



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

OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Profenofos (PC Code 111401). FQPA Update of the HED Chapter of the Reregistration Eligibility Decision Document. Case No. 2540.

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The attached memorandum updates, with particular regard to the requirements of the 1996 Food Quality Protection Act, the HED Human Health assessment (Kathleen Martin, 6/18/96) for the profenofos Reregistration Eligibility Decision Document. Attached is an update of the DRES database and dietary risk estimates.

## I. EXECUTIVE SUMMARY

Profenofos [O-(4-bromo-2-chlorophenyl)-O-ethyl-S-propyl phosphorothioate] is an organo-thiophosphate insecticide/miticide that is applied to cotton for the control of cotton bollworm, tobacco budworm, other insects, and mites. It is applied as an emulsifiable concentrate using ground boom or aerial application techniques.

Profenofos is sold in the United States by its basic producer, Ciba-Geigy Corporation, under the trade name Curacron®. There are two registered products: Technical Profenofos (EPA Reg. No. 100-598; 89% a.i.) and Curacron 8E Insecticide-Miticide (EPA Reg. No. 100-669; 72.7% a.i.).

Because cotton is also a food crop, the Agency has assessed the potential risks from both dietary and occupational exposure. The potential for exposure due to drinking water contaminated with profenofos has also been considered. The Agency has concluded that profenofos dietary exposure estimates for the general U.S. population, children, or any population sub-group, do not exceed levels considered to be significant by the Agency.

The Agency has concluded that the product chemistry, residue chemistry, and toxicological data for profenofos are adequate for risk assessment and for reregistration.

Dietary risk assessment is based on a dose of 0.5 mg/kg/day for acute exposure estimates and a Reference Dose of 0.00005 mg/kg/day for chronic exposure estimates. Profenofos has been classified as a Group E chemical for human carcinogenicity. Occupational risk assessment is based on a dose (NOEL) of 1.0 mg/kg/day for short and intermediate exposure durations and a dose (NOEL) of 0.005 mg/kg/day for chronic exposure. Inhalation risk assessment is based on a dose (LEL) of 0.068 mg/L (11.2 mg/kg/day in males and 12.5 mg/kg/day in females). All endpoints are based on observed cholinesterase inhibition as measured in plasma, blood, and brain.

Current data indicate that profenofos use on cotton has increased since a previous risk assessment in 1990 for the Special Review "Exceeders" project. An upper-end percent crop treated assumption of 25% has been used for this assessment compared to 7% in 1990. Anticipated residue estimates have been used for this risk assessment and are based on 25% crop treated, processing data, and feeding studies. Dietary risk estimates for potential drinking water contamination are based on peak and annualized concentrations modeled with the Agency's PRZM-EXAMS computer programs. Based on the aggregate acute and chronic dietary exposure estimates for profenofos, the Agency concludes that there is a reasonable certainty that no harm will result to children or any significant population sub-group.

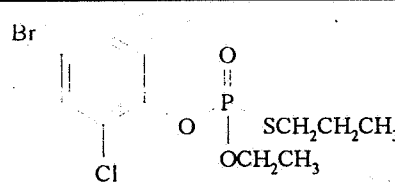
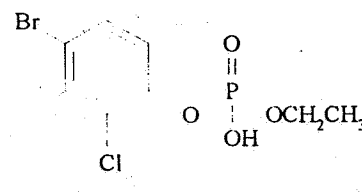
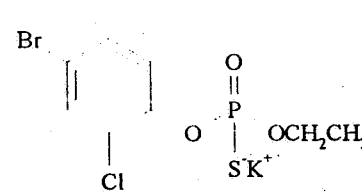
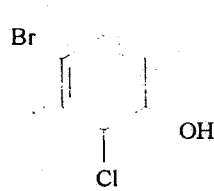
Exposure estimates for workers mixing/loading for aerial application and for applying profenofos from fixed-wing aircraft exceed a level considered significant by the Agency. Resolution of these worker risk issues remains to be resolved with the registrant.

## II. SCIENCE ASSESSMENT

### A. Physical Chemistry Assessment

Profenofos [O-(4-bromo-2-chlorophenyl)-O-ethyl-S-propyl phosphorothioate] is an organo-thiophosphate pesticide. In this document, profenofos is often referred to as CGA-15324. Primary metabolites of interest include: CGA-55960 (4-bromo-2-chlorophenol), CGA-15324, CGA-47196, and CGA-65867. Provided in Table 1 is the chemical structure of profenofos and the structures of these primary metabolites.

Table 1. Structures and Names of Profenofos and its Primary Metabolites

STRUCTURE	NAME
	Profenofos CGA-15324
	CGA-47196
	CGA-65867
	CGA-55960 Bromochlorophenol (4-bromo-2-chlorophenol)

#### 1. Identification of Active Ingredient

Technical profenofos is a pale yellow liquid with a boiling point of 100°C (1.8 Pa) and a density of 1.46 g/cm<sup>3</sup> at 20°C. Its empirical formula is C<sub>11</sub>H<sub>15</sub>O<sub>3</sub>PSBrCl and its molecular weight is 373.65 g/mole. The CAS Registry No. and PC Code for profenofos are: 41198-08-7 and 111401, respectively. Pure profenofos is an amber-colored oily liquid with a boiling point of 110°C (0.001 mm Hg). Profenofos has limited solubility in water (20 ppm), but is completely soluble in organic solvents (ethanol, acetone, toluene, n-octanol, and n-hexane) at 25°C. Profenofos is stable under neutral and slightly acidic conditions, and is unstable under alkaline conditions.

## 2. Manufacturing-Use Products

The Agency's Reference Files System (REFS) identifies a single profenofos manufacturing-use product: the Ciba-Geigy Corporation 89%T (EPA Reg. No. 100-598). Only the Ciba-Geigy 89%T is subject to a reregistration eligibility decision.

## 3. Regulatory Background

The Profenofos Phase IV Review (dated 11/30/90 by C. Olinger) determined that Ciba-Geigy data submissions for 61 and 62 series requirements met the acceptance criteria for Phase V review; additional data were required concerning 63 series requirements. Analysis of the technical product for dioxin (i.e., 2,3,7,8-TCDD) contaminants was required during Phase V review. Dioxin data have been submitted. EPA concludes that this chemical is not formed or carried over from starting materials during the manufacture of technical profenofos, and that it does not need to be included on the Confidential Statement of Formulation.

The current status of the product chemistry data requirements for Ciba-Geigy technical profenofos is presented in Appendix 1. Refer to Appendix 1 for a listing of the outstanding product chemistry data requirements.

## 4. Conclusions

All pertinent data requirements are satisfied for the profenofos 89%T. Provided that the registrant *either* certifies that the suppliers of beginning materials and the manufacturing process for the profenofos technical product have not changed since the last comprehensive product chemistry review *or* submits a complete updated product chemistry data package, EPA has no objections to the reregistration of profenofos with respect to product chemistry data requirements.

## B. Human Risk Assessment

## **1. Hazard Assessment**

The Agency has concluded that the available toxicological database for profenofos is adequate and will support a reregistration eligibility determination for the currently registered uses.

### **a. Acute Toxicity**

Profenofos has been tested in a variety of studies for acute toxicity by the oral, dermal, and inhalation routes of exposure. The results obtained in these studies, which are listed in Table 2 for the technical grade of the active ingredient (TGAI), satisfy the acute toxicity data requirements (Guidelines 81-1 through 81-8).

Table 2. Acute Toxicity Values for Technical Profenofos

TEST (Guideline)	RESULT [MRID]	TOXICITY CATEGORY
Oral LD <sub>50</sub> in rat (81-1)	LD <sub>50</sub> = Males: 492 (363-666) mg/kg Females: 809 (600-1090) mg/kg Combined: 630 mg/kg [MRID 41714801]	II
Oral LD <sub>50</sub> in mouse (81-1)	LD <sub>50</sub> = 298 (268-332) mg/kg [MRID 00105226]	II
Oral LD <sub>50</sub> in rabbit (81-1)	LD <sub>50</sub> = 300 mg/kg [MRID 00105228]	II
Dermal LD <sub>50</sub> in rat (81-2)	LD <sub>50</sub> = 1610 (1073-2415) mg/kg [MRID 00105231]	II
Dermal LD <sub>50</sub> in rabbit (81-2)  See note below:	LD <sub>50</sub> = Intact skin -- Males: 146.8 mg/kg Females: 143.4 mg/kg Abraded skin -- Males: 97.5 mg/kg Females: 15.9 mg/kg [MRID 00109427]	I
Inhalation LC <sub>50</sub> in rat (81-3)	LC <sub>50</sub> = 3.36 mg/L [MRID 0019428]	IV
Eye irritation in rabbit (81-4)	Minimal irritation, reversible within 7 days; no corneal opacity [MRID 00109429].	III
Dermal irritation in rabbit (81-5)	Moderately irritating at 72 hours; PIS = 3.3/8.0 [MRID 41714802]	III
Dermal sensitization in guinea pig (81-6)	Sensitization was induced [MRID 00109431].	--
Acute delayed neurotoxicity in hen (81-7)	No delayed neurotoxicity; NOEL = 52 mg a.i./kg 100% mortality at next highest dose (104 mg a.i./kg) LD <sub>50</sub> = 56.3 mg a.i./kg [MRID 00126485]	--
Acute oral neurotoxicity in rat (81-8)	NOEL for neurotoxicity = 95 mg/kg; multiple effects were seen in each sex at 190 mg/kg (LEL); NOEL for inhibition of cholinesterase activities in plasma and RBC < 95 mg/kg (LDT) [MRIDs 42939801 and 42939802].	--

**NOTE:**

Technical profenofos was used in all these acute studies except for the acute delayed neurotoxicity in the hen (81-7). For this study, a formulation (44.3% technical profenofos) was used.

Dermal toxicity in rabbit: Another acceptable study demonstrating lower toxicity is available (MRID 42021501). The registrant suggests the lower toxicity demonstrated in this study is most likely due to the fact that the test substance was applied to surgical gauze held against the skin by a semi-permeable dressing, rather than the direct application of test material under impermeable polyethylene film as used in MRID 00109427; the occlusion by the impermeable film could lead to enhanced dermal absorption and greater toxicity.

**b. Subchronic Toxicity**

### *Dermal Toxicity*

In a repeated dose 21-day dermal toxicity study (MRID 41644501), profenofos technical (92% a.i.) was administered topically to the clipped dorsal trunk and flanks (intact skin) of HAR:PF/CF (NZW) BR albino rabbits (5/sex/dose) as suspensions in U.S.P. purified water containing 0.5% Tween 80 at daily dose levels of 0, 0.05, 1, or 10 mg/kg/day for 5 days/week for a three-week period.

The only clinical sign observed was hyperactivity in the high-dose (10 mg/kg/day) animals. There were no other treatment-related effects in the in-life observations or at gross or microscopic examination. After three weeks, well defined erythema, but no edema, was noted at the treatment site for all mid-dose (1 mg/kg/day) animals and high-dose (10 mg/kg/day) females.

After three weeks of treatment, red blood cell and serum cholinesterase (ChE) activities were statistically significantly ( $p < 0.01$ ) decreased (range: 51-83% control values) only in high-dose (10 mg/kg/day) males and females. Brain ChE activity was also significantly decreased only in high-dose (10 mg/kg/day) males (70% control value) and females (85% control value). The LEL is 10 mg/kg/day, based on significant decreases in cholinesterase activities in red blood cells, serum, and brain. The NOEL is 1 mg/kg/day.

### *Oral Toxicity in Rodents*

In a 90-day feeding study in rats (MRID 00105255), Charles River strain albino rats (28 days of age; 15/sex/group) were fed (for 90 days) diets containing 0, 2, 20, or 200 ppm of CGA-15324 technical (corrected for purity; 94.8% a.i.), equivalent to 0, 0.2, 2, or 20 mg/kg/day. Separate groups of animals were used for recovery studies: five additional animals/sex/group in the control (0 mg/kg/day) and high-dose (20 mg/kg/day) groups were fed diets containing no CGA-15324 technical for four weeks of recovery from treatment received during the initial 90-day study period. Although this study was conducted by Industrial BioTest Laboratories, Inc., Northbrook, Illinois, a testing facility known to have falsified certain toxicology data, this study (MRID 00105255) was independently reviewed, validated, and subsequently accepted by the Agency.

Body weights were recorded weekly for all animals; food consumption data were determined weekly for 5 animals/sex/group. Animals were observed at unspecified time periods for mortality, moribundity, and clinical signs of toxicity.

After 90 days on test, or after an additional four weeks of no treatment for recovery animals, the animals were sacrificed and a gross necropsy performed. Microscopic examination of a standard selection of tissues was conducted with 10 animals/sex/group in the control (0 mg/kg/day) and high-dose (20 mg/kg/day) groups exposed for 90 days with no recovery period. Tissues from recovery animals were not examined microscopically. Weights of adrenals, brain, gonads, heart, kidneys, and livers were recorded for each animal and organ-to-brain and body-weight ratios determined. Standard hematology, clinical chemistry, and urinalysis studies were conducted, and cholinesterase activities were determined in plasma, red blood cells, and brain. Ophthalmological examinations were conducted at study start and at termination.

CGA-15324 technical, at all doses tested, had no effect on any of the parameters monitored, except for inhibition of ChE activities at study termination (90-days). No compound-related effects on body weight, gross pathology, or organ histopathology were demonstrated in either male or female rats. ChE activities in plasma and red blood cells were inhibited (range: 12-98% control) in some animals in all groups treated with CGA-15324 technical, but these values returned to control values with four weeks of recovery. Brain ChE activity was not significantly inhibited in females at any dose level. Brain ChE was inhibited in males (range: 56-65% control) at the 2 and 20 mg/kg/day doses but returned to normal (in the recovery group) after four weeks.

However, the Industrial BioTest (IBT) Validation Report, indicates that the raw data (which are not available) demonstrate that brain ChE activity was significantly inhibited at 0.2 mg/kg/day (LDT). The RBC and Plasma ChE NOEL < 0.2 mg/kg/day (LDT; 0.2 mg/kg/day; 2-32% inhibition) and the Brain ChE NOEL < 0.2 mg/kg/day (LDT; 0.2 mg/kg/day; "significant inhibition").

### *Oral Toxicity in Dogs*

#### *i. 13-Week Feeding Study*

In a 13-week feeding study (MRID 00108016), groups of Beagle dogs (4/sex/group) were fed diets containing profenofos technical at dosage levels of 0, 2, 20 or 200 ppm (corresponding to 0, 0.05, 0.5, and 5 mg/kg/day, respectively). One additional male and female were added to the control (0 mg/kg/day) and high-dose (5 mg/kg/day) groups for use in a recovery phase.

Ophthalmological examinations were conducted on all animals prior to study initiation and at 85 days on test. At sacrifice, brain cholinesterase activity was determined. Standard procedures were followed in the selection of organs for weight and organ weight/body weight determinations, as well as the



selection of organs from all animals for microscopic examination.

The only effect elicited by profenofos at any dose level tested consisted of inhibition of plasma, red blood cell, and brain cholinesterase (ChE) activities. Plasma ChE activity was depressed at least 40% in all profenofos treatment groups. Red blood cell ChE activity was depressed at least 10% in the mid- (0.5 mg/kg/day) and high-dose (5 mg/kg/day) groups. In males, brain cholinesterase was decreased (21% decrease) only at the high-dose (5 mg/kg/day) level, and in females only a slight decrease (5% decrease) occurred at this dose level. In the recovery animals, plasma and brain ChE activities returned to pretest values, but the red blood cell ChE activity remained depressed at about 50% of pretest values (although some recovery was seen with respect to values at 90 days on test).

The systemic NOEL is > 5 mg/kg/day (HDT) based on a lack of effects other than cholinesterase inhibition. The Plasma ChE NOEL is < 0.05 mg/kg/day (LDT), based on 52-58% inhibition at 0.05 mg/kg/day. The RBC ChE NOEL is 0.05 mg/kg/day (LDT), based on 10-31% inhibition at 0.5 mg/kg/day. The Brain ChE NOEL is 0.5 mg/kg/day, based on a 21% decrease in brain ChE activity in males at 5 mg/kg/day.

#### ii. Six-Month Feeding Study

In a six-month feeding study (MRID 00081687), groups of Beagle dogs (7/sex/group) were administered diets containing profenofos technical (88.1 - 89.3% a.i.) at 0, 0.2, 2, 100, or 500 ppm for 182 consecutive days (26 weeks; six months). These dosage levels correspond to 0, 0.005, 0.05, 2.5, or 12.5 mg/kg/day, respectively. One animal/sex/group was maintained on laboratory diet containing no profenofos for a one-month recovery period following the six months of treatment.

Animals were examined daily for mortality, clinical signs of toxicity, and moribundity. Food consumption was monitored daily and weekly food efficiency values were calculated. Body weight and auditory response were determined weekly. Standard hematology, blood chemistry (including determination of plasma and red blood cell cholinesterase inhibition), and urinalysis determinations were conducted pretest and during weeks 4, 9, 13, 18, 22, and 26 (and at week 31 for recovery-group animals). Ophthalmological examinations were conducted pretest and after 26 weeks (and at week 31 for recovery-group animals). After 23 weeks of treatment, all animals from the control (0 mg/kg/day) and high-dose (12.5 mg/kg/day) groups were subjected to a neurological examination.

At the end of the treatment or recovery period, animals were sacrificed and standard parameters measured, including microscopic examination of selected organs. Brain cholinesterase inhibition was determined at sacrifice on six males and six females, one of each sex per dose group.

The only significant effect elicited by dietary administration of technical profenofos, at any dose level tested, was cholinesterase inhibition. ChE inhibition was measured in brain (range: 0-11%), plasma (range: 0-79%), and red blood cells (range: 0-81%). A one-month recovery only partially restored cholinesterase activities in plasma and red blood cells in males, but completely restored these activities in females.

Brain cholinesterase activity was not significantly inhibited in males at any dose level. In females, significant (10-11%) inhibition of brain cholinesterase activity was observed at 0.05 and 2.5 mg/kg/day dietary profenofos levels, respectively. No recovery data were available for brain cholinesterase inhibition. The LEL is 0.05 mg/kg/day based on cholinesterase inhibition (27-54%) in plasma in male and female dogs, and in RBC (1-81%) in male dogs only. The NOEL is 0.005 mg/kg/day.

### **c. Chronic Toxicity**

In a chronic toxicity/oncogenicity study (MRID 00081685), groups of Fisher 344 rats (60/sex/group) were fed diets containing CGA-15324 technical (90.6% a.i.) at dose levels corrected for purity of 0, 0.3, 10, or 100 ppm for 105 weeks (two years). These dose levels approximately correspond to 0, 0.015, 0.5, or 5 mg/kg/day. Five animals/sex/group were added to the control (0 mg/kg/day) and high-dose (5 mg/kg/day) groups for interim sacrifice at 12 months. Additionally, 5 animals/sex/group were added to these same two groups as recovery animals, receiving control (0 mg/kg/day) or high-dose (5 mg/kg/day) diets for 52 weeks, followed by a basal-only diet for an additional 11 weeks, with sacrifice at week 63.

Red blood cell and plasma cholinesterase (ChE) activities were determined in 10 animals/sex/group from all study groups at weeks 13, 26, and 52; these same determinations were made in 5 animals/sex/group in the control (0 mg/kg/day) and high-dose (5 mg/kg/day) recovery animals at weeks 57, 78, and 105. Brain ChE activity was determined in 5 animals/sex/group in the control and high-dose groups at 52 weeks, and in 10 animals/sex/group from all groups at week 105.

Treatment with CGA-15324 technical caused no effects, at any dose level tested, on survival with respect to control values at either 54 weeks (range:

83-99%) or 104 weeks (range: 72-90%). There were no biologically significant differences from control values noted in any treated group with respect to body weights or food consumption. In addition, CGA-15324 technical, at all doses tested, caused no effects on organ weights, organ/body weight or organ/brain weight ratios, hematological parameters, clinical chemistry and urinalysis values, or gross or microscopic pathology.

The only treatment-related effect observed was inhibition of red blood cell (RBC), plasma, and brain cholinesterase activities. Significant (> 10%) inhibition of brain ChE occurred only in females in the 5 mg/kg/day group at 105 weeks only. This study was conducted at adequate dose levels, since at the highest dose tested (5 mg/kg/day), ChE activity was inhibited in red blood cells up to 69% and up to 62% in blood plasma. The NOEL for chronic systemic effects is 0.015 mg/kg/day (LDT), based on inhibition (> 20%) of ChE activity in red blood cells and plasma at 0.5 mg/kg/day (MDT).

#### **d. Carcinogenicity**

##### **i. Two-Year Carcinogenicity Study**

In a two-year carcinogenicity study (MRID 00082901), groups of HaM/ICR Swiss, Charles River CD<sup>®</sup> mice (65/sex/group) were administered diets containing CGA-15324 technical at levels of 0, 1, 30, or 100 ppm (approximately corresponding to 0, 0.15, 4.5, or 15 mg/kg/day) for 85 weeks (males) or 97 weeks (females).

Five animals/sex/group were used for 12-month erythrocyte, plasma, and brain cholinesterase (ChE) determinations (interim sacrifice animals). No treatment-related clinical signs were observed in any animal on test.

The survival rate for males at 85 weeks was not dose-dependent and averaged (including controls) 39%. Similarly, for females the survival rate at 96 weeks averaged 28%. No differences from controls were noted for any CGA-15324-treated animals with respect to gross or microscopic lesions. The incidence of tumors observed in all of the profenofos-treated groups were similar to those observed in the control groups. No biologically significant differences in mean body weight or food consumption were observed between controls and profenofos-treated animals.

Cholinesterase (ChE) inhibition (> 20%) occurred in plasma and red blood cells in both males and females at 53 weeks and at study termination at dose levels of 4.5 and 15 mg/kg/day, but not at 0.15 mg/kg/day. Adequate dose levels were used in this study, since at the highest dose tested (15

mg/kg/day), ChE activity was inhibited up to 74.2% in red blood cells, and up to 76.1% in blood plasma. Under the study conditions, technical profenofos did not demonstrate a carcinogenic potential. The carcinogenic NOEL is > 15 mg/kg/day (HDT).

#### ii. Chronic Toxicity/Carcinogenicity Study

In a chronic toxicity/carcinogenicity study in rats (MRID 00081685), there was no increase in tumor incidence observed in any of the treated groups as compared with those in the control groups (details of this study are provided above under "Chronic Toxicity"). This study was conducted at adequate dose levels, since at the highest dose tested (5 mg/kg/day) ChE activity was inhibited in red blood cells up to 69% and up to 62% in blood plasma. Higher dose levels would likely lead to unsatisfactory survival of test animals. Under the study conditions, profenofos did not demonstrate a carcinogenic effect. Therefore, the carcinogenic NOEL is > 5 mg/kg/day (HDT) in rats.

#### e. Developmental Toxicity

In a developmental toxicity study (MRID 00045031), groups of pregnant rats (strain not specified; 20-27 per group) were administered (orally) CGA-15324 technical, with carboxymethyl-cellulose as the vehicle, at dose levels of 0, 10, 30, or 60 mg/kg/day during gestation days 6 through 15.

Animals were observed daily for mortality, moribundity, and clinical signs of toxicity. Food consumption and body weights were monitored. At day 15 of gestation, the dams were sacrificed and organs were examined grossly. Fetuses were weighed and subjected to an examination of body cavity sites and viscera (using a slicing technique, and a skeletal examination).

Mean food consumption was markedly decreased (86% control value) during the treatment period in the 60 mg/kg/day group of pregnant females and was slightly decreased (92% control value) in the 30 mg/kg/day group. These decreases in food consumption during the treatment period resulted in slightly decreased (95% control value) body weights in the 60 mg/kg/day group, but no effect on body weights in the 30 mg/kg/day group. No differences from the control group were observed in any CGA-15324 treated group with respect to implantation ratio, embryoletality, fetal average body weight, or fetal skeletal abnormalities.

From these data, it is concluded that CGA-15324 technical at all doses tested caused no treatment-related developmental (teratogenic) effects. The Developmental NOEL is > 60 mg/kg/day (HDT); the Maternal NOEL is

30 mg/kg/day (MDT), based on decreased food consumption and slightly decreased body weight at 60 mg/kg/day (Maternal LEL).

Other available developmental toxicity studies on profenofos include an unacceptable study in rats (MRID 00109313) and supplementary studies in rabbits (MRIDs 00140827 and 00128870).

In a (supplemental) developmental toxicity study (MRID 00128870), pregnant New Zealand white rabbits were given a single oral dose of profenofos at 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 observed. 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 significantly higher than the doses that elicited cholinesterase inhibition in other studies.

The RfD Peer Review Committee concluded (11/9/95) that sufficient information is available to determine that developmental toxicity was elicited by profenofos in these studies only at dose levels equal to or much greater than dose levels causing significant inhibition of cholinesterase activity in other studies. Therefore, additional developmental toxicity studies are not necessary since they would not contribute meaningful additional information to the toxicological assessment of profenofos.

#### f. Reproductive Toxicity

In a two-generation reproduction study (MRIDs 43213308 and 43213309), groups of CrI:CD<sup>®</sup>(SD) BRVAF/Plus<sup>™</sup> rats (30/sex/group) were continuously fed diets containing technical profenofos at 0, 5, 100, or 400 ppm (corresponding to 0, 0.36, 7.3, and 29 mg/kg/day, respectively).

In each generation, parental males and females were weighed weekly during the growth phase. Males were then weighed weekly until sacrifice. Females were weighed weekly during mating (until conception); on gestation days 0, 6, 13, and 20; and on postpartum days 0, 4, 7, 14, and 21. P<sub>0</sub> parental males were necropsied at 177-180 days of age following 134-137 days of dietary treatment. P<sub>0</sub> parental females were necropsied at 183-186 days of age following 140-143 days of dietary treatment.

Administration of the chemical at the stated doses had no effect on mating behavior, mean gestation length, numbers of litters with live pups, total numbers of pups born per litter, preweaning losses, number of live pups (on

lactational days 0, 7, 14, and 21), pup survival indices, external observations during lactation, or incidence of adverse observations during macroscopic examination of pups (dying during lactation/culled on day 4/weaned on day 21), or during histopathological examination of organs from high-dose (29 mg/kg/day diet) and control (0 mg/kg/day diet) P<sub>0</sub> and P<sub>1</sub> parental males and females.

The NOEL for parental systemic toxicity is 7.3 mg/kg/day (MDT) and the LEL is 29 mg/kg/day (HDT), based on decreased body weight (range: 4-11% decrease;  $p \leq 0.01$ ), and cumulative body weight gain (range: 6-16% decrease;  $p \leq 0.01$ ) in males and females of the P<sub>0</sub> and P<sub>1</sub> generations at all time periods throughout the study, and decreased food consumption (range: 7-15% decrease;  $p \leq 0.01$ ) for males and females of both generations during the growth (pre-mating) phase.

The NOEL for perinatal and reproductive effects is (7.3 mg/kg/day (MDT) and the LEL is 29 mg/kg/day (HDT), based on decreased pup (both sexes; both F<sub>1</sub> and F<sub>2</sub> litters) body weight (range: 2-9% decrease;  $p \leq 0.01$ ) and cumulative body weight gain (range: 3-10% decrease;  $p \leq 0.01$ ) measured *only* on days 14 and 21 of lactation.

#### g. Mutagenicity

In a bacterial/mammalian microsome reverse gene mutation assay (MRID 41866901), triplicate cultures of four Salmonella strains (TA100, TA1535, TA98, TA1537) and the WP2uvrA strain of Escherichia were exposed in independent replicate trials to concentrations of CGA-15324 technical (90.7% a.i.) up to the limit, 5000  $\mu\text{g}/\text{plate}$ , both in the absence and presence of a mammalian microsomal activation system (S9). No increases over solvent control in revertant colonies were observed in any strain treated at any concentration in either trial.

In an *in vitro* cytogenetic assay (MRID 41945103), cultures of Chinese hamster ovary cells were exposed for three hours to a series of technical (90.6% a.i.) profenofos doses (4.69 through 75  $\mu\text{g}/\text{mL}$ ), with and without a metabolic activation system, and microscope preparations of metaphase cells scored for chromosome aberrations 21 hours later. No aberrations were reported in any trial of the test article administered up to cytotoxic levels (37.5 to 75  $\mu\text{g}/\text{mL}$ ).

In an *in vivo* cytogenetic assay (MRID 41945102), male and female mice were gavaged orally with single doses of test article (profenofos technical 90.7% a.i.; 50, 100 or 200 mg/kg), and bone marrow cells prepared for

examining the presence of micronuclei in polychromatic erythrocytes (indirect evidence of chromosome breakage or non-disjunction) 16, 24 and 48 hours later. No induction of micronuclei was found, even at a dose causing death (200 mg/kg).

In an *in vitro* DNA damage/repair assay (MRID 41945101), primary rat hepatocyte cultures were exposed to 0.01, 0.12, 0.58 or 2.91  $\mu\text{g}/\text{mL}$  profenofos (91.8% a.i.) for five hours, and evidence of potential unscheduled DNA synthesis (UDS) ascertained autoradiographically by net nuclear silver grain counts. No increased grain count was found up to a dose producing 50% cytotoxicity (the HDT, 2.91  $\mu\text{g}/\text{mL}$ ).

In summary, profenofos was not shown to be mutagenic in any of the above assays.

#### **h. Metabolism**

In a metabolism study (MRID 42334301), the absorption, distribution, metabolism and elimination of profenofos were studied in groups of CD<sup>®</sup> rats administered a single oral dose of 1 or 100 mg/kg of (phenyl-UL-<sup>14</sup>C)-labeled pesticide, and in a second group of rats pre-exposed to non-radiolabeled profenofos (1 mg/kg oral gavage) daily for 14 days before being given a single oral dose of 1 mg/kg of [<sup>14</sup>C] profenofos.

Profenofos was rapidly and extensively absorbed through the gastrointestinal tract. Recovery of radioactivity ranged from 97% to 108% of the administered dose for combined fecal and urine samples, with >97% of the radioactivity excreted in the urine within 48 hours. Less than 0.2% of the <sup>14</sup>C was expired as volatiles. Insignificant amounts of the labeled compounds were retained in any tissue at seven days post-exposure. Analysis of fecal material indicated that <4% of the parent compound or its metabolites are unabsorbed or excreted via the biliary system into the intestinal tract.

Profenofos is absorbed into the circulation and appears to be metabolized by hydrolysis of its thiophosphate ester followed by dephosphorylation to form 4-bromo-2-chlorophenol (CGA-55960), which undergoes sulfate or glucuronide conjugation. Metabolites were identified as unconjugated 4-bromo-2-chlorophenol, CGA-47196, and CGA-65867. There were no apparent dose or sex-related differences in the absorption, distribution, metabolism, or excretion of profenofos administered orally to rats.

#### **i. Neurotoxicity**

i. Acute Neurotoxicity Study

In an acute neurotoxicity study in rats [MRIDs 42939801 (range-finding study) and 42939802 (main study)], profenofos (89.3% a.i.) was administered in a single gavage dose to Sprague-Dawley rats (10/sex/dose) at doses of 0, 95, 190, or 380 mg/kg in corn oil.

These rats were assessed for reactions in the functional observational battery (FOB), and motor activity measurements, at the predetermined estimated peak effect time of 5-6 hours postdosing, day 7, and day 14. An additional group of animals (5/sex/dose) were assessed for cholinesterase (AChE or ChE) inhibition at the peak effect time and on study day 14.

Neurotoxicity was observed only at the time of peak effect. At 190 mg/kg, males exhibited an increased incidence of staining of the nose and compulsive licking (stereotypy). Females at this dose exhibited an increased incidence of diarrhea, miosis, staining of the nose, abnormal gait, and increased ease of handling. Rats at 380 mg/kg also exhibited an increased incidence of salivation (females only), lacrimation, impaired respiration, soiled fur, ataxia, impaired righting reflex, impaired hindlimb extensor reflex (females only), flattened body position (females only), tremors, decreased arousal, decreased number of rears, dehydration, decreased core body temperature (females only), and decreased motor activity.

The LOEL for neurotoxicity was 190 mg/kg based on multiple effects in each sex. The NOEL for neurotoxicity was 95 mg/kg. Effects on serum ChE and RBC AChE were noted both at the time of peak effect and at day 14. At 95 mg/kg, serum ChE activity was inhibited 84% in males and 94% in females, and RBC AChE was inhibited 74% in males and 68% in females at time of peak effect. By day 14, serum ChE had returned to control levels at all doses and RBC AChE had returned to 41-75% of control. No effect on brain AChE was noted at day 14. The LEL for cholinesterase inhibition is 95 mg/kg (LDT), based on inhibition of serum ChE and RBC AChE. The NOEL for cholinesterase inhibition is <95 mg/kg.

ii. Subchronic Neurotoxicity Study

In a study designed to assess neurotoxicity resulting from subchronic exposure to profenofos (MRIDs 43213303 and 43213304), four groups of Sprague-Dawley rats (10/sex/group) were fed diets containing 0, 30, 135 or 600 ppm of technical profenofos, corresponding to 1.70, 7.7 or 36 mg/kg/day in males and 1.84, 8.4 or 37.9 mg/kg/day in females, for 13 weeks.



The rats were assessed daily for clinical signs, FOB, and motor activity effects. Plasma ChE and RBC AChE were assessed at 4, 8 and 13 weeks; neurohistopathological changes and brain AChE were assessed at 13 weeks. The study included acrylamide (16 mg/kg/day) and trimethyltin (3 mg/kg/day) as positive controls. No compound-related clinical signs, changes in the FOB motor activity parameters were reported at any dose level or time interval. There were no histopathological effects of profenofos noted. The positive controls acrylamide and trimethyltin produced the expected findings on motor activity and histopathology.

The NOEL for neurotoxicity is > 36 mg/kg/day (HDT). Profenofos decreased body weight gain slightly in both sexes in the high dose group (approximately up to 7% in males and 9% in females). The LEL for systemic toxicity is 36 mg/kg/day, based on slight decreases in body weight; the NOEL is 7.7 mg/kg/day. Profenofos inhibited ( $p < 0.01$ ) plasma ChE (58-61% in females and 28-31% in males) and RBC AChE (54 to 74% in males and 51 to 56% in females) at 1.7 and 1.84 mg/kg/day at each assay interval. Progressively higher degrees of inhibition were noted at higher dose levels. Brain AChE became significantly inhibited (12% males and 20% females;  $p < 0.01$ ) only at the high doses of 36 mg/kg/day for males and 37.9 mg/kg/day for females. The LEL for plasma ChE and RBC AChE is 1.7 mg/kg/day; no NOEL was established. The LEL for brain AChE is 36 mg/kg/day and the NOEL for brain AChE is 7.7 mg/kg/day.

### iii. Acute Delayed Neurotoxicity Study

In an acute delayed neurotoxicity study in hens using a 38% emulsifiable concentrate (44.3% a.i.) formulation of profenofos (MRID 00126485), no effects were noted at dose levels up to 52 mg a.i./kg of body weight, and 100% mortality occurred at the next highest dose (104 mg a.i./kg). Negative results for delayed neurotoxicity were also reported in two supplementary studies with technical grade profenofos (MRIDs 00082083 and 00082085).

## 2. **Dose/Response Assessment**

As part of the reregistration process, the Health Effects Division's Reference Dose (RfD) Committee met on November 9, 1995 to discuss the toxicological data for profenofos, and on January 16, 1996 the HED Toxicity Endpoint Selection (TES) Committee met to discuss the toxicological endpoints (other than Reference Dose) to be used in profenofos risk assessment and characterization.

On September 8, 1997, the Committee (now called the Health Effects Division's Hazard Identification Assessment Review Committee) met again to evaluate the toxicological data for profenofos with special reference to the reproductive, developmental, and neurotoxicity data. These data were re-reviewed specifically, as required by the Food Quality Protection Act (FQPA) of 1996, to address the potential for enhanced sensitivity of infants and children to profenofos exposure. FQPA requirements were not addressed in the 6/18/96 HED chapter for the Reregistration Eligibility Decision Document.

Following review on 9/8/97, the Hazard Identification Committee concluded that the additional 10x Uncertainty Factor (UF) to account for enhanced sensitivity of infants and children, as required by FQPA, should be removed. The existing UF of 100 (used to calculate the Reference Dose) is adequate to ensure protection of this population from exposure to profenofos since there was no indication of increased sensitivity to young animals following pre-and/or post-natal exposure to profenofos as shown by: 1) no increased sensitivity to fetuses as compared to maternal animals following *in utero* exposures in rats and rabbits in developmental toxicity studies; 2) no increased sensitivity to pups as compared to adults in a multi-generation reproduction study; and 3) an adequate toxicological database (no significant data gaps) exists in relation to infant and child sensitivity to profenofos.

2. Enhanced Sensitivity to Infants and Children

To assess the potential for enhanced sensitivity to profenofos in infants and children, the Committee re-reviewed the following studies (all studies are summarized above in the Hazard Assessment):

*Developmental toxicity:* 1) a developmental toxicity study in rats, and 2) a (supplementary) developmental study in rabbits.

*Reproductive toxicity:* 1) a two-generation reproduction study in rats.

*Neurotoxicity:* 1) an acute delayed neurotoxicity study in hens (and two supplementary studies), 2) an acute neurotoxicity study in rats, and 3) a subchronic neurotoxicity study in rats.

*Developmental Neurotoxicity:* The Committee also concluded (9/8/97) that sufficient data are available to adequately assess the potential for toxicity to young animals following pre-and/or post-natal exposure to profenofos. These include an acceptable developmental toxicity study in rats; a supplementary developmental toxicity study in rabbits; and an acceptable 2-generation reproduction study in rats. In addition, no treatment-related neuropathology was seen in studies conducted in hens or rats. Therefore, based on a weight-of-the-evidence consideration of the data base, the Committee determined that a

developmental neurotoxicity study is *not* required.

**a. Chronic Dietary Exposure / Reference Dose**

On November 9, 1995 the HED Reference Dose Peer Review Committee met to discuss and evaluate the existing and recently submitted toxicology data in support of profenofos reregistration and to reassess the RfD. At that time, the Committee recommended that the study on which the profenofos Reference Dose was based, and the Uncertainty Factor (100) remain unchanged (previous review on 3/3/87). The profenofos Reference Dose is based on plasma and red blood cell cholinesterase inhibition observed at 0.05 mg/kg/day (study LOEL) in a six-month dog study (MRID 00081687). The NOEL was 0.005 mg/kg/day (0.2 ppm). An Uncertainty Factor of 100 is applied to account for both interspecies extrapolation and intraspecies variability. On this basis, the RfD is calculated to be 0.00005 mg/kg/day (U.S. EPA, 1996b).

In 1990 the World Health Organization established an ADI of 0.01 mg/kg body weight/day for profenofos.

**b. Carcinogenic Classification**

The carcinogenic potential of profenofos was also evaluated by the RfD Peer Review Committee on November 9, 1995. The Committee recommended that profenofos be classified as a Group E chemical (i.e., not likely to be carcinogenic in humans via relevant routes of exposure) (U.S. EPA, 1996b). This weight-of-the-evidence judgment is largely based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies (rat: MRID 00081685; mouse: MRID 00082901). Carcinogenic risk assessment is *not required* for profenofos.

**c. Acute Dietary Exposure**

An endpoint and dose for the acute dietary risk assessment of profenofos has been established based on the results of the following non-guideline study:

In a two-phase study (MRID 43213302), a NOEL for acute toxicity and NOELs for cholinesterase inhibition in blood cells, plasma, and brains of male and female CrI:CD®BR VAF/Plus® rats were determined. In Phase One, groups of five males received a single oral dose of undiluted profenofos technical (89.2% a.i.) by gavage at dosage levels of 100, 200, 400, 600, or 800 mg/kg and groups of five female rats were similarly treated at dosage levels of 100, 200, 300, or 400 mg/kg.

Animals were observed for mortality, moribundity, and clinical signs for a 14-day period. Body weights were determined on Days 0, 7, and 14. Three males in the 800 mg/kg group were found dead (one on Day 1; two on Day 2); one male in the 600 mg/kg group was found dead on Day 5; and one female in the 400 mg/kg group died on Day 1. Surviving animals were subjected to gross necropsy at study termination (Day 14); others were necropsied on the day of death.

The NOEL for both males and females was determined to be 100 mg of profenofos technical/kg of body weight, based on clinical signs (soft stool, few feces) observed in both sexes at the next highest dose level (200 mg/kg). As noted below, cholinesterase inhibition (plasma, red blood cell, and brain) occurred at much lower dosage levels.

In Phase Two, 5 animals/sex/group were administered single oral gavage doses of corn oil containing profenofos technical (89.2% a.i.) at dosage levels of 0, 0.1, 0.5, 25, 100, or 400 mg/kg of body weight. Body weights were determined only prior to study initiation.

Animals were observed for mortality, moribundity, and clinical signs at 1, 2, and 4 hours post-treatment. At four hours post-treatment, animals were anesthetized, bled, and the brains flash-frozen for the determination of cholinesterase activities in red blood cells, plasma, and brain. All animals were subjected to gross necropsy, but no treatment-related findings were observed. The only clinical sign observed was soft feces. The NOEL for profenofos technical for plasma cholinesterase inhibition is 0.5 mg/kg in male rats and 0.1 mg/kg in female rats; the NOEL for inhibition of brain cholinesterase activity in both male and female rats is 25 mg/kg; and the NOEL for inhibition of red blood cell cholinesterase activity is 25 mg/kg for male rats and 0.5 mg/kg for female rats.

The TES Committee concluded that risk assessment for acute (one-day) dietary exposure to profenofos should be based on the NOEL of 0.5 mg/kg, which was based on statistically significant decreases in cholinesterase activities in plasma in both sexes and in red blood cells in females at 25 mg/kg (LOEL). The Committee's conclusion that a MOE of 10 (instead of the usual 100) is adequate for profenofos acute dietary exposure for all population groups is based on the following observations.

In setting the dose to be used for risk assessment on the above NOELs for statistically significant inhibition of plasma and red blood cell cholinesterase activities, a MOE of greater than 10 (actually a MOE of 16, as discussed below) is already applied with respect to doses of profenofos eliciting brain

cholinesterase inhibition (of greater toxicological concern) or adverse clinical signs. Therefore, this inherent MOE of 16 negates the need for the customary 10-fold MOE for intraspecies variation, leaving the customary MOE of 10 for interspecies variation as the appropriate one to apply for acute dietary exposure.

In the acute oral toxicity study described above (MRID 43213302), a profenofos dose of 25 mg/kg (LOEL) elicited statistically significant inhibition of plasma cholinesterase activity in both males and females, and red blood cell cholinesterase activity in males. On the other hand, a dose of 400 mg/kg (LOEL) was required to elicit statistically significant inhibition of brain cholinesterase activity in both sexes. Thus, a 16-fold higher dose of profenofos was required to cause inhibition of brain cholinesterase activity with respect to the dose required to inhibit plasma or red blood cell cholinesterase activity. Comparing the NOEL for statistically significant inhibition of plasma and brain cholinesterase activity in males and females (0.5 mg/kg) and the NOEL for inhibition of brain cholinesterase activity in both sexes (100 mg/kg), it is evident that the NOEL for inhibition of brain cholinesterase activity is 200-fold greater than the NOEL for inhibition of plasma or red blood cell activities. In this same study (MRID 43213302), adverse clinical signs were observed only at profenofos dose levels of 400 mg/kg (LOEL) and above [16 times the dose (LOEL) eliciting inhibition in plasma and red blood cells].

A similar difference in the dose of profenofos required to elicit inhibition of brain cholinesterase compared to the dose required to cause inhibition of plasma and red blood cell cholinesterase activities is demonstrated in the acute neurotoxicity study of profenofos in rats (MRID 42939801). At doses up to 380 mg/kg (highest dose tested), profenofos elicited no demonstrable effect on brain cholinesterase activity in either sex. However, at the lowest dose tested (95 mg/kg), statistically significant inhibition (68 to 94% inhibition) of red blood cell and plasma cholinesterase activities was observed in both males and females at the time of peak effect. Thus, much greater doses of profenofos were required to inhibit brain cholinesterase compared to the doses eliciting inhibition of both plasma and red blood cell cholinesterase activities.

Collectively, these data indicate that, with respect to acute oral exposures, much higher doses of profenofos are required to inhibit brain cholinesterase activity or cause adverse clinical signs than those required to inhibit plasma or red blood cell cholinesterase activities. Thus, the Committee recommended the use of a MOE of 10 (rather than the customary 100) for use in assessing the risk of acute dietary exposure because: 1) the NOEL selected for the endpoint was based on inhibition of plasma and red blood cell cholinesterase activities; 2) there is an inherent MOE of at least 16 between profenofos doses eliciting these two effects and doses causing inhibition of brain

cholinesterase activity; 3) use of the customary MOE of 10 for intraspecies variation is not required in view of this inherent MOE; and 4) use of the customary MOE of 10 for interspecies variation therefore provides a sufficient degree of protection.

It should be noted, however, that this relationship between doses of profenofos eliciting inhibition of cholinesterase activities in plasma and red blood cells to the much higher doses causing inhibition in brain apparently applies *only* to acute exposures. In a 21-day dermal toxicity study in rabbits (MRID 41644501), significant inhibition of plasma, red blood cell, and brain cholinesterase activities occurred at the same profenofos dosage level (LEL = 10 mg/kg/day).

#### **d. Short-term Occupational and Residential Exposure**

For the risk assessment of 1 to 7 day durations of *dermal* exposure to profenofos, the Toxicology Endpoint Selection Committee recommended (1/16/96) that the dose (NOEL) of 1 mg/kg/day from the 21-day dermal toxicity study in rabbits (MRID 41644501) be used. The endpoint was selected based on significant decreases in cholinesterase activities in red blood cells, serum, and the brain at the LOEL of 10 mg/kg/day. The Committee concluded that an MOE of 100 is adequately protective.

#### **e. Intermediate-Term Occupational and Residential Exposure**

For the risk assessment of one-week to several-month duration dermal exposure to profenofos, the Committee recommended that the dose (NOEL) of 1.0 mg/kg/day from the 21-day dermal toxicity study in rabbits (MRID 41644501) be used, with a required MOE of 100.

#### **Dermal Absorption**

In addition to the toxicological endpoints listed in Table 3, the TES Committee discussed the dermal absorption of profenofos and decided that, in the absence of specific data on the dermal absorption of profenofos, a dermal absorption of no greater than 50% should be assumed. This conclusion is based on the fact that the combined sex LD<sub>50</sub> value obtained in an acute oral toxicity study in rats (630 mg/kg; MRID 41714801) is approximately 39% of the combined sex LD<sub>50</sub> value obtained in an acute dermal toxicity study in the same species (1610 mg/kg; MRID 00105231), indicating that dermal absorption of profenofos is likely to be in the range of 39-50%.

#### f. Chronic Occupational and Residential Exposure

For the risk assessment of chronic (several-month to lifetime) dermal exposure to profenofos, the Committee recommended using a dose (NOEL) of 0.005 mg/kg/day from the six-month feeding study in dogs (MRID 000881687). This study and NOEL are also the basis for the (oral) Reference Dose. The Committee concluded that an MOE of 100 is adequately protective. *Dermal Exposure estimates should be adjusted by the 50% dermal absorption factor.*

#### g. Inhalation Exposure / All Durations

Risk assessment for inhalation exposure is based on dose levels established in the following study:

In a 21-day inhalation toxicity study in rats (MRID 00082079), groups (9/sex/group) were individually exposed to aerosols containing technical profenofos at 0, 68, 219, or 449 mg/m<sup>3</sup> (0, 0.068, 0.219, or 0.449 mg/L) for 6 hours/day, 5 days/week, for 3 weeks.

Four animals/sex/group were sacrificed at the end of the 21-day exposure period, and 4 rats/sex/group were observed during a 21-day post-treatment period and then sacrificed. Complete clinical observations were made daily; ophthalmological and food consumption data were collected weekly. Hematologic, urinalysis, and blood chemistry data were collected at the end of the 21-day treatment period and, in selected rats, at the end of the recovery period. Gross and microscopic pathology studies were conducted.

All rats of the high-dose group (0.449 mg/L) and one female of the mid-dose (0.219 mg/L) group died during the first week. Food intake of male rats of the mid-dose group decreased during the entire exposure period, while the weights of females of this group and all rats in the low-dose (0.068 mg/L) decreased during the first week of exposure only. Animals in the high-dose group lost weight until unscheduled death. Food intake and body weight gain of males in the mid-dose group, depressed during the exposure period, was comparable to controls by the end of the recovery period. Hematological and blood chemistry values of all treated animals were comparable to control values. However, the cholinesterase activities in plasma, red blood cells, and brain were significantly depressed (20% to 65% of control values) in all treated animals.

Thus, a NOEL for cholinesterase inhibition was not determined in this study. The most common gross observation in treated animals was acute congestion of the nasal mucous membrane and some intermittent or purulent keratitis in all rats at the highest test concentration in animals that died on the

3rd to 5th test day (this was confirmed by the microscopic histopathology). The LEL for ChE inhibition in brain, red blood cells, and plasma is 0.068 mg/L (LDT). The NOEL is <0.068 mg/L.

The TES Committee (1/16/96) recommended that, for the purpose of inhalation risk assessment, an endpoint (converted from an inhalation dose in mg/L to an oral dose in mg/kg/day) of 11.2 mg/kg/day (12.5 mg/kg/day for females) be used, based on the LEL of 0.068 mg/L which demonstrated inhibition of ChE activities in red blood cells, plasma, and the brain (NOEL not determined).

Table 3. Toxicological Endpoints for Profenofos

TYPE OF EXPOSURE (duration and route)	ENDPOINT (AND DOSE)
Acute Dietary (one day)	0.5 mg/kg [NOEL for inhibition of cholinesterase activities in plasma (males) and red blood cells (females) in a non-guideline acute oral toxicity study in rats (MRID 43213302)]. MOE: 10
Short-Term Occupational or Residential (one to seven days)	1.0 mg/kg/day [NOEL for significant decreases in cholinesterase activities in red blood cells, serum, and brain in a 21-day dermal toxicity study in rabbit (MRID 41644501)]. MOE: 100
Intermediate Term Occupational or Residential (one week to several months)	
Chronic (noncancer) Occupational or Residential	0.005 mg/kg/day [NOEL for inhibition of cholinesterase activities in plasma and red blood cells in a six-month feeding study in dogs (MRID 00081687)]. MOE: 100
Inhalation (any duration)	11.2 mg/kg/day for males and 12.5 mg/kg/day for females. These doses were calculated for route-to-route extrapolation based on the LEL of 0.068 mg/L [the lowest dose used in a 21-day inhalation toxicity study in rat (MRID 00082079)], which inhibited brain, red blood cell, and plasma cholinesterase activities.

### 3. Aggregate Exposure and Risk Assessment / Characterization

#### a. Food Sources

Profenofos is an insecticide-miticide used for the control of cotton bollworm, tobacco budworm, certain other insects, and mites on cotton. It is formulated as an emulsifiable concentrate (73% a.i.) and can be applied by groundboom sprayer, helicopter, and fixed-wing aircraft. The single registered end-use product is Curacron 8E Insecticide-Miticide (EPA Reg. No. 100-669; 72.7% a.i.).

EPA expects dietary exposure resulting from the use of profenofos since



cottonseed is processed into the commodities of cottonseed meal and oil. An indirect exposure to humans may also be due to the use of cottonseed by-products and gin trash as a ruminant feed item. As determined by the Hazard Identification Committee, dietary risk for profenofos is estimated for both acute (one-day ) and chronic (assumed lifetime) exposure durations.

### *Reregistration Background*

EPA completed the Profenofos Phase 4 Chemistry Review on 11/30/90. A Profenofos DCI Notice was subsequently issued 9/18/91. The Agency has conducted Phase 5 Review of residue chemistry studies that were submitted in response to the DCI as well as studies that were deemed acceptable for review during Phase 4. The information listed under "Summary of Science Findings" (below) outlines the Residue Chemistry Science Assessments with respect to the reregistration of profenofos. Provided in Appendix 2 is a listing of the data requirements, the current tolerances, and additional data needs.

Tolerances for residues of profenofos in/on plant, animal, and processed commodities are currently expressed in terms of profenofos and its metabolites converted to 4-bromo-2-chlorophenol and calculated as profenofos [40 CFR 180.404 and 40 CFR 186.4975]. Tolerances have been established for cottonseed at 3.0 ppm; eggs, poultry, and the fat, meat, and meat byproducts of cattle, goats, hogs, horses, and sheep at 0.05 ppm; and milk at 0.01 ppm. Feed additive tolerances have been established for cottonseed hulls at 6.0 ppm and soapstock at 15.0 ppm. The Pesticide Analytical Manual (PAM) Volume II lists two gas chromatography (GC) methods, Methods I and II, for the enforcement of tolerances (as currently expressed) for cottonseed and animal commodities, respectively. Codex Maximum Residue Limits (MRLs) have been established for plant commodities and animal products and are expressed in terms of profenofos *per se*. Provided in the "Risk Management and Reregistration Decision" section of this document are the Codex MRLs (see Table 9).

### *Summary of Science Findings*

#### i. Directions for Use

The Agency's Reference Files System Database identifies one profenofos end-use product, registered to ~~Giba-Geigy Corporation~~. The 8 lb/gal emulsifiable concentrate formulation (EC; EPA Reg. No. 100-669; Curacron® 8E Insecticide-Miticide) is a restricted-use pesticide registered for multiple foliar spray applications to cotton (label accepted 2/10/94). The label specifies 5 to 7 day retreatment intervals at 0.25 - 1.0 lb a.i./application. Applications may be made with profenofos alone or as a tank mix with other pesticides. Applications

*Novartis*

may be made by ground equipment with a minimum of 3 gals. of water/A) or by air with a minimum of 1 gal. of water/A. The label specifies a maximum seasonal rate of 6 lb a.i./A and a preharvest interval (PHI) of 14 days (or 30 days if mixed with oil).

*ULV Application:* Curacron 8E may be diluted with once-refined vegetable oil (1-2 qts. finished spray/A) for ULV application. Water may be added for application in a minimum of one gal. of finished spray/A. When oil is used, a maximum of three applications may be made per growing season with a PHI of 30 days.

The label restricts the feeding of gin trash or foliage from treated cotton plants to livestock and specifies that fields treated with the 8 lb/gal EC formulation may be rotated to other crops.

*Required label amendments:* The restriction against the feeding of cotton gin trash is now considered impractical and should therefore be removed from the label. Since adequate confined rotational crop studies have not been submitted, the following statement must be added to the product label: "Fields grown to cotton and treated with profenofos should be rotated to cotton only." Currently, the label allows aerial application in a minimum of 1 gal. of water/A. Unless field residue data reflecting aerial applications in  $\leq 1$  gal. of water/A with a 14-day PHI are submitted, the product label must be amended to specify that aerial applications be made in a minimum of 2 gal. of water/A.

#### ii. Nature of the Residue - Plants

The qualitative nature of the residue in plants is adequately understood based on studies depicting the metabolism of profenofos in cotton following foliar treatment. Profenofos is metabolized in plants primarily to a glucosyl sulfate conjugate of 4-bromo-2-chlorophenol. Profenofos *per se* and the glucosyl sulfate conjugate of 4-bromo-2-chlorophenol are the predominant residues of profenofos in plants.

The Health Effects Division (HED) Metabolism Committee (now called the Metabolism Assessment Review Committee) concluded (7/28/95) that profenofos *per se* is the compound of toxicological concern in plants. The current tolerance expression is for the combined residues of profenofos and its metabolites converted to 4-bromo-2-chlorophenol and calculated as profenofos. The tolerance expression should be revised to reflect that profenofos *per se* is the only regulated residue.

#### iii. Nature of the Residue - Livestock

The qualitative nature of the residue in animals is adequately understood based on the results of acceptable ruminant and poultry metabolism studies. The HED Metabolism Committee concluded (7/28/95) that profenofos *per se* is the compound of toxicological concern in milk and livestock tissues. The Committee also concluded there is no reasonable expectation of finite residues of profenofos in poultry tissues and eggs. Residues of profenofos were not present in any of the poultry tissues analyzed (meat, fat, and eggs), even at exaggerated dosing levels. Thus, there is presently no need for tolerances for residues of profenofos in poultry tissues and eggs.

#### iv. Residue Analytical Methods

The requirements for residue analytical methods are fulfilled for the purposes of reregistration. Acceptable methods are available for enforcement and data collection purposes for both plant and animal commodities.

PAM (Volume II) lists Methods I and II for the enforcement of tolerances for profenofos residues of concern in/on plant and animal commodities, respectively. These methods determine combined residues of profenofos and its metabolites converted to 4-bromo-2-chlorophenol and calculated as profenofos. Because profenofos *per se* is now the residue of concern, the PAM Volume II methods are no longer suitable for enforcement purposes. EPA recommends that the primary enforcement methods be FDA multi-residue protocol methods D and E (PAM Volume I, Sections 302, 303 and 304); profenofos is adequately recovered using these methods. The data collection methods for profenofos in plant (Ciba-Geigy AG-282) and animal (Ciba-Geigy AG-297) commodities will be submitted to FDA as confirmatory (lettered) methods for inclusion in PAM Volume II. Independent laboratory and EPA method validation are not required for these confirmatory methods.

#### v. Multiresidue Methods

The FDA PESTDATA database dated 1/94 (PAM Volume I, Appendix I) indicates that profenofos is completely recovered (> 80%) using multiresidue method Section 302 (Luke method; Protocol D) and partially recovered (50 - 80%) using Sections 303 (Mills, Olney, Gaither method; Protocol E, nonfatty) and 304 (Mills fatty food method; Protocol E, fatty).

#### vi. Storage Stability

Adequate storage stability data are available to support the established tolerances. For *plant commodities*, storage stability studies have been submitted demonstrating that weathered residues of profenofos are stable for up to nine

months of frozen storage in cottonseed, but decline 30% after 14 months and 40% after 24 months of frozen storage. Samples of cottonseed that were used for tolerance reassessment were stored for less than nine months. For *processed commodities*, storage stability studies have been submitted that demonstrate weathered residues of profenofos are stable for up to 24 months of frozen storage in cottonseed hulls, crude oil, and soapstock. For *animal commodities*, storage stability studies have been submitted that demonstrate that fortified residues of profenofos are stable for up to 12 months in frozen beef muscle, liver, and milk.

vii. Crop Field Trials

The reregistration requirements for magnitude of the residue in/on cottonseed and cotton gin byproducts are fulfilled. Adequate field trial data, reflecting use of the registered EC formulation at the maximum registered use patterns, have been submitted for cottonseed and cotton gin byproducts. Based on the available data and the Metabolism Committee decision regarding the residues to be regulated, HED recommends that the established tolerances for cottonseed be lowered from 3 ppm to 2 ppm.

Data requirements for magnitude of the residue in/on cotton gin byproducts have been fulfilled. Additional data are not required. An additional tolerance *must* be proposed for cotton gin byproducts at 55 ppm.

vii. Processed Food/Feed

The reregistration requirements for magnitude of the residue in processed cottonseed commodities are fulfilled. An acceptable cottonseed processing study has been submitted; residues of profenofos *per se* were observed to concentrate marginally (1.4x) in cottonseed hulls, and no concentration of residues was observed in cottonseed meal and refined, bleached, and deodorized oil.

Based on the HED Metabolism Committee decision (7/28/95) regarding the residues to be regulated, the Agency concludes that a separate Section 408 tolerance for cottonseed hulls is not warranted. The expected residue level of profenofos in cottonseed hulls is less than the reassessed RAC tolerance (2 ppm). Therefore, the established feed additive tolerance of 6 ppm for cottonseed hulls should be revoked. The established feed additive tolerance of 15 ppm for soapstock should also be revoked since this commodity is no longer considered a significant feed item (Pesticide Assessment Guidelines Subdivision O, Table 1; August 1996).

ix. Residue in Meat, Milk, Poultry, and Eggs

There are no registered direct treatments for profenofos on cattle, goats, hogs, horses, sheep, or poultry. Reregistration requirements for magnitude of the residue in meat, milk, poultry, and eggs are fulfilled. Acceptable animal feeding studies have been conducted with dairy cows and laying hens. Based on the results of these feeding studies, animal metabolism studies, and the HED Metabolism Committee decision (7/28/95) regarding residues to be regulated, the Agency has reassessed the established tolerances for animal commodities.

The established tolerances for the fat, meat, and meat byproducts of cattle, goats, hogs, horses, and sheep (0.05 ppm) and for milk (0.01 ppm) are adequate but should be redefined in terms of profenofos *per se*. The HED Metabolism Committee concluded there is no reasonable expectation of finite residues of profenofos in poultry tissues and eggs. The established 40 CFR 180.404 tolerances for eggs and poultry fat, meat, and meat byproducts should be revoked. These commodities will be considered under 40 CFR 180.6(a)3 (Category 3). However, if additional uses of profenofos that would result in a higher poultry dietary intake (burden) are registered in the future, then tolerances for poultry tissues and eggs may be required.

x. Residue in Water, Fish and Irrigated Crops

Profenofos is presently not registered for direct use on water and aquatic food and feed crops. No residue chemistry data are required under these guideline topics.

xi. Residue in Food-Handling Establishments

Profenofos is presently not registered for use in food-handling establishments. No residue chemistry data are required under this guideline topic.

xii. Confined Accumulation in Rotational Crops

A new confined rotational crop study is required; this requirement should not impinge on the reregistration eligibility decision for profenofos, provided that the registrant amends the product label for the 8 lb/gal EC formulation to add a rotational crop restriction (see "GLN 171-3: Directions for Use"). The Agency has evaluated all available confined rotational crop studies and found them to be deficient because: application rates were < 1x the maximum registered rate; no residue identification/characterization was performed; and supporting storage stability data were not provided. Once the

required confined rotational crop study has been submitted and evaluated, the need for limited and/or extensive field rotational crop studies will be examined, and the appropriate plantback interval restrictions will be determined.

xiii. Anticipated Residue and Percent Usage Estimates

Profenofos tolerances are published in 40 CFR 180.404 and 186.4975 for cottonseed at 3 ppm; the fat/meat/meat byproducts of cattle, goats, hogs, horses, and sheep at 0.05 ppm; milk at 0.01 ppm; and eggs/poultry at 0.01 ppm. Dietary risk estimates based on the above tolerances and an assumption of 100% use on cotton (termed a Theoretical Maximum Residue Contribution, or TMRC) greatly exceed 100% of the profenofos Reference Dose.

Consistent with HED guidance, a refinement of the *chronic* dietary risk assessment for profenofos has been made by using percent crop treatment data and residue data (cottonseed processing and ruminant/poultry feeding studies) to estimate anticipated residues.

The chronic dietary risk estimates in this assessment are based, in part, on the current Agency (A. Grube memo, 10/15/97) estimate of 25% use of profenofos on total cotton acres. Percent crop treated estimates are derived from federal and private market survey data. Typically, a range is assumed for the estimate and the upper-end of this range is used for risk assessment. By using this upper-end estimate of percent crop treated, the Agency is reasonably certain that exposure is not underestimated for any significant population subgroup. Additionally, the HED Dietary Risk Evaluation System (DRES) program uses regional (northeast/ southern/western/north-central) consumption information to estimate chronic dietary risk. The estimated profenofos exposure was not significantly greater in these areas than exposure estimated for the overall U.S.

To provide for the periodic evaluation of these estimates of percent crop treated, the Agency will require under Section 408(b)(2)(F) percent crop treated data to be submitted every 5 years as long as the tolerances remain in force.

The chronic dietary risk estimates of the ~~HED RED~~ chapter of June, 1996 were based on the anticipated residue estimates of the ~~C. Olinger memo of 9/12/90 to the Special Review and Reregistration Division~~. In this memo, A review was made of previously submitted processing studies in cottonseed, and livestock feeding studies (and an estimate of 7% crop treated was used). The anticipated residue estimates were 0.025 ppm (one-half the limit of determination) in cottonseed oil, 1.6 ppm in cottonseed meal (measured in the

1x processing study), 0.0002 ppm in ruminant meat, 0.0002 pm in ruminant fat, 0.002 ppm in ruminant byproducts, and 0001 ppm in milk. This review also estimated residues of 0.002 ppm in eggs and poultry commodities.

The above anticipated residue estimates were rereviewed as part of the reregistration/tolerance reassessment process (C. Eiden memo 4/11/96). This review concluded that the residue estimates for cottonseed commodities and ruminant commodities were still appropriate, but that poultry commodities could be excluded from tolerances and risk assessment since data indicate no finite residues will occur. However, since the percent crop treated estimate was revised from 7 to 25%, and new guidance directs the inclusion of cotton gin trash in the "dietary burden", it became necessary to reassess dietary exposure. A rereview (J. Garbus, 10/21/97) based on this new information indicates that the anticipated residue levels in ruminant kidney should be revised to 0.39 ppm (and tolerance for meat byproducts revised to 0.4 ppm). The revisions outlined above resulted in a slight reduction of the estimated exposure and risk of all population groups.

To provide for the periodic evaluation of these anticipated residues, the Agency will require under Section 408(b)(2)(E) residue data to be submitted every 5 years as long as the tolerances remain in force.

A summary of the residue information used in the dietary risk assessment is provided in Table 1 of Appendix 4 (U.S. EPA, 1996c). A summary of dietary exposure estimates is provided in Table 2 of Appendix 4 (U.S. EPA, 1996c).

#### **b. Drinking Water Sources**

No Maximum Contaminant Level (MCL) or Health Advisory Level (HAL) has been established for profenofos. Water supply systems are not required to analyze for its presence and there are presently no Agency requirements for surface or groundwater monitoring. However, the following information has been used to satisfy the FQPA requirement that all *possible* routes of exposure be evaluated to determine aggregate exposure to profenofos.

##### **i. Potential Ground Water Contamination**

The Environmental Fate and Effects Division (EFED) has drawn the following conclusions regarding the potential for profenofos groundwater contamination; 1) laboratory mobility data indicate profenofos is not likely to leach to groundwater under normal use (a confirming terrestrial field dissipation study is needed); 2) the mobility and leaching potential of the degradates is

unknown; and 3) profenofos was not detected in any of the 188 wells sampled in a Texas study (1987-88).

## ii. Potential Surface Water Contamination

The potential for profenofos to contaminate surface water was also addressed in the EFED chapter for the Reregistration Eligibility Document. Specifically, the Agency does not have data on the concentrations of profenofos in surface water, and no entries for profenofos in surface water were found in the STORET Database.

However, profenofos can contaminate surface water at application via spray drift and through rainstorm runoff following application. Substantial fractions of applied profenofos should be available for runoff for only a few days however because of its relatively rapid dissipation in soil. The persistence of profenofos in the water column may vary substantially depending on the pH, microbiological activity, and the hydrologic residence time of the water body. The major primary degradates of profenofos under both aerobic and anaerobic conditions in soil are 4-bromo-2-chlorophenol and O-ethyl-S-propyl phosphorothioate. A major secondary degradate under aerobic/anaerobic conditions is 4-bromo-2-chlorophenyl ethyl ether. A major tertiary degradate under anaerobic conditions is cyclohexadienyl sulfate.

For the purpose of estimating risk to *aquatic organisms*, EFED has modeled the fate of profenofos in surface water with the PRZM 2.3 and EXAMS II computer programs. The intended site was a silt loam soil in Mississippi, modeled to represent a reasonable high-runoff and high-erosion scenario over a 36-year period, in an area where cotton is grown. The model assumes a 10 hectare cotton field draining into a body of water with a 1 hectare surface and 2 meters deep. For the profenofos loaded into the body of water, 84% was transported as spray drift and 16% in runoff water (15% dissolved and 1% adsorbed to particles).

The models have estimated a one in 10 year *peak* concentration of 5.9 ug/L and an *annualized* concentration 0.1 ug/L.

As noted above, the Agency models pesticide contamination of surface waters to assess risk to aquatic organisms. The results of the above model are not intended to be, and are not considered by the Agency to be an accurate representation of the levels that might be found in drinking water derived from surface water sources. A number of factors such as dilution (with other sources) and treatment are not factored into the modeled estimates. However, at this time, the Agency is using GENEEC and PRZM-EXAMS estimates as an



upper-end (Tier 1) screening method similar to the use of TMRC (tolerances and 100% crop treated) exposure estimates as a food source screening method.

### c. Residential Sources

There are no profenofos uses in or around homes, offices, etc. This potential source can be excluded from aggregate profenofos exposure/risk assessment.

### d. Aggregate Risk Assessment/Characterization

Dietary (food and water) risk for profenofos is assessed both for acute (one-day) exposure and chronic (assumed life-time) exposure. To assess *acute* dietary risk from *food* sources, the DRES program calculates exposure based on both upper-end food consumption and residue estimates, and then compares these estimates to the appropriate dose (typically a NOEL), with risk expressed as a Margin-of-Exposure (the ratio of exposure to endpoint). The acute analysis estimates the distribution of single-day exposures for the overall U.S. population and four population subgroups (males 13+yrs, females 13+yrs, infants < 1 yr, and children 1-6 yrs). The analysis is based on individual food consumption as reported by respondents in the USDA 1977-78 Nationwide Food Consumption Survey. To assess acute dietary risk from *water* sources, the best estimate available (in this case the PRZM-EXAMS estimate of 5.9 ug/L) of peak contamination is used with default drinking water consumption estimates (2 liter/day-adult, 1 liter/day-child).

To assess chronic risk, the DRES program calculates exposure based on averaged food consumption estimates and on tolerances and/or appropriate anticipated residue estimates. Chronic risk is expressed as a percent of the Reference Dose and is estimated by the DRES system for the General (Overall) U.S. population and 22 population sub-groups, including infants and children (which typically demonstrate the highest exposure). Chronic drinking water risk estimates are based on long-term (annualized) contamination estimates and the default assumptions of 2 liters/day for a 70 kg adult male or 60 kg female, and 1 liter/day for a 10 kg child.

#### i. Acute Dietary Risk Estimates

The profenofos acute analysis in this review is considered an upper-end estimate (Tier 1) since it has included all published uses of profenofos (even those commodities that are being recommended for revocation). Also, residues in assessed commodities are assumed to be at tolerance level and percent crop treated data is not factored in.

The Margin of Exposure for each population group was calculated by dividing the profenofos acute dietary dose (0.5 mg/kg/day) by the DRES exposure estimate. The DRES program, based on the above assumptions, estimates Margins of Exposure no lower than 250 (0.002 mg/kg/day) for any population group (see Table 4 of Appendix 4). Since the exposure estimates are considered upper-end, no further analysis is considered necessary at this time by the Agency.

The MOE estimate for acute drinking water risk, based on the modeled peak contamination level of 5.9 ug/L, is > 800 (children or adults).

ii. Chronic Dietary Risk

*Food Sources*

DRES assessments for chronic profenofos exposure are based on both profenofos tolerances and on the more refined estimates termed "anticipated residues". A summary of tolerances, anticipated residues and percent crop treated is provided in Table 1 of Appendix 4. Provided in Table 2 of Appendix 4 are the percent RfD (TMRC and ARC) values for the U.S. general population and 22 population sub-groups.

The following table summarizes dietary risk assessment for profenofos *excluding* exposure due to water contamination. The MOE estimates for acute exposure are based on tolerance level residues and an assumption of 100% crop treated. The percent RfD estimates are based on crop treatment data and anticipated residues as discussed above (and are not considered an upper-end estimate).

Table 4. Acute and Chronic Dietary Risk Evaluation for Profenofos (Food Sources Only)

POPULATION SUBGROUP	MOE (Acute)	%RfD (Chronic - noncancer)
General U.S. Population	333	4

Table 4. Acute and Chronic Dietary Risk Evaluation for Profenofos (Food Sources Only)

Infants (< 1 year)	250	15
Children (1-6 years)	250	11
Females (13+ years)	500	3
Males (13+ years)	500	4

*Drinking Water Sources*

For drinking water *only*, based on surface water contaminated with profenofos at the estimated annualized level of 0.1 ug/L are: <25% RfD for infants/children; and <10% RfD for male/female adults.

*Aggregate Risk: Conclusions*

*Acute:* The Agency, following rereview by the HED Hazard Identification Assessment Review Committee (memo final 9/25/97), considers an estimated Margin of Exposure of 10 to be adequate protection concerning acute dietary exposure estimates for profenofos. The Margins of Exposure estimated by the Agency for profenofos in *food*, as outlined above in Table 4, are 250 for infants and children and are, in turn, based on upper-end residue and upper-end food consumption estimates. Acute exposure and risk due to *drinking water* contaminated at the level modeled as a 10-yr peak, does not add significantly to the food source exposure (and also is considered an upper-end estimate). The Agency concludes that there is a reasonable certainty that no harm will result to infants, children, or any significant population sub-group from acute dietary exposure to profenofos.

*Chronic:* The Agency considers chronic dietary exposure to profenofos to be without significant concern for the general U. S. population (or any population sub-group such as infants and children) if the estimated exposure does not equal or exceed 0.00005 mg/kg/day (the RfD). Estimated chronic dietary risk for profenofos in *food* does not exceed 15 percent of this RfD, including infants which are estimated to be the most highly exposed. Chronic exposure due to *drinking water* contaminated at the modeled annualized level does not add significantly to the food source exposure estimate (and is considered an upper-end estimate). The Agency concludes that there is a reasonable certainty that no harm will result to infants, children, or any significant population sub-group from chronic exposure to profenofos.

## Endocrine Disruptor Effects

EPA is required to develop a screening program to determine whether certain substances (including all pesticides and inert) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect..." The Agency is currently working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists in developing a screening and testing program and a priority setting scheme to implement this program. Congress has allowed 3 years from the passage of FQPA (August 3, 1999) to implement this program. At that time, EPA may require further testing of profenofos and associated end use products for endocrine disruptor effects.

## Cumulative Risk

Profenofos is a member of the phenyl organophosphate class of pesticides. Other members of this class include methyl parathion, ethyl parathion, and coumaphos.

Section 408(b)(2)(D)(v) of the Food Quality Protection Act requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity". The Agency believes that "available information" in this context might include not only toxicity, chemistry, and exposure data, but also scientific policies and methodologies for understanding common mechanisms of toxicity and conducting cumulative risk assessments. For most pesticides, although the Agency has some information in its files that may turn out to be helpful in eventually determining whether a pesticide shares a common mechanism of toxicity with any other substances, EPA does not at this time have the methodologies to resolve the complex scientific issues concerning common mechanism of toxicity in a meaningful way. EPA has begun a pilot process to study this issue further through the examination of particular classes of pesticides. The Agency hopes that the results of this pilot process will increase the Agency's scientific understanding of this question such that EPA will be able to develop and apply scientific principles for better determining which chemicals have a common mechanism of toxicity and evaluating the cumulative effects of such chemicals. The Agency anticipates, however, that even as its understanding of the science of common mechanisms increases, decisions on specific classes of chemicals will be heavily dependent on chemical-specific data, much of which may not be presently available.

Although at present the Agency does not know how to apply the

information in its files concerning common mechanism issues to most risk assessments, there are pesticides as to which the common mechanism issues can be resolved. These pesticides include pesticides that are toxicologically dissimilar to existing chemical substances (in which case the Agency can conclude that it is unlikely that a pesticide shares a common mechanism of activity with other substances) and pesticides that produce a common toxic metabolite (in which case common mechanism of activity will be assumed).

HED does not have, at this time, available data to determine whether profenofos has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For the purposes of reregistration therefore, HED has not assumed that profenofos has a common mechanism of toxicity with other substances.

### **Epidemiological Information (U.S. EPA, 1996a)**

EPA obtained incident information concerning profenofos from two sources: the Office of Pesticide Programs (OPP) Incident Data System (IDS) and Poison Control Centers (PCC). The IDS contains reports of incidents from various sources including registrants, other federal and state health and environmental agencies, and individual consumers, going back to 1992. The PCC data was obtained as a result of a Data Call-In (DCI) Notice that was issued in 1993. Accordingly, the Agency received PCC data covering the years 1985 through 1992 for 28 organophosphate and carbamate chemicals, including profenofos.

#### *IDS Data*

Two cases reported to the IDS involved three men who developed systemic signs of illness after handling mixtures of pesticides, which included profenofos. Another case involved an unknown number of sick and dead Holstein cows on a dairy farm. The owner of the farm claimed that an aerial application of the chemical was made too near to the premises. High levels of profenofos were found near pasture grass, but none was found in the tissues of an animal at necropsy.

#### *PCC Data*

There were a total of eight cases of occupational exposure to profenofos reported to the PCCs; three involved exposure to profenofos alone and five involved exposure to multiple chemicals, including profenofos. In addition, there was a total of 15 non-occupational exposures (i.e., workers indirectly exposed); four involved profenofos only and 11 were attributed to multiple

chemicals.

In conclusion, the number of cases of poisonings reported to the National PCCs for profenofos was very low in comparison to the other 27 organophosphate and carbamate pesticides involved in the DCI. Further analysis of the cases (handlers and workers indirectly exposed) showed that 100% of the exposures to profenofos alone resulted in symptoms. With multiple chemical exposures in a non-occupational setting, 90.7% resulted in symptoms. While these percentages seem very high, it should be noted that they are based on a low number of cases and therefore, are unlikely to be reliable.

#### 4. Occupational Exposure and Risk Assessment/Characterization

##### a. Occupational Exposure

An occupational risk assessment is required for profenofos since there is potential exposure to workers during treatment (mixers/loaders/applicators), and to workers (scouts/harvesters/hoers) entering treated sites post-application.

At this time all products containing profenofos are intended *only* for use on cotton. The Agency expects that, based on the cotton use patterns, worker exposure to profenofos will be short to intermediate in duration (chronic exposure is not expected), and exposure will occur via both the dermal and inhalation routes. Based on the profenofos toxicity endpoints and doses for risk assessment, the Agency is characterizing loader and applicator risk by the Margin of Exposure approach and characterizing re-entry worker risk by the required duration of the restricted entry interval (REI).

##### i. Application Exposure

During the Phase IV review (1/21/91 by W. Dang) EPA required the registrants to submit applicator exposure data in support of profenofos reregistration. Instead of submitting chemical-specific data, the registrant conducted a surrogate assessment using the Pesticide Handlers Exposure Database (PHED) Version 1.01.

The following is a summary of the Agency's review of the registrant's submission titled: *"Assessment of Worker Exposure for the Profenofos EC Formulation Using the Pesticide Handlers Exposure Database"* (EPA MRID 426288-01). PHED Version 1.01 was used to estimate the dermal and inhalation exposure resulting from the use of the emulsifiable concentrate formulation of profenofos. The study investigated mixer/loader, aerial

(38)

applicator and groundboom applicator exposure. The results indicated that the mixer/loaders for aerial applications had a daily dose of 63  $\mu\text{g}/\text{kg}/\text{day}$ . For pilots (aerial applicators) the daily dose was determined to be 73  $\mu\text{g}/\text{kg}/\text{day}$ . For groundboom applicators, the daily dermal dose was estimated to be 48  $\mu\text{g}/\text{kg}/\text{day}$ .

Subsequent to the above submission, a new version (V1.1) of PHED was developed and used by the Agency. For this risk assessment, the Agency reassessed profenofos mixer/loader/applicator exposure using the new version. The resultant exposure estimates are significantly different from those provided by the registrant. These differences are attributed to: (1) the registrant's submission is based on PHED V1.01 while EPA's assessment is based on PHED V1.1; (2) the registrant and EPA used different assumptions (i.e., number of acres treated/day; etc.); and, (3) the registrant used different clothing scenarios.

The Agency identifies five major exposure scenarios based on the use patterns of profenofos: (1a) mixing/loading liquid formulations for aerial equipment; (1b) mixing/loading liquid formulations for ground equipment; (2) applying the liquid formulation using a helicopter (enclosed cockpit); (3) applying the liquid formulation using fixed wing aircraft (enclosed cockpit); (4) applying the liquid formulation using a groundboom sprayer; and (5) flagging during aerial application of liquids.

Potential dermal and inhalation baseline unit exposures (derived from PHED V1.1), along with their corresponding calculated daily exposures, are presented in Table 5. Baseline unit exposure is the PHED exposure estimate with just the clothing scenario that was provided in the PHED data base (i.e., the baseline clothing).

Please note that estimated dermal exposure is several orders of magnitude greater than estimated inhalation exposure. Typical (350) and maximum (800) "Daily Acres Treated" are provided for fixed-wing aerial applications because, depending on the size and capacity of individual planes, there is a significant range of acreage that can be treated in a single day.

Potential Daily Exposure is calculated using the following formula:

$$\text{Daily Exposure} \left( \frac{\text{mg}}{\text{Day}} \right) = \text{Unit Exposure} \left( \frac{\text{mg}}{\text{lb. a.i.}} \right) \cdot \text{Appl. Rate} \left( \frac{\text{lb. a.i.}}{\text{Acre}} \right) \cdot \text{Area Treated} \left( \frac{\text{Acres}}{\text{Day}} \right)$$

Provided in Appendix 3 are the caveats and parameters specific to each exposure scenario.

ii. Post-Application Exposure

Based on the use patterns of profenofos, EPA has determined that there is potential exposure to workers (harvesters/hoers/scouts) entering treated sites after application is complete.

The registrant submitted post-application profenofos exposure data in response to the data requested by the Agency during Phase 4 of the reregistration process. Two foliar dissipation (dislodgeable residue) studies (Study 1 and Study 2 below) and one worker re-entry study (Study 3 below) using profenofos were submitted.



Table 5. Profenofos Baseline Unit Exposures and Daily Exposures (Short and Intermediate-Term)

EXPOSURE SCENARIO (Number)	BASELINE DERMAL UNIT EXPOSURE (mg/lb a.i.) <sup>a</sup>	BASELINE INHALATION UNIT EXPOSURE (mg/lb a.i.) <sup>b</sup>	APPLICATION RATE (lb a.i./A) <sup>c</sup>	DAILY ACRES TREATED <sup>d</sup>	DAILY DERMAL EXPOSURE (mg/day) <sup>e</sup>
<b>Mixer/Loader Exposure</b>					
Mixing/Loading Liquid Formulations for Aerial Equipment (1a)	2.9	$1.2 \times 10^{-3}$	1	Typ: 350 Max: 800	Typ: 1015 Max: 2320
Mixing/Loading Liquid Formulations for Groundboom Equipment (1b)				80	232
<b>Applicator Exposure</b>					
Applying the Liquid Formulation Using a Helicopter (enclosed cockpit) (2)	$2 \times 10^{-3}$	$2 \times 10^{-6}$	1	350	0.7
Applying the Liquid Formulation Using a Fixed-Wing Aircraft (enclosed cockpit) (3)	$5 \times 10^{-3}$	$7 \times 10^{-5}$	1	Typ: 350 Max: 800	Typ: 1.75 Max: 4
Applying the Liquid Formulation Using a Groundboom Sprayer (4)	$1 \times 10^{-2}$	$7 \times 10^{-4}$	1	80	0.8
<b>Flagger Exposure</b>					
Flagging During Aerial Application of Liquids (5)	$1 \times 10^{-2}$	$3 \times 10^{-4}$	1	Typ: 350 Max: 800	Typ: 3.5 Max: 8

**NOTES:**

<sup>a</sup>Baseline dermal unit exposure (from PHED V1.1) represents long pants, long sleeve shirts, no gloves, open mixing/loading, enclosed cockpit (no data available for open cockpits), open cab tractor.

<sup>b</sup>Baseline inhalation unit exposure (from PHED V1.1) represents no respirator.

<sup>c</sup>Application rate based on values found in EPA label Reg. No. 100-669.

<sup>d</sup>Acres treated values are from EPA estimates of acreage that could be treated in a single day for each exposure scenario of concern.

<sup>e</sup>Daily dermal exposure (mg/day) = Unit Exposure (mg/lb a.i.) \* Application Rate (lb a.i./A) \* Acres treated/day.

Daily inhalation exposure (mg/day) = Unit Exposure (mg/lb a.i.) \* Application Rate (lb a.i./A) \* Acres treated/day.

<sup>f</sup>Total daily exposure (mg/day) = Daily dermal exposure (mg/day) + Daily inhalation exposure (mg/day).

41

*Study 1. Dissipation of Dislodgeable Foliar Residues of Profenofos (Curacron® 8E) Applied to Cotton, Texas (MRID 428513-04)*

The test site was in Burlington County, TX. Curacron® 8E was applied to cotton at an application rate of 1.0 lb a.i./A. In total, six applications were made for a total of 6.0 lb a.i./A. The applications were made on July 8, 13, 18, 23, 28 and August 2, 1991. Application was made with a tractor-drawn groundboom sprayer. The first samples were collected after the sixth (i.e., final) application, day after treatment (DAT) 0 after sprays had dried. On DAT 0 the mean residues were 1.95  $\mu\text{g}/\text{cm}^2$  and by DAT 35 the residues were 0.01  $\mu\text{g}/\text{cm}^2$ .

*Study 2. Dissipation of Dislodgeable Foliar Residues of Profenofos (Curacron® 8E) Applied to Cotton in California (EPA MRID 428513-03)*

The test site was in Madera, CA. Curacron® 8E was applied to cotton at an application rate of 1.0 lb a.i./A. In total, six applications were made for a total of 6.0 lb a.i./A. The applications were made on July 24, 29, August 3, 8, 13, and 19, 1991. Application was made with a commercial cotton sprayer. The first samples were collected after the sixth (i.e., final) application, day after treatment (DAT) 0 after sprays had dried. On DAT 0 the mean residues were 1.4  $\mu\text{g}/\text{cm}^2$  and by DAT 35 the residues were 0.0088  $\mu\text{g}/\text{cm}^2$ .

*Study 3. Worker Reentry Exposure to Profenofos in Cotton Treated With Curacron® 8E (MRID 428513-02)*

The first DFR test site was in Cheraw, SC. Curacron® 8E was applied to cotton at an application rate of 1.0 lb a.i./A. In total, six applications were made for a total of 6.0 lb a.i./A. The applications were made on August 11, 18, 25, and 31 and September 6, and 11, 1992. Application was made with a tractor-drawn groundboom sprayer. The first samples were collected after the sixth (i.e., final) application, days after treatment (DAT) 0 after sprays have dried. On DAT 0 the mean residues were 2.7  $\mu\text{g}/\text{cm}^2$  and by DAT 35 the residues were 0.01  $\mu\text{g}/\text{cm}^2$ .

The second DFR test site was in McFarland, NC. Curacron® 8E was applied to cotton at an application rate of 1.0 lb a.i./A. In total, six applications were made for a total of 6.0 lb a.i./A. The applications were made on August 6, 13, 21, and 27 and September 1, and 8, 1992. Application was made with a tractor-drawn groundboom sprayer. The first samples were collected after the sixth (i.e., final) application, days after treatment (DAT) 0 after sprays have dried. On DAT 0 the mean residues were 2.13  $\mu\text{g}/\text{cm}^2$  and by DAT 35 the residues were 0.056  $\mu\text{g}/\text{cm}^2$ .

The third DFR test site was in Chesterfield, SC. Curacron® 8E was applied to cotton at an application rate of 1.0 lb a.i./A. In total, six applications were made for a total of 6.0 lb a.i./A. The applications were made on July 29, August 5, 12, 19, and 26 and September 2, 1992. Application was made with a tractor-drawn groundboom sprayer. The first samples were collected after the sixth (i.e., final) application, days after treatment (DAT) 0 after sprays have dried. On DAT 0 the mean residues were 2.63  $\mu\text{g}/\text{cm}^2$  and by DAT 35 the residues were 0.056  $\mu\text{g}/\text{cm}^2$ .

In addition to these three DFR studies, a worker re-entry portion of this study was also conducted. This reentry took place at the same three sites: Cheraw, SC, McFarland, NC, and Chesterfield, SC. This study examined worker exposure under reentry conditions pertaining to scouting and hoeing of cotton which had been previously treated with profenofos. There were two days of reentry activities for each site. Five volunteers worked at each site on both reentry days. Three of the workers acted as scouts (looking for insects) while the remaining two workers hoed around cotton plants. Dermal exposure was measured using face/neck swipes, hand washes and whole body dosimeters. The outer dosimeter was coveralls, while the inner dosimeter was one-piece cotton underwear. Inhalation monitoring was also conducted using personal sampling pumps. The sample collector was composed of a Chromosorb 102 air sorbent tube. There was a preloaded filter cassette attached to the end of the Chromosorb tube to capture particulate matter.

On DAT 0, the scouts were exposed to 1174.5  $\mu\text{g}/\text{day}$  (inner dosimeter plus inhalation data), while on DAT 1, the scouts were exposed to 763.7  $\mu\text{g}/\text{day}$ . The resulting average transfer coefficient for scouts is 765  $\text{cm}^2/\text{hr}$  (888  $\text{cm}^2/\text{hr}$  on DAT 0 and 642  $\text{cm}^2/\text{hr}$  on DAT 1). On DAT 0, the hoers were exposed to 859.9  $\mu\text{g}/\text{day}$  (inner dosimeter plus inhalation data), while on DAT 1, the hoers were exposed to 365.4  $\mu\text{g}/\text{day}$ . The resulting average transfer coefficient for hoers is 479  $\text{cm}^2/\text{hr}$  (650  $\text{cm}^2/\text{hr}$  on DAT 0 and 307  $\text{cm}^2/\text{hr}$  on DAT 1).

## **b. Occupational Risk**

### **i. Applicators**

Provided in Table 6 are Margin of Exposure estimates for the profenofos application scenarios. The "Daily Total Dose" includes the contributions from both the dermal and inhalation exposure components. The Daily Inhalation Dose is not presented in the Table because it makes such a small contribution to the "Daily Total Dose".

Table 6. Short-Term and Intermediate-Term Risks from Profenofos (Baseline and Risk Mitigation MOEs)

EXPOSURE SCENARIO (Number)	MOE CALCULATION USING BASELINE EXPOSURE			MOE CALCULATIONS CONSIDERING RISK				
	Daily Dermal Dose <sup>a</sup> (mg/kg/day)	Daily Total Dose <sup>b</sup> (mg/kg/day)	Baseline MOE <sup>c</sup> (Total)	ADDITIONAL PPE <sup>d</sup>				Dermal Un Exposure (mg/lb a.i.)
				Dermal Unit Exposure (mg/lb a.i.)	Inhalation Unit Exposure (mg/lb a.i.)	Daily Total Dose <sup>b</sup> (mg/kg/day)	PPE MOE <sup>e</sup> (Total)	
<b>Mixer/Loader Risk</b>								
Mixing/Loading Liquid Formulations for Aerial Equipment (1a)	Typ: 14.5 Max: 33.2	Typ: 14.5 Max: 33.2	Typ: 0.07 Max: 0.03	0.024	2.4x10 <sup>-4</sup>	Typ: 0.12 Max: 0.28	Typ: 8 Max: 4	0.007
Mixing/Loading Liquid Formulations for Groundboom Equipment (1b)	3.3	3.3	0.3	0.024	2.4x10 <sup>-4</sup>	0.027	37	0.007
<b>Applicator Risk</b>								
Applying the Liquid Formulation Using a Helicopter (enclosed cockpit) (2)	0.01	0.01	100	No data	No data	No data	No data	No data
Applying the Liquid Formulation Using a Fixed-Wing Aircraft (enclosed cockpit) (3)	Typ: 0.025 Max: 0.057	Typ: 0.025 Max: 0.058	Typ: 40 Max: 17	No data	No data	No data	No data	No data
Applying the Liquid Formulation Using a Groundboom Sprayer (4)	0.011	0.012	82	0.01	7.0x10 <sup>-4</sup>	0.012	83	0.004
<b>Flagger Risk</b>								
Flagging During Aerial Application of Liquids (5)	Typ: 0.05 Max: 0.11	Typ: 0.05 Max: 0.12	Typ: 20 Max: 8	0.0065	6.0x10 <sup>-5</sup>	Typ: 0.033 Max: 0.07	Typ: 31 Max: 14	0.0002

**NOTES FOR TABLE 6:**

aDaily Dermal Dose = Daily Dermal Exposure/70 kg; where Daily Dermal Exposure is obtained from Table 5.

bDaily Total Dose = (daily dermal exposure + daily inhalation exposure)/70 kg

cMOE = NOEL/total dose (which is the sum of the dermal and inhalation exposures); where NOEL = (1 mg/kg/day)

dAdditional PPE (unit exposures from PHED V1.1)

Scenario 1a: Double layer of clothing and chemical resistant gloves.

Scenario 1b: Double layer of clothing and chemical resistant gloves.

Scenario 2: No data.

Scenario 3: No data.

Scenario 4: Double layer of clothing and chemical resistant gloves.

Scenario 5: Double layer of clothing and chemical resistant gloves.

eEngineering Controls (unit exposures from PHED V1.1)

Scenario 1a: Closed system, single layer clothing and no gloves.

Scenario 1b: Closed system, single layer clothing and no gloves.

Scenario 2: No data.

Scenario 3: No data.

Scenario 4: Closed-cab single layer clothing and no gloves.

Scenario 5: Closed-cab single layer clothing and no gloves.

The daily dose is calculated using the following formula:

$$\text{Daily Dose} \left( \frac{\text{mg}}{\text{kg day}} \right) = \text{Daily Exposure} \left( \frac{\text{mg}}{\text{day}} \right) \cdot \left( \frac{1}{\text{Body Weight (kg)}} \right)$$

The MOEs are calculated using the following formula:

$$\text{MOE} = \frac{\text{NOEL} \left( \frac{\text{mg}}{\text{kg day}} \right)}{\text{Daily Dose} \left( \frac{\text{mg}}{\text{kg day}} \right)}$$

"MOE (total)" means that the exposure values used in the calculations reflect combined dermal and inhalation exposures. As noted earlier, dermal exposure is much greater than inhalation exposure. The "Baseline" MOEs reflect dermal and inhalation exposures where only baseline clothing (e.g., long pants, long-sleeved shirts, and shoes) were worn. Two types of risk mitigation were evaluated: (1) adding personal protective equipment (PPE) to the baseline clothing; and (2) instituting engineering controls (e.g., closed system). Again, the "Risk Mitigation Measure" MOEs reflect combined dermal and inhalation exposures, where added PPE were used and engineering controls were applied, respectively. The unit exposure values for PPE and Engineering Controls are from PHED. Provided in Appendix 3 are the assumptions used for these calculations.

Provided in Table 6 are the MOEs calculated from Baseline and Risk Mitigation unit exposures (combined dermal and inhalation). Because a toxicological endpoint/dose was derived for inhalation toxicity, EPA has calculated the individual MOEs for inhalation exposure. These are listed in Table 7.

Table 7. Inhalation MOEs for Profenofos

EXPOSURE SCENARIO (Number)	BASELINE DAILY INHALATION DOSE* (mg/kg/day)	BASELINE MOE <sup>b</sup>
<b>Mixer/Loader Risk</b>		
Mixing/Loading Formulations for Aerial Equipment (1a)	Typ: 0.006 Max: 0.014	Typ: 1,617 Max: 693
Mixing/Loading Formulations for Groundboom Equipment (1b)	0.0014	6,929
<b>Applicator Risk</b>		
Applying the Liquid Formulation Using a Helicopter (enclosed cockpit) (2)	0.00001	970,000
Applying the Liquid Formulation Using a Fixed-Wing Aircraft (enclosed cockpit) (3)	Typ: 0.0003 Max: 0.0008	Typ: 32,333 Max: 12,125
Applying the Liquid Formulation Using a Groundboom Sprayer (enclosed cockpit) (4)	0.0008	12,125
<b>Flagger Risk</b>		
Flagging During Aerial Application of Liquids (5)	Typ: 0.0015 Max: 0.003	Typ: 6,467 Max: 3,233

**NOTES** (for Table 7):

\*Daily Inhalation Dose = daily inhalation exposure/70 kg; where daily inhalation exposure is obtained from Table 4.

<sup>b</sup>MOE = LEL (9.7 mg/kg/day)/daily inhalation dose (where the inhalation LEL is 0.068 mg/L;  $(0.068 \text{ mg/L} * 1,000 \text{ l/m}^3 * 10 \text{ m}^3/\text{day})/70 \text{ kg} = 9.7 \text{ mg/kg/day}$ )

*Application Exposure Conclusions*

For profenofos, the Agency considers a Margin of Exposure of 100 (or greater) to be adequate protection concerning worker risk. Despite the utilization of additional mitigation measures (added PPE and engineering controls), MOE estimates for short-term risk and intermediate-term worker risk are less than 100 for two exposure scenarios:

Scenario (1a): Mixing/loading liquids for aerial application.

Based on an assumption of a closed system for loading and 350 acres application/day at the maximum label rate, the PHED based exposure estimate provides a MOE estimate of 30. PHED data for this scenario is described as "high confidence". The estimated exposure is greater than the level considered significant by the Agency and additional mitigation of risk must be discussed with the registrant.

46

Scenario (3): Applying liquids with a fixed wing air-craft.

Based on an assumption of engineering controls (enclosed cockpit) and application of 350 acres/day at the maximum label rate, PHED based exposure estimates provide a MOE estimate of 40. PHED data for this scenario is described as "medium confidence". The estimated exposure is greater than the level considered significant by the Agency and additional mitigation of risk must be discussed with the registrant.

As shown in Table 7, the estimated MOEs for inhalation only exposure are well over 100 and is not a significant issue for reregistration.

ii. Post-Application

The REI is established, in general, based on the number of days, following application, that must elapse before the pesticide residues dissipate to a level where estimated worker MOE's equal or exceed 100. REI requirements for profenofos are based on the averaged residue measurements from foliar dislodgeable residue (FDR) studies conducted in several geographical areas (Texas, California, South Carolina, and North Carolina) (see Tables 4-7 of U.S. EPA 1996f for reentry interval calculations for scouts and hoers). EPA has estimated that under the present assumptions and use-rates, the following REIs would apply for occupational exposures to profenofos:

• For scouts the REI would be at least 8 days; and

• For hoers the REI would be at least 4 days.

c. **Additional Occupational Exposure Studies**

i. Handler Studies

Based on the above surrogate (PHED) assessment, the risks for aerial applications are of concern to the Agency (i.e., MOEs less than 100) even when maximum PPE is considered. If the registrant presumes that a chemical-specific mixer/ loader/ applicator study would more accurately reflect the exposures for this use pattern (possibly resulting in MOEs that are greater than 100, then the registrant may consider conducting a study (guidelines 231 and 232). However, the Agency is not requiring additional data at this time.

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ii. Post-Application Studies

Additional post-application studies are not required.

**III. RISK MANAGEMENT AND REREGISTRATION DECISION**

**A. Dietary**

**1. Tolerance Reassessment Summary**

**a. Tolerances Listed Under 40 CFR 180.404**

The tolerances listed in 40 CFR 180.404 are expressed in terms of profenofos and its metabolites converted to 4-bromo-2-chlorophenol and calculated as profenofos. The HED Metabolism Committee has concluded that profenofos *per se* is the compound of toxicological concern. The tolerance expression should be revised to reflect that profenofos *per se* is the only regulated residue.

Sufficient field trial data reflecting the maximum registered use patterns are available to ascertain the adequacy of the established tolerance for cottonseed; these data suggest that the existing cottonseed tolerance should be lowered from 3.0 ppm to 2.0 ppm.

Ruminant metabolism and feeding studies indicate that the established tolerances for the fat, meat, and meat byproducts of cattle, goats, hogs, horses, and sheep (0.4 ppm), and for milk (0.01 ppm) are adequate.

Poultry metabolism and feeding studies indicate that there is presently no need for tolerances for residues of profenofos *per se* in poultry tissues and eggs; the established tolerances should be revoked.

**b. Tolerances To Be Proposed Under 40 CFR 180.404**

The registrant should submit a petition to establish a new tolerance for cotton gin byproducts at 55 ppm.

**c. Tolerances Listed Under 40 CFR 186.4975**

Based on the results of an acceptable cottonseed processing study and the revision to the tolerance expression, the established feed additive tolerance for cottonseed hulls should be revoked.



The Agency no longer recognizes soapstock as a significant feed item. The established feed additive tolerance should be revoked.

A summary of profenofos tolerance reassessments is presented in Table 8.

## **2. Codex Harmonization**

The Codex Alimentarius Commission has established several MRLs for profenofos residues in various commodities (see *Guide to Codex Maximum Limits For Pesticide Residues, Part 2, FAO CX/PR, 4/91*). The Codex and U.S. tolerance expressions will be in harmony when the U.S. tolerance expression is revised to include only profenofos *per se*. Use of profenofos in the U.S. is limited to cottonseed, whereas profenofos is used on various other crops outside the U.S. A comparison of the Codex MRLs and the corresponding reassessed U.S. tolerances is presented in Table 9.

Table 8. Tolerance Reassessment Summary for Profenofos

COMMODITY	CURRENT TOLERANCE (ppm) <sup>a</sup>	TOLERANCE REASSESSMENT (ppm) <sup>b</sup>	COMMENT/ [Correct Commodity Definition]
Tolerances Listed Under 40 CFR 180.404:			
Cattle, fat	0.05	0.05	
Cattle, mbyp	0.05	0.40	
Cattle, meat	0.05	0.05	
Cottonseed	3.0	2.0	Field trial data suggest that the established tolerance for cottonseed should be lowered. [Cotton, undelinted seed]
Eggs	0.05	Revoke	Poultry metabolism and feeding studies indicate that tolerances are not needed for poultry commodities.
Goats, fat	0.05	0.05	
Goats, mbyp	0.05	0.40	
Goats, meat	0.05	0.05	
Hogs, fat	0.05	0.05	
Hogs, mbyp	0.05	0.40	
Hogs, meat	0.05	0.05	
Horses, fat	0.05	0.05	
Horses, mbyp	0.05	0.40	
Horses, meat	0.05	0.05	
Milk	0.01	0.01	
Poultry, fat	0.05	Revoke	Poultry metabolism and feeding studies indicate that tolerances are not needed for poultry commodities.
Poultry, mbyp	0.05	Revoke	
Poultry, meat	0.05	Revoke	
Sheep, fat	0.05	0.05	
Sheep, mbyp	0.05	0.40	
Sheep, meat	0.05	0.05	
Tolerances To Be Proposed Under 40 CFR 180.404:			
Cotton, gin byproducts	None	55.0	New RAC according to the Pesticide Assessment Guidelines Subdivision O, Table II (September 1995).
Tolerances Previously Listed Under 40 CFR 186.4975:			
Cottonseed hulls	6.0	Revoke	Not warranted based on the results of an acceptable cottonseed processing study and the revision to the tolerance expression.
Soapstock	15.0	Revoke	No longer considered a feed item by the Agency (Pesticide Assessment Guidelines Subdivision O, Table II; September 1995).

**NOTES:**

<sup>a</sup>Defined as profenofos and its metabolites converted to 4-bromo-2-chlorophenol and calculated as profenofos.

<sup>b</sup>Defined as profenofos *per se*.

Table 9. Codex MRLs and Applicable U.S. Tolerances

CODEX		REASSESSED U.S. TOLERANCE (ppm)	RECOMMENDATION AND COMMENTS
COMMODITY (as defined)	MRL <sup>a</sup> (mg/kg)		
Beans (common)	0.1 <sup>b</sup>	--	
Beans (dry)	0.05 <sup>*</sup>	--	
Broccoli	0.2	--	
Brussels sprouts	0.5 <sup>c</sup>	--	
Cabbages, head	0.5	--	
Cauliflower	0.2 <sup>d</sup>	--	
Cottonseed	1	2	Codex MRL based on 21-day PHI; U.S. tolerance based on 14-day PHI.
Cottonseed oil, edible	0.05 <sup>*</sup>	--	
Cucumber	0.1	--	
Eggs	0.02 <sup>*</sup>	--	
Maize	0.05 <sup>*</sup>	--	
Meat	0.02 <sup>*</sup>	0.05	U.S. tolerance based on method limit of detection of 0.05 ppm.
Milks	0.01 <sup>*</sup>	0.01	
Onion, bulb	0.2	--	
Oranges, sweet, sour	1 <sup>*</sup>	--	
Peach	0.5	--	
Peppers, chili	5 <sup>f</sup>	--	
Peppers, sweet	1	--	
Potato	0.05 <sup>*</sup>	--	
Soya bean oil, refined	0.05 <sup>*</sup>	--	
Soya bean (dry)	0.05 <sup>*</sup>	--	
Spring onion	2	--	
Sugar beet	0.05 <sup>*</sup>	--	
Sunflower seed	0.05 <sup>*</sup>	--	
Teas (tea and herb teas)	0.5	--	
Tomato	0.5	--	

**NOTES:**

<sup>a</sup>All MRLs are at Step 5 and temporary, unless otherwise indicated, until information on the relevant GAP has been provided (as of the Guide to Codex Maximum Limits For Pesticide Residues, April 1991). An asterisk (\*) signifies that the MRL was established at or about the limit of detection.

<sup>b</sup>April 1994 FAO panel: proposed at 0.1 ppm (new).

<sup>c</sup>April 1994 FAO panel: confirmed 0.5 ppm (recommended for withdrawal by the 1992 JMPR) and proposed to remove temporary status.

<sup>d</sup>April 1994 FAO panel: proposed to increase from 0.2 to 0.5 ppm (recommended for withdrawal by the 1992 JMPR) and to remove temporary status.

<sup>e</sup>April 1994 FAO panel: confirmed 1 ppm (recommended for withdrawal by the 1992 JMPR) and proposed to remove temporary status.

<sup>f</sup>April 1994 FAO panel: proposed at 5 ppm (new).

The following conclusions can be made regarding efforts to harmonize the U.S. tolerances with the Codex MRLs with respect to MRL/tolerance level: (i) compatibility between the U.S. tolerance and Codex MRL exists for milk; (ii) incompatibility of the U.S. tolerance and Codex MRL for cottonseed remains because of differences in agricultural practices; and (iii) incompatibility of the U.S. tolerances and Codex MRL for meat remains because of differences in method limits of quantitation/detection. No questions of compatibility exist with respect to commodities where Codex MRLs have been established but U.S. tolerances do not exist or will be revoked. Recommendations for compatibility are based on conclusions following reassessment of U.S. tolerances (see Table 8).

## **B. Occupational**

EPA is concerned about the risks posed to application workers who are involved in the following scenarios:

(1a) Mixing/loading liquids for aerial application (closed-system); and,

(3) Applying liquids with a fixed wing air-craft (enclosed-cockpit).

Further, even though the Worker Protection Standard provides an exception to the REI for scouts, EPA is concerned about their potential health effects resulting from profenofos exposure until 8 days post-application.

HED recommends that the registrant meet with the Agency to discuss these analyses.

## REFERENCES

Provided in the following list of references are the citations for specific documents (memoranda, etc.) that were cited in the text of this document.

- U.S. EPA. 1996a. Memorandum from V. Dobózy to L. Morris. "Profenofos - Review of Pesticide Poisoning Incident Data." March 4, 1996.
- U.S. EPA. 1996b. Memorandum from G. Ghali to R. Forrest. "RfD/Peer Review Report of Profenofos (Curacron™..." February 6, 1996.
- U.S. EPA. 1996c. Memorandum from B. Steinwand to M. Metzger. "Dietary Exposure Analysis for Profenofos in Support of the Reregistration Eligibility Document." May 9, 1996.
- U.S. EPA. 1996f. Memorandum from L. Morris to M. Metzger. "Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document for Profenofos." March 29, 1996

The references listed below are for the other documents used to write this document. The bibliographic citations for the toxicology MRIDs may be found in PDMS. For residue chemistry, all supporting documentation may be found in the reference section of the Chemistry memorandum (U.S. EPA 1996e).

- U.S. EPA. 1996d. Memorandum from R. Locke to P. Deschamp. "Profenofos: Toxicology Chapter for the RED." January 30, 1996.
- U.S. EPA. 1996e. Memorandum from C. Eiden to M. Metzger. "Profenofos. List B Reregistration Case 3540. Chemical No. 111401. Product and Residue Chemistry Chapters for the Reregistration Eligibility Decision: Amendment. CBRS No. 17094. DP Barcode D224887.

## LIST OF APPENDICES

- Appendix 1 - Product Chemistry Data Summary
- Appendix 2 - Residue Chemistry Science Assessments for Reregistration of Profenofos
- Appendix 3 - Exposure Scenario Descriptions
- Appendix 4 - Memorandum from B. Steinwand to M. Metzger. "Dietary Exposure Analysis for Profenofos in Support of the Reregistration Eligibility Document." May 9, 1996 (U.S. EPA. 1996d).

# APPENDIX 1

## Product Chemistry Data Summary

Case No. 2540  
Chemical No. 111401

Case Name: Profenofos  
Registrant: Ciba-Geigy Corporation  
Product(s): 89%T (EPA Reg. No. 100-598)

### PRODUCT CHEMISTRY DATA SUMMARY

Guideline Number	Requirement	Are Data Requirements Fulfilled? <sup>a</sup>	MRID Number <sup>b</sup>
61-1	Product Identity and Disclosure of Ingredients	Y	<b>40445001</b> , <u>43665301</u>
61-2	Starting Materials and Manufacturing Process	Y	<b>40445001</b> , <u>43665301</u>
61-3	Discussion of Formation of Impurities	Y	<b>40445001</b> , <u>43665301</u>
62-1	Preliminary Analysis	Y	<b>40445002</b> , <u>43665302</u>
62-2	Certification of Ingredient Limits	Y	<b>40445002</b>
62-3	Analytical Methods to Verify the Certified Limits	Y	<b>40445002</b> , <u>43665302</u>
63-2	Color	Y	42030301 <sup>c</sup>
63-3	Physical State	Y	42030301 <sup>c</sup>
63-4	Odor	Y	42030301 <sup>c</sup>
63-5	Melting Point	N/A <sup>d</sup>	
63-6	Boiling Point	Y	42030301 <sup>c</sup> , 42731401 <sup>c</sup>
63-7	Density, Bulk Density or Specific Gravity	Y	42030301 <sup>c</sup> , 42731401 <sup>c</sup>
63-8	Solubility	Y	42030301 <sup>c</sup> , 42731401 <sup>c</sup>
63-9	Vapor Pressure	Y	42030301 <sup>c</sup>
63-10	Dissociation Constant	Y	42030301 <sup>c</sup> , 42731401 <sup>c</sup>
63-11	Octanol/Water Partition Coefficient	Y	<b>40445003</b> <sup>e</sup> , 42854201 <sup>f</sup>
63-12	pH	Y	42030301 <sup>c</sup> , 42731401 <sup>c</sup>
63-13	Stability	Y	<b>40445003</b> <sup>e</sup> , 42854201 <sup>f</sup> , 42968701 <sup>g</sup>

**NOTES:**

<sup>a</sup>Y = Yes; N = No; N/A = Not Applicable.

<sup>b</sup>**Bolded** references were reviewed under CBRS No. 14328, D206007, 10/7/94, L. Cheng; underlined references were reviewed under CBRS No. 15691, D216180, 7/6/95, C. Eiden; and the remaining references were reviewed as noted.

<sup>c</sup>CBRS No. 8674, D169433, 12/29/92, F. Toghrol.

<sup>d</sup>Data are not required because the TGAI is a liquid at room temperature.

<sup>e</sup>CBRS No.11808, D190824, 5/24/93, L. Cheng.

<sup>f</sup>CBRS No. 12323, D193633, 9/1/93, K. Dockter.

<sup>g</sup>CBRS No. 12749, D196268, 12/16/93, F. Toghrol.

Appendix 2 (continued)

GLN: Data Requirements	Current Tolerances, ppm [40 CFR]	Must Additional Data Be Submitted?	References <sup>1</sup>
171-4 (g): Nature and Magnitude of the Residue in Fish	N/A	N/A	
171-4 (h): Nature and Magnitude of the Residue in Irrigated Crops	N/A	N/A	
171-4 (i): Magnitude of the Residue in Food-Handling Establishments	N/A	N/A	
165-1: Rotational Crops (Confined)	--	Yes <sup>14</sup>	00086647 <sup>15</sup> , 00086650 <sup>15</sup>
165-2: Rotational Crops (Field)	--	Reserved <sup>16</sup>	

1. **Bolded** references were evaluated in the Profenofos Phase IV Review by C. Olinger dated 11/30/90; all other references were reviewed as noted.

2. The restriction against the feeding of cotton gin trash is considered impractical and should therefore be removed from the label. In addition, until an adequate confined rotational crop study is submitted, the following statement must be added to the product label: "fields grown to cotton and treated with profenofos should be rotated to cotton only." Finally, unless field residue data reflecting aerial applications in  $\leq 1$  gal. of water/A with a 14-day PHI are available, the product label must be amended to specify that aerial applications be made in a minimum of 2 gal. of water/A.

3. CBRS Nos. 13539 and 13725, DP Barcodes D201827 and D203218, 3/14/95, C. Eiden.

4. CBRS No. 14246, DP Barcode D206732, 4/7/95, C. Eiden.

5. CBRS Nos. 14246, 14700, and 14813, DP Barcodes D206732, D208891, and D209997, 3/28/95, C. Eiden.

6. CB No. 10932, DP Barcode D185021, 4/29/93, M. Bradley.

7. CBRS No. 12636, DP Barcode D195483, 5/19/94, F. Suhre.

8. The registrant should propose to revise the established tolerance for cottonseed from 3.0 ppm to 2.0 ppm, and to establish a new tolerance for cotton gin byproducts at 55 ppm.

9. CBRS No. 15465, DP Barcode D213906, 6/15/95, C. Eiden; and CBRS No. 15908, DP Barcode D217739, 8/1/95, C. Eiden (MRID 92148055 is a reformat of MRIDs 00045035, 00045038, 00046060, 00105217, and 00106649).

10. Based on the results of an acceptable cottonseed processing study and the revision to the tolerance expression, the established feed additive tolerance of 6 ppm cottonseed hulls is not warranted and should be revoked. The established feed additive tolerance of 15 ppm for cottonseed soapstock should also be revoked since this commodity is no longer considered a feed item (Table II: September 1995).



Appendix 2 (continued)

11. CBRS No. 15464, DP Barcode D213907, 6/15/95, C. Eiden; and CBRS No. 15907, DP Barcode D217744, 8/1/95, C. Eiden (MRID 92148057 is a reformat of MRIDs 00046060, 00105217, and 00106649).

12. CBRS No. 15466, DP Barcode D213905, 8/2/95, C. Eiden (MRIDs 92148050 and 92148051 are a summary and reformat, respectively, of MRIDs 00046061, 00046062, 00046065, 00048057, 00105217, and 00106649; and MRIDs 92148052 and 92148053 are a summary and reformat, respectively, of MRIDs 00046061, 00046063, 00046064, 00046067, 00048056, 00105217, and 00106649).

13. The HED Metabolism Committee has determined that there is no reasonable expectation of finite residues of profenofos in poultry tissues and egg. The established 40 CFR §180.404 tolerances for eggs and poultry fat, meat, and meat byproducts should be revoked. (HED Metabolism Committee Outcome memorandum dated 07/28/95 for profenofos.)

14. A new confined rotational crop study is required.

15. CBRS No. 15737, DP Barcode D216329, 7/24/95, C. Eiden.

16. Once the required rotational crop study has been submitted and evaluated, the need for limited and/or extensive rotational crop studies will be examined, and the appropriate plantback interval restrictions will be determined.



## APPENDIX 3

### Exposure Scenario Descriptions

The following table provides the assumptions that were used in developing the daily exposure estimates for the profenofos occupational exposure assessment. For all scenarios, the unit exposure values were derived from PHED V1.1.

EXPOSURE SCENARIO (Number)	STANDARD ASSUMPTIONS <sup>a</sup> (8-hr work day)	COMMENTS <sup>b</sup>
Mixer/Loader Exposure		
Mixing Liquid (1a and b)	80 acres groundboom, and 350 to 800 acres aerial	<p><b>Baseline:</b> "Best Available" grades: Hands, dermal, and inhalation acceptable grades. Hands = 53 replicates; Dermal = 25 to 122 replicates; Inhalation = 85 replicates. High confidence in dermal data; high confidence in inhalation data.</p> <p><b>PPE:</b> "Best Available" grades: Hands and dermal acceptable grades. Hands = 59 replicates; Dermal = 25 to 122 replicates. High confidence in dermal and inhalation data.</p> <p><b>Engineering Controls:</b> "Best Available" grades: Dermal and inhalation acceptable grades. Dermal = 16 to 22 replicates; inhalation = 27 replicates. High confidence in dermal and inhalation data.</p> <p>PHED data used for baseline, no protection factors (PFs) were necessary. 50% PF was used for coveralls (PPE)</p>
Applicator Exposure		
Aerial equipment -- helicopter enclosed cab (liquids) (2)	350 acres	<p><b>Baseline/Engineering Controls:</b> "Best Available" grades: dermal grades A,B,C; inhalation grades "acceptable". Dermal = 2 to 3 replicates; inhalation = 3 replicates. Low confidence in dermal and inhalation data.</p> <p>PHED data used for baseline, no PFs were necessary.</p>
Aerial equipment--fixed wing enclosed cab (liquids) (3)	350 to 800 acres	<p><b>Baseline/Engineering Controls:</b> "Best Available" grades: Hands acceptable grades, dermal and inhalation grades A,B,C. Hands = 34 replicates; Dermal = 24 to 48 replicates; Inhalation = 23 replicates. Medium confidence in dermal and inhalation data.</p> <p>PHED data used for baseline, no PFs were necessary.</p>

EXPOSURE SCENARIO (Number)	STANDARD ASSUMPTIONS <sup>a</sup> (8-hr work day)	COMMENTS <sup>b</sup>
Groundboom (4)	80 acres	<p>Baseline: "Best Available" grades: Hands, dermal, and inhalation acceptable grades. Hands = 29 replicates; Dermal = 32 to 42 replicates; Inhalation = 22 replicates. High confidence in dermal and inhalation data.</p> <p>PPE: "Best Available" grades: Dermal and inhalation acceptable grades. Dermal = 32 to 42 replicates; inhalation = 22 replicates. Medium confidence in dermal data; high confidence in inhalation data.</p> <p>Engineering Controls: "Best Available" grades: Dermal = ABC grades; Inhalation = acceptable grades. Dermal = 20 to 31 replicates; Inhalation = 16 replicates</p> <p>PHED data used for baseline, no PFs were necessary. 50% PF was added for coveralls for PPE.</p>
Flagger		
Liquids (5)	350-800 acres	<p>Baseline: "Best Available" grades: Hands, dermal, and inhalation acceptable grades. Hands = 16 replicates; Dermal = 16 to 18 replicates; Inhalation = 18 replicates. High confidence in dermal and inhalation data.</p> <p>PPE: "Best Available" grades: Dermal, and inhalation acceptable grades. Hands = 16 replicates; Dermal = 16 to 18 replicates; Inhalation = 18 replicates. High confidence in dermal and Low confidence for inhalation data.</p> <p>Engineering Controls: "Best Available" grades: Dermal, and inhalation acceptable grades. Dermal = 16 to 18 replicates; inhalation = 18 replicates. High confidence in dermal and inhalation data.</p> <p>PHED data used for baseline, no PFs were necessary. 50% PF for addition of coveralls PPE. 98% PF added for enclosed cab.</p>

**NOTES:**

<sup>a</sup>Standard Assumptions based on an 8-hour work day as estimated by OPP's Occupational and Residential Exposure Branch (OREB).

<sup>b</sup>"Best Available" grades are defined by OREB Standard Operating Procedure for meeting Subdivision U Guidelines. Best available grades are assigned as follows: matrices with grades A and B data and a minimum of 15 replicates; if not available, then grades A, B, and C data and a minimum of 15 replicates; if not available, then all data regardless of the quality and number of replicates.

50