MEMORANDUM

TO: Larry L. Nelson, Ph.D., Chief
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DATE: July 12, 1993

FROM: Anna M. Fan, Ph.D., Chief HHC for A Fan
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SUBJECT: Review of Avert (Avermectin) Risk Characterization Document

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It is our understanding that the Department of Pesticide Regulation (DPR) has revised the Risk Characterization Document for Avert Prescription Treatment 310. This product contains 0.05% of abamectin B1, in a crack and crevice dust formulation. Its proposed use is to control cockroaches in residential, commercial, industrial and transportation facilities.

In the revised document, the potential acute exposure level for infants is lower than in the original document. Consequently, the new calculated margin of safety (MOS) from acute exposure for the infants is higher (250) than the previous one (177). The potential exposure and resultant MOS for commercial applicators are the same as in the initial risk characterization document.

The MOS for the acute potential exposure to abamectin was based on a NOEL of 0.05 mg/kg-day determined in a mouse teratology study, and based on maternal tremors and/or death.

In the previous risk assessment, when considering the potential exposure to infants from the indoor use of abamectin, the dosage used to calculate the MOS was the value calculated for the first day immediately after the use (0.23 ug/kg-day). In this revised version the value for potential exposure to infants is the average of the two day exposure values [0.23 + 0.064)/2 = 0.147]. This average value is 1.6 times lower than the previous first day value.

The main reasoning for using a two day average, rather than the single day value immediately after application (i.e., day 1) was based on the time after treatment of pregnant mice required to observe the response used to set the NOEL of 0.05 mg/kg-day.

We disagree with this procedure of using an averaged value of daily exposure of abamectin in assessing health risk to infants from acute exposure. The length of time after treatment that is necessary to produce effects in animal experiments has no bearing on the potential daily exposure to children. It was shown that this exposure can be as high as 0.23 ug/kg-day. The severe effects such as tremors and/or death caused by acute exposure to abamectin were certainly preceded by more subtle effects at organ, tissue or cellular levels. These more subtle effects could have occurred much earlier than two days after exposure.

Tremors and death occurred in many other toxicological tests on animals (including acute, subchronic and chronic tests) as a result of exposure to abamectin. These effects occurred at different times after one, two or more doses. The time lag depended on the magnitude and conditions of exposure.

The justification provided in the document for using a two day average for calculating the exposure value for infants is not convincing. Extrapolation from mice to human beings involves many uncertainties which include not only inherent intraspecies differences but also uncertainties about the neurotoxic effects of abamectin on humans. These effects are not fully evaluated at present. Only the final outcomes of abamectin's interference with the nervous system (tremors and deaths) have been measured. A dose-response relationship for neuorotoxic effects at levels below those causing tremors and deaths is unknown.

A MOS of 100 is currently assumed by DPR to be adequate to protect against potential deaths and tremors caused by acute exposure to abamectin. Because of the severity of effects and inherent uncertainty with regard to mechanism of toxicity we think this margin should be at least 300. This would be similar to the MOS (uncertainty factor) applied by the U.S. Environmental Protection Agency (U.S. EPA) in its derivation of the reference dose (RfD of 0.0004 mg/kg-day) established to protect against adverse effects from long-term exposures. The additional three-fold uncertainty factor (100 x 3 = 300) was applied by U.S. EPA to account for severity of toxic effects produced by exposure to abamectin.

The original version of the risk characterization document for abamectin used a lower MOS to protect against adverse effects from acute exposure than from chronic exposure. No justification was given. We provided comments on this issue in a memorandum to Dr. Nelson from Dr. Jackson dated July 24th, 1992. In response, an explanation was given that rodents reacted differently and were more sensitive to abamectin toxicity than primates. This explanation however, is not substantiated by good scientific data and should not serve as the basis for accepting a lesser MOS for acute effects that are comparable to those observed after chronic exposure, and for which U.S. EPA has determined a higher MOS is needed for health protection.

The lack of information on the mechanism of abamectin's action in mammals, the lack of complete neurotoxicity data, the uncertainties involved in extrapolation from animals to humans, the severity of adverse effects caused by abamectin, and the vulnerability of infants* justifies a more health protective approach in health risk assessment than used in the current version.

In summary, we do not concur with the approach of calculating potential exposure to abamectin for children based on two day average exposure used in the revised document. The highest single day value should be used for this purpose. Consequently, the MOS from the acute exposure to abamectin for infants is 177, not 250. Furthermore, neither of these two MOS's is sufficiently protective. They offer 41% or 17% (respectively) less "protection" than the RfD established for long-term effects.

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* In the original DPR risk characterization document dated May 11, 1992 infants were identified as the most sensitive subpopulation based on the amount of exposure. They may also be more sensitive than adults to abamectin's neurological and lethal effects.