UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Note to Reader
September 9, 1998

Background: As part of its effort to involve the public in the implementation of the Food Quality Protection Act of 1996 (FQPA), which is designed to ensure that the United States continues to have the safest and most abundant food supply, EPA is undertaking an effort to open public dockets on the organophosphate pesticides. These dockets will make available to all interested parties documents that were developed as part of the U.S. Environmental Protection Agency's process for making reregistration eligibility decisions and tolerance reassessments consistent with FQPA. The dockets include preliminary health assessments and, where available, ecological risk assessments conducted by EPA, rebuttals or corrections to the risk assessments submitted by chemical registrants, and the Agency's response to the registrants' submissions.

The analyses contained in this docket are preliminary in nature and represent the information available to EPA at the time they were prepared. Additional information may have been submitted to EPA which has not yet been incorporated into these analyses, and registrants or others may be developing relevant information. It's common and appropriate that new information and analyses will be used to revise and refine the evaluations contained in these dockets to make them more comprehensive and realistic. The Agency cautions against premature conclusions based on these preliminary assessments and against any use of information contained in these documents out of their full context. Throughout this process, if unacceptable risks are identified, EPA will act to reduce or eliminate the risks.

There is a 60 day comment period in which the public and all interested parties are invited to submit comments on the information in this docket. Comments should directly relate to this organophosphate and to the information and issues

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available in the information in this docket. Once the comment period closes, EPA will review all comments and revise the risk assessments, as necessary.

These preliminary risk assessments represent an early stage in the process by which EPA is evaluating the regulatory requirements applicable to existing pesticides. Through this opportunity for notice and comment, the Agency hopes to advance the openness and scientific soundness underpinning its decisions. This process is designed to assure that America continues to enjoy the safest and most abundant food supply. Through implementation of EPA's tolerance reassessment program under the Food Quality Protection Act, the food supply will become even safer. Leading health experts recommend that all people eat a wide variety of foods, including at least five servings of fruits and vegetables a day.

Note: This sheet is provided to help the reader understand how refined and developed the pesticide file is as of the date prepared, what if any changes have occurred recently, and what new information, if any, is expected to be included in the analysis before decisions are made. **It is not meant to be a summary of all current information regarding the chemical.** Rather, the sheet provides some context to better understand the substantive material in the docket (RED chapters, registrant rebuttals, Agency responses to rebuttals, etc.) for this pesticide.

Further, in some cases, differences may be noted between the RED chapters and the Agency's comprehensive reports on the hazard identification information and safety factors for all organophosphates. In these cases, information in the comprehensive reports is the most current and will, barring the submission of more data that the Agency finds useful, be used in the risk assessments.

Jack Housenger, Acting Director
Special Review and Reregistration
Division

Waldrop

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: September 25, 1997

MEMORANDUM

SUBJECT: PROFENOFOS - *FQPA REQUIREMENT* - Report of the Hazard Identification Assessment Review Committee.

FROM: Jess Rowland 9/25/97
Branch Senior Scientist,
Science Analysis Branch, Health Effects Division (7509C)

THROUGH: K. Clark Swentzel 9/25/97
Chairman, Hazard Identification Assessment Review Committee
Toxicology Branch II, Health Effects Division (7509C)

TO: Mike Metzger
Reregistration Branch 2
Health Effects Division (7509C)

BACKGROUND: On September 8, 1997, the Health Effects Division's Hazard Identification Assessment Review Committee met to evaluate the toxicology data base of Profenofos with special reference to the reproductive, developmental and neurotoxicity data. These data were re-reviewed specifically to address the sensitivity of infants and children from exposure to Profenofos as required by the Food Quality Protecting Act (FQPA) of 1996. The FQPA requirement was not addressed in the Reregistration Eligibility Document. The Committee's decisions are summarized below.

CC: Rick Whiting, Science Analysis Branch
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A. INTRODUCTION

The Health Effects Division's Hazard Identification Assessment Review Committee met to evaluate the toxicology data base of Profenofos with special reference to the reproductive, developmental and neurotoxicity data. These data were re-reviewed specifically to address the sensitivity of infants and children from exposure to Profenofos as required by the Food Quality Protecting Act (FQPA) of 1996. The FQPA requirement was not addressed in the Reregistration Eligibility Document.

B. RESULTS:

1. Neurotoxicity

- In an acute delayed neurotoxicity study in hens with a formulation (38% a.i), no neurotoxicity was seen at dose levels up to 52 mg/kg, with 100% mortality at next highest dose level of 104 mg/kg. Negative results for delayed neurotoxicity were also reported in two supplementary studies with the technical product. The Committee noted that these studies did not assess for the potential of Profenofos to inhibit neurotoxic esterase (NTE) in hens (MRID Nos. 00082083, 00082085, 00097797).

- In an acute neurotoxicity study, Sprague-Dawley rats (10/sex/dose) were given a single oral administration of Profenofos in corn oil at 0, 95, 190 or 380 mg/kg/day. Neurotoxicity was seen only at the time of peak effect. For neurotoxicity, the NOEL was 95 mg/kg and the LOEL was 190 mg/kg based on an increased incidence of staining of the nose and compulsive licking (stereotypy) in males and an increased incidence of diarrhea, miosis, staining of the nose, abnormal gait, and ease of handling. For cholinesterase inhibition, theLOEL was 95 mg/kg (LDT) based on a dose-related inhibition of plasma and red blood cell cholinesterase activities seen in both sexes; a NOEL was not established. Brain cholinesterase activity was unaffected in both sexes (MRID No. 42939801).

- In a subchronic neurotoxicity study, Sprague-Dawley rats (10/sex/dose) were fed diets containing Profenofos at 0, 30, 135 or 600 ppm (0, 1.7, 7.7 or 36 mg/kg/day in males and 1.84, 8.4 or 37.9 mg/kg/day in females, respectively) for 13 weeks. No treatment-related neurotoxicity or pathological lesions of the central or peripheral nervous system were observed. For neurotoxicity, the NOEL was >36 mg/kg/day (HDT); a LOEL was not established. For plasma and red blood cell ChEI, the LOEL was 1.7 mg/kg/day (LDT); a NOEL was not established. For brain ChEI, the NOEL was 7.7 mg/kg/day and the LOEL was 36 mg/kg/day (MRID Nos. 43213303 and 43213304).

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2. Developmental Toxicity

- The developmental toxicity studies in rats and rabbits showed no evidence of additional sensitivity to young rats or rabbits following pre- or postnatal exposure to Profenofos and comparable NOELs were established for adults and offspring.

- In a developmental toxicity study pregnant Sprague-Dawley rats received oral doses of Profenofos in carboxymethylcellulose at 0, 10, 30 or 60 mg/kg/day during gestation days 6 through 15. For maternal toxicity, the NOEL was 30 mg/kg/day and the LOEL was 60 mg/kg/day based on decreased food consumption and slightly decreased body weight gain. No developmental toxicity was seen. For developmental toxicity, the NOEL was 60 mg/kg/day (HDT); a LOEL was not established (MRID No. 00045031).

- In a developmental toxicity study, pregnant New Zealand White rabbits were given a single oral dose of Profenofos 0, 30, 60, 90 or 175 mg/kg/day during gestation day 6. For maternal toxicity, the NOEL was 30 mg/kg/day and the LOEL was 60 mg/kg/day based on decreased body weight gain. No developmental toxicity was seen. For developmental toxicity, the NOEL was 175 mg/kg/day (HDT). Although the animals were dosed only on gestation day 6, the RfD Committee concluded that the dose levels used in this study were equal to or higher than the doses that elicited cholinesterase inhibition in other studies (MRID No. 00128870).

3. Reproductive Toxicity

- In a two-generation reproduction study, when administered in the diet at 0, 5, 100 or 400 ppm, to Crl:CD (SD) BR VAF/Plus rats , no increased sensitivity to pups compared to the adults was seen. For parental systemic toxicity, the NOEL was 100 ppm (7.3 mg/kg/day) and the LOEL was 400 ppm (29 mg/kg/day) based on decreased body weight gains in males and females of both the F_0 and F_1 generations at all time period throughout the study and decreased food consumption. For reproductive toxicity, the NOEL was 100 ppm (7.3 mg/kg/day) and the LOEL was 400 ppm (29 mg/kg/day) based on decreased pup body weight in both sexes of F_1 and F_2 litters and cumulative body weight gain on days 14 and 21 of lactation (MRID Nos.43213308 and 43213309).

4. Cholinesterase Inhibition

- Cholinesterase activity was not measured in the adults and offspring either in the developmental (rats and rabbits) or the reproductive toxicity studies. Therefore, no comparisons could be made for this endpoint between adults and offspring.

5. Developmental Neurotoxicity

- There are sufficient data available to adequately assess the potential for toxicity to young animals following pre-and/or post-natal exposure to Profenofos. These include acceptable developmental toxicity studies in rats and rabbits and a 2-generation reproduction study in rats. In addition, no treatment-related neuropathology was seen in studies conducted in hens or rats. Therefore, based upon a weight-of-the-evidence consideration of the data base, the Committee determined that a developmental neurotoxicity study is not required.

6. Reference Dose (RfD)

- An RfD of 0.00005 mg/kg/day was derived from the NOEL of 0.005 mg/kg/day and an Uncertainty Factor (UF) of 100. The LOEL was based on plasma and red blood cell ChEI observed at 0.05 mg/kg/day in dogs. The UF of 100 included a 10 for intra-species and 10 for inter-species variation.

C. CONCLUSIONS

The Committee's conclusions on the Uncertainty Factors for acute and chronic dietary risk assessments are as follows:

1. Acute Dietary Risk Assessment

The endpoint selected for acute dietary risk assessment is based on the NOEL of 0.5 mg/kg/day for inhibition of cholinesterase activity of plasma (males) and red blood cell (females) in rats at 25 mg/kg/day in rats. For inhibition of brain cholinesterase inhibtion, the NOEL was 25 mg/kg/day and the LOEL was 100 mg/kg/day. When the dose selected is from an animal study, usually a UF of 100 would be applied for inter and intra species variability. In this case, however, the Toxicology Endpoint Selection Committee determined that a Margin of Exposure of of 10 is adequate because of the comparison between the doses of Profenofos eliciting plasma and red blood cell ChEI (25 mg/kg/day) and the much higher dose (100 mg/kg/day) required to cause brain ChEI which is of greater toxicological concern.

For acute dietary risk assessment, the Committee determined that the **10 x** factor to account for enhanced sensitivity of infants and children **(as required by FQPA) should be removed. A Margin of Exposure of 10 is adequate** to ensure protection of this population from acute exposure to Profenofos for reasons stated below:

(i) No increased sensitivity to fetuses as compared to maternal animals following an acute *in utero* exposure in developmental toxicity studies.

(ii) No increased sensitivity to pups as compared to adults in a multi-generation

reproduction study in rats.

2. Chronic Dietary Risk Assessment

The endpoint for chronic dietary risk assessment is based on the plasma and red blood cell cholinesterase inhibition observed at 0.05 mg/kg/day (LOEL) in a six moth dog study. The NOEL was 0.005 mg/kg/day. An UF of 100 applied to the NOEL; 10 x each for inter and intra species variability. Thus an RfD of 0.00005 mg/kg/day was derived.

For chronic dietary risk assessment, the Committee determined that the **10 x** factor to account for enhanced sensitivity of infants and children **(as required by FQPA) should be removed. The present UF of 100 is adequate** to ensure protection of this population from chronic exposure to Profenofos since there was not indication of increased sensitivity to young animals following pre-and/or post-natal exposure to Profenofos as shown below:

(i) Developmental toxicity studies showed no increased sensitivity to fetuses as compared to maternal animals following *in utero* exposures in rats and rabbits.

(ii) A multi generations reproduction toxicity study in rats showed no increased sensitivity to pups as compared to adults.