the degradation and translocation of abamectin in plants, the contribution of photodegradation to residue dissipation, and the potential uptake of abamectin residues by growing plants were addressed.

The inclusion of the environmental section in this risk characterization is not directly related to the health risk assessment. Nevertheless, it is quite valuable in the light of constantly expanding uses of the chemical. The information provided indicates that abamectin has the potential for environmental persistence. However, the environmental fate of abamectin formulations requires further research since only some of the residues were chemically identified. More importantly, a data gap exists for fate of the abamectin formulation as it is applied indoors. Since photolysis is apparently a primary method for degradation, the persistence of abamectin indoors would be expected to be significantly longer than outdoors, particularly since it would be applied in cracks and crevices. The revised risk characterization document should address this concern. Exposure estimates may also need to be revised.

Also, according to the label, Avert (abamectin) is "toxic to fish and wildlife" and "highly toxic to bees exposed to direct treatment or residues on blooming crops or weeds". Including this information in the risk characterization would give a more complete characterization of environmental issues concerning abamectin.

5.0 TOXICOLOGY PROFILE

5.1 Pharmacokinetics

This section provides some pharmacological data on abamectin (also referred to as avermectin) and its two derivatives ivermectin (a synthetic derivative of abamectin, 22, 23-dihydroavermectin B_1) and the delta-8, 9-isomer of avermectin B_1a.

Pharmacokinetic studies with avermectin B_1a on rats and goats indicate that the majority of the parent compound is excreted unchanged in the feces in both species. There were two metabolites identified in rats (24-hydroxymethyl avermectin B_1a and 3"-desmethyl avermectin B_1a) and one metabolite was identified in the goats (24-hydroxymethyl metabolite).

A study in lactating goats showed that avermectin B_1a has the potential to partition from the blood into the milk. As early as one day after the initial dosing, the concentrations found in the milk were two to three times higher than the concentrations determined in blood. In lactating cows there was no tendency for excretion of the compound in milk. However, the conditions of the experiments were different and the very general description of the studies provided in the report does not allow one to draw a responsible conclusion as to the true difference in excretion of avermectin in milk in these two species.

The partitioning from the blood into the milk was also studied with ivermectin in rats and humans. According to the report, ivermectin showed high concentrations in the milk of lactating rats and "was probably responsible for the acute toxicity observed in the offspring during the neonatal period". On the other hand, clinical studies in human volunteers showed that ivermectin is not excreted with breast milk when applied at therapeutic doses tested in the treatment of onchocerciasis.

The results of the metabolism study in rats showed that a delta 8,9-isomer similar to abamectin is excreted mainly in feces. The two main metabolites identified were 3'-desmethyl-delta-8,9-isomer and 24-hydroxymethyl-delta 8,9-isomer.

The current risk characterization provides relatively more useful information on abamectin's pharmacokinetics than the previous documents. However, HIRAB's main concern about possible excretion of abamectin (or its metabolites) in human maternal milk has not been alleviated. The human study discussed in the report concerns ivermectin and not abamectin. The issue should be addressed in a revised risk characterization document.

5.2 Acute Toxicity

Acute toxicity data were summarized for the technical material, emulsifiable concentrate (1.8%), delta-8,9-photoisomer, polar metabolites, and Avert formulation. Abamectin (technical product) belongs to a group of highly toxic chemicals. Its oral LD 50 in rats is 8.7 mg/kg. Acute toxicity estimates for abamectin formulations and isomers are much higher (lower toxicity).

5.3 Adverse Effects

According to the Summary of Toxicology Data, possible adverse effects were identified in a chronic toxicity-oncogenicity study in mice, in a reproductive toxicity study in rats, and in a teratogenicity study in mice.

The adverse effects caused by abamectin which were identified in the currently available toxicological studies at various testing levels consist of: lethality, decreased weight gain, tremors, retinal alterations, mydriasis, fetotoxicity, teratogenicity (skeletal malformations, exencephaly, cleft

palate, and clubbed foot), possible testicular degeneration, and alterations of clinical chemistry. Severe effects such as tremors and increased mortality were seen in several acute and long-term studies. Under the acute conditions of exposure (teratology studies in mice), these severe effects were found to be the most sensitive toxicological endpoints observed at the level of 0.075 mg/kg. The next lower level of 0.05 mg/kg was established as a no-observed adverse effect level (NOAEL) and served as a relevant dose in the acute dietary exposure assessment.

The lowest NOAEL established under conditions of long-term feeding exposure was 0.12 mg/kg-day. This NOAEL determined in a two generation reproductive toxicity study in rats was based on decreased survival, decreased weight gain, and retinal alterations observed in pups. The NOAEL is used by the U.S. EPA as a basis for establishing a reference dose (RfD). The U.S. EPA applied an uncertainty factor of 300 (to account for the severity of adverse effects produced by abamectin) to the NOAEL to derive an RfD of 0.0004 mg/kg-day.

6.0 RISK ASSESSMENT

The NOAEL of 0.05 mg/kg-day (discussed above) was used by DPR to evaluate the health risks to children and to adult applicators from potential acute exposure to abamectin from residential use of Avert and from dietary sources.

The risk assessment does not contain an estimate of the potential long-term (chronic) toxicological risk from either the residential use or the dietary sources of abamectin. However, based on the risk estimates from the acute exposure, it can be reasonably assumed that the potential chronic risk is low.

6.1 Exposure Assessment

An assessment of the potential human exposure from the single indoor application of Avert was performed by the Worker Health and Safety Branch of DPR. Estimates were provided for commercial applicators and for small children who may come in contact with the bait through crawling activities. These indoor exposures should take into account the probability of a greater persistence of the active ingredient indoors compared to outdoors. Potential acute dietary exposures were also determined for abamectin residues in all currently registered commodities. The residue levels used in analyses were at the action level for raw agricultural commodities and at the anticipated residue levels supplied by the registrant for beef, milk products, and canned pears.

The highest estimates for acute exposure for residential use of Avert and for acute dietary exposure were determined for infants (< 1 year). Absorbed daily dosages were 0.23 μg/kg-day from residential use and 0.053 μg/kg-day from dietary sources. Parallel estimates for females were 0.105

μg/kg-day and 0.145 μg/kg-day. For males they were 0.082 μg/kg-day and 0.138 μg/kg-day. Combined exposures from residential and dietary sources were 0.283 μg/kg-day for infants, 0.250 μg/kg-day for females, and 0.220 μg/kg-day for males. These exposures correspond to the following margin of safety values (MOS): 177 for infants, 200 for females and 227 for males. The MOS values were calculated as the ratio of the acute NOAEL (50 μg/kg-day) and the pertinent combined exposure estimates.

Appendix D on Dietary Assessment shows that DPR used a NOEL of 0.0004 mg/kg-day as a basis for its analysis. It can be assumed that this is an error and that the NOAEL used for analysis was 0.05 mg/kg-day (as indicated within the body of the document).

7.0 ISSUES OF CONCERN

7.1 The main concern relates to the "protectiveness" of the MOS of 100. This is currently assumed by DPR to be adequate for even the most severe toxicological responses produced, including death. Death and tremors were toxicological endpoints used in assessing risk from acute exposure to abamectin. Although the determined MOS was higher than 100 (but less than 300), its protectiveness against mortality remains questionable. U.S. EPA included a 300-fold uncertainty factor in its derivation of an RfD for long-term exposures. A factor of three was added to account for the severity of effects. DPR should also include *at least* a factor of three in its minimum MOS (i.e., MOS of 300 or more is acceptable) for acute effects. If an MOS of 300 or more cannot be achieved for the most sensitive subpopulation and exposure, DPR should consider denying the registration of this product. Also, it should be underlined that children and infants were identified as the most sensitive subpopulations based on the degree of the exposure. Children and infants may also be the most sensitive subpopulations to the neurotoxic effects of abamectin.

7.2 Indoor use of abamectin contributes 80% of the total exposure to abamectin. The remaining 20% comes from dietary sources. According to DPR, the current risk assessment MOS for mortality and tremors in children younger than one year (from acute combined exposure) is 177. This estimated MOS based on combined indoor and acute dietary exposure seems to be highter than expected and inconsistent with the MOS of 128 determined for children (one to six years old) from acute dietary exposure only to abamectin residues in the crop combination of celery/head lettuce/strawberries (see the most recent DPR Revised Section 18 Emergency Exemption Dietary Risk Assessment for Abamectin on Celery). It can be reasonably assumed that the MOS for total acute abamectin exposure (if the residential exposure is taken into account) would be lower than 128, and possibly lower than 100. This issue should be addressed by DPR.

7.3 The DPR dietary exposure analysis for nursing infants less than one year old (who are identified in this risk assessment as the most sensitive subpopulation) does not include maternal milk as a source of abamectin. The issue of abamectin excretion in maternal milk is not clearly addressed in the draft risk characterization document.

7.4 DPR previously committed itself to obtaining more information on premorphological changes due to the neurochemical properties of abamectin. No such information was provided in the current risk assessment.

7.5 Differences between rodents and primates regarding the pharmacology and toxicology of abamectin should be addressed.

7.6 Efforts should be made to provide more information on abamectin's neurotoxic effects in humans.