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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

February 6, 1998

Robert E.M. Wurz, Ph.D.
Senior Regulatory Manager
Regulatory Affairs
Novartis Crop Protection, Inc.
PO Box 18300
Greensboro, NC 27419-8300

Re: Profenofos Reregistration
HED Chapter with FQPA Update
HED's Response to Rebuttal on Toxicology section in HED Chapter

Dear Mr. Wurz:

Enclosed for your review is the revised Health Effects Division (HED) chapter which includes the FQPA piece, and consideration and incorporation of your rebuttal of October 19, 1997. I am also sending you the Agency's response to your rebuttal (October 29, 1997) on the Toxicology section of the chapter.

The chapter has not changed significantly (with the exception of the addition of the FQPA requirements). Therefore, we do not anticipate many additional comments. We also do not see major problems (other than has been noted) in the HED portion of the RED, though more FQPA guidance may be forthcoming. The Toxicology Branch reviewed your rebuttal and adjusted the toxicity table on page 6 to reflect the change in the toxicity category from I to III for the endpoint used (from the acute dermal toxicity in the rabbit study). Other minor adjustments to the chapter were made, and are discussed in the 10/19/97 memo. The HED chapter appears to be in relatively good shape: Profenofos is classified as a Group E chemical, and no Maximum Contaminant Level (MCL) or Health Advisory Level (HAL) has been established for profenofos. In the studies that were evaluated, profenofos was not shown to be mutagenic, nor cause treatment-related reproductive and developmental effects.

Profenofos does inhibit red blood cell, plasma and brain cholinesterase activities by dietary administration. Low Margin of Exposures (MOEs) for two exposure scenarios, mixing/loading for aerial application, and for aerial applicators, pose short-term and intermediate-term worker risks. The estimated MOEs for inhalation only exposure are over

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100, and therefore not an issue.

The Environmental Fate and Environment chapter and your rebuttal is under review and portions of the chapter may be revised. The Agency is evaluating fish kills related to use of profenofos on cotton. Once the review is finished, we will forward the chapter.

We hope to meet with you soon to discuss the mitigation proposed in your rebuttal, and other issues.

Sincerely,

Kylie Rothwell
Chemical Review Manager
Special Review and Reregistration Division

OCT 29 1997

MEMORANDUM

SUBJECT: HED's Responses to the Registrant's Rebuttal of the Toxicology Chapter of the Draft HED RED on Profenofos

Rereg. Case No. 2540 CAS No. 41198-08-7
P.C. Code No. 111401 Tox. Chem. No. 266AA

TO: Kylie Rothwell. PM-25 CRM
~~Accelerated~~ Reregistration Branch
Special Review and Reregistration Division (7508W)

FROM: Raymond K. Locke, Toxicologist
Reregistration Branch I
Health Effects Division (7509C)

THRU: Whang Phang, Ph.D., Senior Scientist
Reregistration Branch I
Health Effects Division (7509C)

HED's responses to the Registrant's (Novartis) comments on the toxicology section of the draft HED RED chapter for profenofos are addressed below in the order in which these comments appear in the Registrant's letter of October 19, 1997.

Comment: For acute dermal toxicity in the rabbit, the values from a more recent (1988) acceptable study (MRID 42021501) should be substituted for the values used in the draft HED RED from an acceptable 1982 study (MRID 00109427), changing the Toxicity Category for this endpoint from I to III.

Response: HED was aware of the 1988 study (MRID 42021501) and has evaluated it, finding that the study was acceptable. The dermal LD_{50}s determined in this study were 2450 mg/kg for males, 2790 mg/kg for females, and 2560 mg/kg for the combined sexes. Data from this study place profenofos in Toxicity Category III for this endpoint. However, there is no valid reason to select the data from this 1988 study (MRID 42021501) over that obtained in the equally acceptable 1982 study (MRID 00109427), which demonstrated dermal LD_{50}s of 97.5 mg/kg (abraded skin) and 146.8

mg/kg (intact skin) in males and 15.9 mg/kg (abraded skin) and 143.4 mg/kg (intact skin) in females, placing profenofos in Toxicity Category I for this endpoint. Dermal LD_{50} values for intact skin equal to or less than 200 mg/kg result in a Toxicity Category classification of I for this endpoint. The Phase IV review of the toxicology data on profenofos indicated that the 1982 study was acceptable and placed the pesticide in Toxicity Category I for this endpoint. Since these two studies are equally acceptable, it is HED's policy in these circumstances to select the study demonstrating the higher toxicity.

Comment: Table 2 should be corrected to indicate that the NOEL for acute delayed neurotoxicity in the hen (81-7) was 52 mg a.i./kg and that 100% mortality occurred at 104 mg a.i./kg. Similar changes should be made in the text section (II.B.i.iii.) of the draft HED RED chapter describing this study.

Response: HED agrees with the Registrant. The values presented in the text section describing this study are, in fact, correct and refer to doses of the a.i. This should be indicated in the text section and the phrase, "38% a.i. formulation" changed to "a 38% emulsifiable concentrate formulation (44.3% a.i.)". In preparing Table 2, the correct numbers in the text for the dose of the a.i. were inadvertently corrected once again for purity. Formulation data were used because no acceptable study was available on the technical material; these data were considered together with data from two supplementary studies using technical profenofos. The conclusion of negative results for delayed neurotoxicity in the hen is unaffected by these changes.

the text is correct

Comment: The results cited for the acute oral neurotoxicity study in the rat (81-8) should indicate that there was no histopathological evidence of neurotoxicity at any dose level tested.

Response: Histopathological data represent only one expression, often less sensitive than others, of neurotoxic effects. The complete Data Evaluation Record (DER) for this study does, in fact, note that no histopathological evidence of neurotoxicity was found. However, had a positive finding been made, it would have appeared in the executive summary of the DER and in the draft HED chapter of the RED. Since the RfD for profenofos was determined using another endpoint of neurotoxicity, inhibition of cholinesterase activities, HED emphasized this endpoint, as well as clinical signs indicative of neurotoxicity, in the summary of this study. No inclusion of the negative histopathological data is warranted.

Comment: The statement in Table 2 that "multiple effects were seen in each sex at 190 mg/kg" does not accurately represent the findings in the acute oral neurotoxicity study in rats.

Response: HED regards this as a matter of semantics. More than one effect was observed in each sex; in order to avoid enumerating all of these effects in Table 2, the word "multiple" was appropriately used. This word was also used appropriately in the text describing this study, after the enumeration of the effects observed.

Comment: The Registrant does not agree that females in the acute oral neurotoxicity study receiving profenofos as 190 mg/kg exhibited an increased incidence of diarrhea, miosis, abnormal gait, or increased ease of handling when compared with controls.

Response: Diarrhea: 1/10 of females in the 190 mg/kg group exhibited this effect, while 0/10 females in the controls did so. This is a definite increased incidence, and the treatment-relatedness of this effect is demonstrated by the fact that 5/10 females in the next higher dose group (380 mg/kg) also exhibited diarrhea. In view of the dose-response relationship observed for this effect, it is prudent to consider the increased incidence at 190 mg/kg to be treatment-related.

Miosis: The Registrant accurately indicates that 6/10 females in the 190 mg/kg group exhibited miosis, but 5/10 female controls also exhibited this same effect at this time period, and, at pretest, 6/10 female controls exhibited this effect. However, the important fact here is that at the next higher dose (380 mg/kg), 8/10 females exhibited this effect--demonstrating a dose-response relationship. In the propoxur positive control group, this effect was observed in 10/10 females. Given these data, the increased incidence of miosis in the 190 mg/kg group should be considered treatment-related.

Abnormal gait: 1/10 of females in the 190 mg/kg group exhibited an abnormal (hunched) gait, while 0/10 controls did so. This is an increased incidence with respect to controls and may be treatment-related. At the next higher dose level (380 mg/kg), 6/10 females exhibited this same effect, indicating a positive dose-response relationship. Therefore, this effect should be considered to be treatment-related at 190 mg/kg.

Increased Ease of Handling: The Registrant notes that 10/10 females in the 190 mg/kg were easy to handle versus 6/10 female controls and indicates that these were exactly the same incidences observed pretest for these groups. However, the figures of note are that 6/10 females in the control and low-dose (95 mg/kg) groups exhibited this effect, but ALL 10/10 females in the mid-dose (190 mg/kg) and high-dose (380 mg/kg) groups

exhibited this effect. This indicates a positive dose-response relationship and, therefore, the increased incidence of this effect at 190 mg/kg should be considered to be treatment-related.

Comment: The Registrant believes that, in the non-guideline, two-phase acute oral toxicity study in rats used for determination of the endpoint to be used for acute dietary exposure, the NOEL for plasma cholinesterase inhibition in females is 0.5 mg/kg rather than 0.1 mg/kg and that the NOEL for inhibition of brain cholinesterase for both males and females is 100 mg/kg rather than 25 mg/kg.

Plasma Cholinesterase Inhibition: In females, plasma cholinesterase activities were 81% of control value at 0.1 mg/kg, 79% ~~74~~% at 0.5 mg/kg, 11%* (* indicates statistical significance) at 25 mg/kg, 6%* at 100 mg/kg, and 2%* at 400 mg/kg. As a general rule thumb, HED considers an inhibition of plasma cholinesterase activity ≥ 20% to be biologically significant. Although the inhibition at 0.5 mg/kg was not statistically significant, the inhibition was > 20% and a positive dose-response relationship is apparent. Therefore, the NOEL for females for plasma cholinesterase inhibition is 0.1 . However, the Committee did not select this value as the NOEL to be used in assessing the risk of acute dietary exposure, but rather a NOEL of 0.5 mg/kg, since statistically significant effects were observed in both sexes at the next higher dose (25 mg/kg; decreased plasma cholinesterase in males and females; decreased red blood cell cholinesterase activity in females).

Brain Cholinesterase Inhibition: With respect to brain cholinesterase inhibition, as a general rule, HED considers inhibitions ≥ 10% to be biologically significant. Although not statistically significant, females in the 100 mg/kg group exhibited a brain cholinesterase activity of only 86% of control value, and a clear positive dose-response relationship existed. Therefore, the Committee considered the NOEL for inhibition of brain cholinesterase in females to be 25 mg/kg. With respect to males, the two lower doses (0.1 and 0.5 mg/kg) produced an apparent 104 % increase in brain cholinesterase activity, the next two higher doses (25 and 100 mg/kg) yielded a consistent decrease of 3%, while the highest dose (400 mg/kg yielded a 37% decrease. Given the positive dose-response relationship from 100 mg/kg and above, and the fact that females showed a 14% decrease at 100 mg/kg, the Committee considered it prudent to conclude that the NOEL brain cholinesterase inhibition should also be considered to be 25 mg/kg in males. However, neither of these NOELs were used for risk assessment purposes.