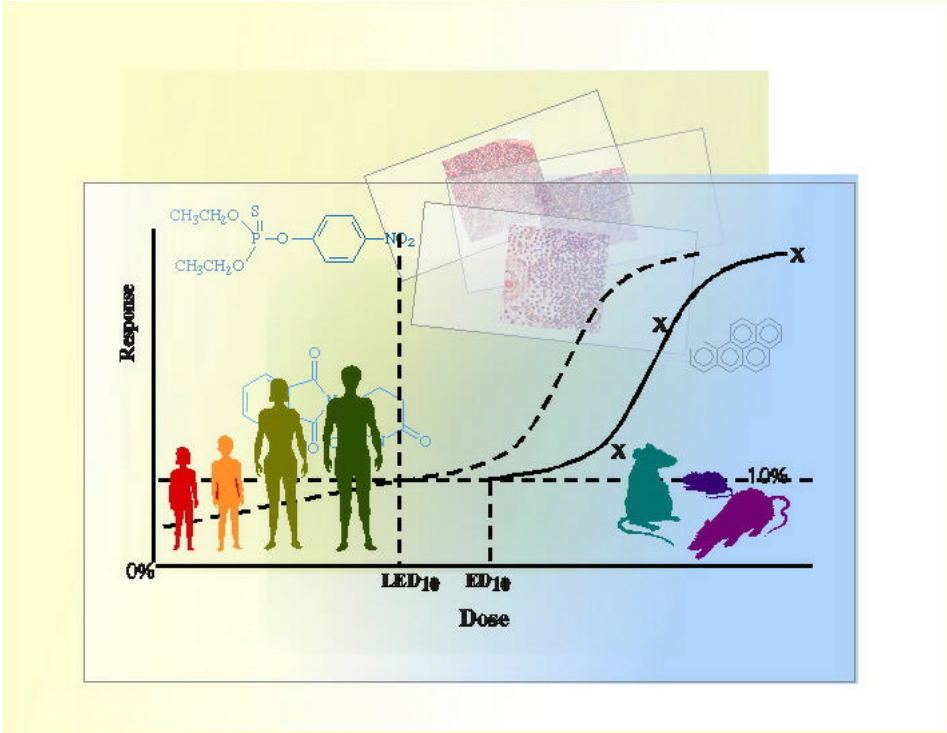
# HUMAN HEALTH RISK ASSESSMENT

# *PROFENOFOS*




U.S. Environmental Protection Agency
Office of Pesticide Programs
Health Effects Division (7509C)

Richard Griffin, Risk Assessor
June 16, 1999

# HUMAN HEALTH RISK ASSESSMENT for

# *Profenofos*

# Phase IV

## Risk Assessment Team:

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## I. 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 groundboom or aerial application techniques.

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

The Agency has concluded that the product chemistry, residue chemistry, and toxicological data for profenofos are adequate for risk assessment and for reregistration. Because cotton is also a food crop, the Agency has assessed the potential risks from both occupational and dietary exposure; there are no residential uses. The potential for exposure due to drinking water contaminated with profenofos has also been considered.

Dietary risk assessment for acute exposure is based on a Reference Dose (RfD) of 0.005 mg/kg/day and dietary risk assessment for chronic exposure is based on a RfD of 0.00005 mg/kg/day. Profenofos has been classified as a Group E carcinogen (not likely to be carcinogenic in humans via relevant routes of exposure). The Food Quality Protection Act (FQPA) Safety Factor was removed.

Occupational risk assessment is based on a dermal dose (NOEL)[1] of 1.0 mg/kg/day for short and intermediate exposure durations. Inhalation risk assessment is based on a concentration (LOEL) of 0.068 mg/L (9.7 mg/kg/day). All endpoints are based on observed cholinesterase inhibition as measured in plasma, blood, and brain.

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 infants, children, or other population subgroups.

When inhalation and dermal risks are aggregated, 2 out of 5 major occupational scenarios produce MOEs less than 100 even with engineering controls (closed systems for mixer/loaders for aerial application, and enclosed cockpits for aerial applicators). Risks (MOEs) were below 100

[1]NOTE: This document uses the terminology "NOELs" and "LOELs" instead of the terms "NOAELs" and "LOAELs," as is our current policy. The NOELs and LOELs contained in this document and supporting documentation do reflect adverse effect levels, as has always been OPP's policy.

despite additional personal protective equipment (PPE) for all scenarios.

Risk estimates for handlers using engineering controls were as follows: MOE = 23 (350 acres) and 10 (800 acres) for mixing/loading liquid formulations for aerial equipment using a closed system; MOE = 101 for mixing/loading liquid formulations for groundboom equipment using a closed system; MOE = 40 (350 acres) and 17 (800 acres) for applying spray using aircraft (enclosed cockpit); MOE = 172 (80 acres) for applying spray using a groundboom (enclosed cab); and MOE = 1,000 (350 acres) and 417 (800 acres) for flagging during aerial spray (enclosed cab).

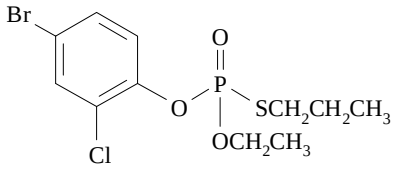
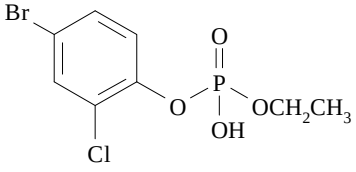
Postapplication risk estimates were calculated from registrant submitted studies on dislodgeable foliar residue dissipation and field monitoring exposure studies on scouts and hoers. Risk estimates for hoers indicate that the MOE exceeds 100 (110) on day 4 following application. Risk estimates for scouts/crop advisors indicate that the MOE exceeds 100 (108) on day 8 following application.

## II. SCIENCE ASSESSMENT

### A. Physical Chemistry Assessment

Profenofos [O-(4-bromo-2-chlorophenyl)-O-ethyl-S-propyl phosphorothioate] is an organo-thiophosphate pesticide. Primary metabolites of interest include: CGA-55960 (4-bromo-2-chlorophenol), 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<br>CGA-15324 |
|  | CGA-47196 |

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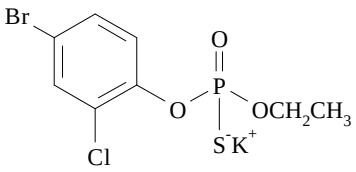
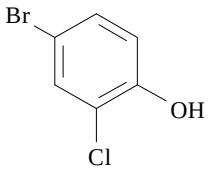
|---|---|
|  | CGA-65867 |
|  | Bromochlorophenol (4-bromo-2-chlorophenol) CGA-55960 |

## 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$^3$ at 20°C. Its' empirical formula is $C_{11}H_{15}O_3PSBrCl$ 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 subject to a reregistration eligibility decision: the 89% Technical (EPA Reg. No.100-598).

## 3. Regulatory Background

The Profenofos Phase IV Review (dated 11/30/90 by C. Olinger) determined that data submissions for residue chemistry requirements met the acceptance criteria for Phase V review; additional data were required concerning product chemistry 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 profenofos Technical is presented in Appendix 1. Refer to Appendix 1 for a listing of the outstanding product chemistry data requirements.

*Conclusions*

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

## B. Human Risk Assessment

### 1. Hazard Assessment

#### 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.

Table 2. Acute Toxicity Values for Technical Profenofos

| TEST (Guideline) | RESULT [MRID] | TOXICITY CATEGORY |
|---|---|---|
| Oral $LD_{50}$ in rat (870.1100) | $LD_{50}$ = Males: 492 (363-666) mg/kg<br>Females: 809 (600-1090) mg/kg<br>Combined: 630 mg/kg<br>[MRID 41714801] | II |
| Oral $LD_{50}$ in mouse (870.1100) | $LD_{50}$ = 298 (268-332) mg/kg [MRID 00105226] | II |
| Oral $LD_{50}$ in rabbit (870.1100) | $LD_{50}$ = 300 mg/kg [MRID 00105228] | II |
| Dermal $LD_{50}$ in rat (870.1200) | $LD_{50}$ = 1610 (1073-2415) mg/kg<br>[MRID 00105231] | II |

Table 2. Acute Toxicity Values for Technical Profenofos

| TEST (Guideline) | RESULT [MRID] | TOXICITY CATEGORY |
|---|---|---|
| Dermal $LD_{50}$; in rabbit (870.1200)<br><br>See note below: | $LD_{50}$ = Intact skin --<br>Males: 146.8 mg/kg<br>Females: 143.4 mg/kg<br>Abraded skin --<br>Males: 97.5 mg/kg<br>Females: 15.9 mg/kg<br>[MRID 00109427] | I |
| Inhalation $LC_{50}$ in rat (870.1300) | $LC_{50}$ = 3.36 mg/L [MRID 0019428] | IV |
| Eye irritation in rabbit (870.2400) | Minimal irritation, reversible within 7 days; no corneal opacity [MRID 00109429]. | III |
| Dermal irritation in rabbit (870.2500) | Moderately irritating at 72 hours; PIS = 3.3/8.0 [MRID 41714802] | III |
| Dermal sensitization in guinea pig (870.2600) | Sensitization was induced [MRID 00109431]. | -- |
| Acute delayed neurotoxicity in hen (870.6100) | No delayed neurotoxicity; NOEL[2] = 52 mg ai/kg 100% mortality at next highest dose (104 mg ai/kg $LD_{50}$ = 56.3 mg ai/kg [MRID 00126485] | -- |
| Acute oral neurotoxicity in rat (870.6200) | 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]. | -- |

NOTES:

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.

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**b. Subchronic Toxicity**

*Dermal Toxicity*

In a repeated dose 21-day dermal toxicity study (MRID 41644501), technical profenofos (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 (RBC) and serum cholinesterase 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 cholinesterase activity was also significantly decreased only in high-dose (10 mg/kg/day) males (70% control value) and females (85% control value). The LOEL is 10 mg/kg/day, based on significant decreases in cholinesterase activities in RBC, serum, and brain. The NOEL is 1 mg/kg/day.

*Oral Toxicity in Rats*

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 technical profenofos (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 profenofos technical for four weeks of recovery from treatment received during the initial 90-day study period.

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, RBC's, and brain. Ophthalmological examinations were conducted at study start and at termination.

Technical profenofos, at all doses tested, had no effect on any of the parameters monitored, except for inhibition of cholinesterase 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. Cholinesterase activities in plasma and RBC's were inhibited (range: 12-98% control) in some animals in all groups treated with technical profenofos, but these values returned to control values with four weeks of recovery. Brain cholinesterase activity was not significantly inhibited in females at any dose level. Brain cholinesterase 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 cholinesterase activity was significantly inhibited at 0.2 mg/kg/day, the Lowest Dose Tested (LDT). RBC and plasma cholinesterase was observed at 0.2 mg/kg/day (LDT; 0.2 mg/kg/day; 2-32% inhibition) and brain cholinesterase inhibition was observed at 0.2 mg/kg/day (LDT; 0.2 mg/kg/day; "significant inhibition"); a NOEL was not established.

*Oral Toxicity in Dogs*

**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 group 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, RBC, and brain cholinesterase activities. Plasma cholinesterase activity was depressed at least 40% in all profenofos treatment groups. RBC cholinesterase 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 cholinesterase activities returned to pretest values, but the RBC cholinesterase 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 was >5 mg/kg/day (HDT) based on a lack of effects other than cholinesterase inhibition. The plasma cholinesterase NOEL was <0.05 mg/kg/day (LDT), based on 52-58% inhibition at 0.05 mg/kg/day. The RBC cholinesterase NOEL was 0.05 mg/kg/day (LDT), based on 10-31% inhibition at 0.5 mg/kg/day. The brain cholinesterase NOEL was 0.5 mg/kg/day, based on a 21% decrease in brain cholinesterase activity in males at 5 mg/kg/day.

**Six-Month Feeding Study**. In a six-month feeding study (MRID 00081687), groups of Beagle dogs (7/sex/group) were administered diets containing technical profenofos (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 RBC 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 profenofos technical, at any dose level tested, was cholinesterase inhibition. Cholinesterase inhibition was measured in brain (range: 0-11%), plasma (range: 0-79%), and RBC's (range: 0-81%). A one-month recovery only partially restored cholinesterase activities in plasma and RBCs 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 LOEL 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 was 0.005 mg/kg/day.

**b. Chronic Toxicity**

In a chronic toxicity/oncogenicity study (MRID 00081685), groups of Fisher 344 rats (60/sex/group) were fed diets containing profenofos 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.

RBC and plasma cholinesterase 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 cholinesterase 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 technical profenofos 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, technical profenofos, 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 RBC, plasma, and brain cholinesterase activities. Significant (>10%) inhibition of brain cholinesterase 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), cholinesterase activity was inhibited in RBC's 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 cholinesterase activity in RBC's and plasma at 0.5 mg/kg/day (MDT).

**c. Carcinogenicity**

*Two-Year Carcinogenicity Study in Mice*

In a two-year carcinogenicity study (MRID 00082901), groups of HaM/ICR Swiss, Charles River CD® mice (65/sex/group) were administered diets containing profenofos 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 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 profenofos-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 inhibition (>20%) occurred in plasma and RBC's 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), cholinesterase activity was inhibited up to 74.2% in RBC's, and up to 76.1% in blood plasma. Under the study conditions, technical profenofos did not demonstrate a carcinogenic potential.

*Two-Year Toxicity/Carcinogenicity Study in Rats*

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) cholinesterase activity was inhibited in RBC's 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.

**d. Developmental Toxicity**

In a developmental toxicity study (MRID 00045031), groups of pregnant rats (strain not specified; 20-27 per group) were administered (orally) technical profenofos, 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% of 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 profenofos-treated group with respect to implantation ratio, embryolethality, fetal average body weight, or fetal skeletal abnormalities. From these data, it is concluded that profenofos technical at all doses tested caused no treatment-related developmental (teratogenic) effects. The Developmental NOEL was >60 mg/kg/day (HDT); the Maternal NOEL was 30 mg/kg/day (MDT), based on decreased food consumption and slightly decreased body weight at 60 mg/kg/day (Maternal LOEL).

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 Reference Dose Peer Review Committee concluded that the dose levels used in this study were significantly higher than the doses that elicited cholinesterase inhibition in other studies.

Also, 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.

**e. Reproductive Toxicity**

In a two-generation reproduction study (MRIDs 43213308 and 43213309), groups of Crl:CD®(SD) BRVAF/Plus™ 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. $P_0$ parental males were necropsied at 177-180 days of age following 134-137 days of dietary treatment. $P_0$ 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) $P_0$ and $P_1$ parental males and females.

The NOEL for parental systemic toxicity is 7.3 mg/kg/day (MDT) and the LOEL 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 $P_0$ and $P_1$ 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 LOEL is 29 mg/kg/day (HDT), based on decreased pup (both sexes; both $F_1$ and $F_2$ 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.

**f. 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 profenofos technical (90.7% a.i.) up to the limit, 5000 $\mu$g/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 $\mu$g/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 $\mu$g/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 $\mu$g/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 $\mu$g/mL).

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

**g. Metabolism**

In a metabolism study (MRID 42334301), the absorption, distribution, metabolism and elimination of profenofos were studied in groups of CD® rats administered a single oral dose of 1 or 100 mg/kg of (phenyl-UL-$^{14}$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 [$^{14}$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 $^{14}$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.

**h. Neurotoxicity**

*Acute Neurotoxicity in Rats*

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. 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 post dosing, day 7, and day 14. An additional group of animals (5/sex/dose) were assessed for cholinesterase 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 cholinesterase and RBC cholinesterase were noted both at the time of peak effect and at day 14. At 95 mg/kg, serum cholinesterase activity was inhibited 84% in males and 94% in females, and RBC cholinesterase was inhibited 74% in males and 68% in females at time of peak effect. By day 14, serum cholinesterase had returned to control levels at all doses and RBC cholinesterase had returned to 41–75% of control. No effect on brain cholinesterase was noted at day 14. The LOEL for cholinesterase inhibition is 95 mg/kg (LDT), based on inhibition of serum cholinesterase and RBC cholinesterase. The NOEL for cholinesterase inhibition is <95 mg/kg.

*Subchronic Neurotoxicity in Rats*

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 cholinesterase and RBC cholinesterase were assessed at 4, 8 and 13 weeks; neurohistopathological changes and brain cholinesterase 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, or 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 cholinesterase (58-61% in females and 28-31% in males) and RBC cholinesterase (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 cholinesterase 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 LOEL for plasma cholinesterase and RBC cholinesterase is 1.7 mg/kg/day; no NOEL was established. The LEL for brain cholinesterase is 36 mg/kg/day and the NOEL for brain cholinesterase is 7.7 mg/kg/day.

*Acute Delayed Neurotoxicity in Hens*

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

### a. Considerations for Special Sensitivity in Infants and Children (FQPA)

On September 8, 1997, the Health Effects Division's (HED) Hazard Identification Assessment Review Committee (HIARC) met 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.

The Committee concluded that sufficient data are available to adequately assess the potential for toxicity to young animals following pre-and/or post-natal exposure to profenofos. To assess the potential for enhanced sensitivity to profenofos in infants and children, the Committee reviewed the following studies (studies are summarized above in the Hazard Assessment): (1) a developmental toxicity study in rats; (2) a supplemental developmental study in rabbits; (3) a two-generation reproduction study in rats; (4) an acute delayed neurotoxicity study in hens (and two supplementary studies); (5) an acute neurotoxicity study in rats; and (6) a subchronic neurotoxicity study in rats.

Based on the data listed above, the HIARC 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 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. This recommendation was confirmed in HED's *FQPA Safety Factor Recommendations for the Organophosphates* (Combined Report of the HIARC and the FQPA Safety Factor Committee, 8/6/98).

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.

**b. Endpoints and Doses for Risk Assessment** (a summary is provided in Table 3)

*Acute Population Adjusted Dose (aPAD)*

An acute Population Adjusted Dose (PAD) of 0.005 mg/kg/day has been established for acute dietary risk assessment based on the results of a single dose oral study. Groups of rats (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 RBC's, 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 NOELs for cholinesterase inhibition are 0.5 mg/kg for plasma in both sexes, 100 mg/kg (males) and 0.5 mg/kg (females) for RBC's; 100 mg/kg for brain in both sexes.

The HED Peer Review Committee concluded (1/16/96) 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 plasma cholinesterase activity in both sexes and RBC cholinesterase activity in females. The HIARC convened on May 12, 13, 14 1998 (report dated July 7, 1998) for a comprehensive review of the organophosphate pesticides to evaluate the endpoints' uncertainty factors and FQPA safety factors. The Committee determined that profenofos would retain the conventional 100X UF (10X for intraspecies variation and 10X for interspecies extrapolation). This decision is reported in the August 6, 1998 FQPA Safety Factor Recommendations for the Organophosphate.

*Chronic Population Adjusted Dose (cPAD)*

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 chronic RfD (now termed the chronic PAD or cPAD). At that time, the Committee recommended that the study on which the profenofos RfD was based, and the Uncertainty Factor (100) remain unchanged (previous review on 3/3/87). The profenofos cPAD is based on plasma and RBC 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 cPAD 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.

*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 judgement 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.

*Short-Term Occupational Exposure*

For the risk assessment of 1 to 7 day durations of *dermal* exposure to profenofos, the HED Peer Review 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 RBC's, serum, and the brain at the LOEL of 10 mg/kg/day. An Uncertainty Factor of 100 is applied to account for interspecies extrapolation and intraspecies variability. Risk is expressed as a Margin of Exposure (the ratio of a NOEL level to an estimated dose/exposure).

*Intermediate-Term Occupational Exposure*

For the risk assessment of one-week to several-month duration dermal exposure to profenofos, the 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. An Uncertainty Factor of 100 is applied to account for interspecies extrapolation and intraspecies variability. Risk is expressed as a Margin of Exposure.

*Dermal Absorption*

HED's HIARC concludes in the *Organophosphates: Evaluation of the Dermal Absorption Factor* (February 24, 1999) that a default assumption of 50% dermal absorption should be made for risk assessment. However, it should be noted that short- and intermediate-term worker risk estimates for profenofos are based on the endpoint and dose established in a dermal study, and a dermal absorption factor is not applied.

*Long-Term (Chronic) Occupational Exposure*

For the risk assessment of chronic (several-month to lifetime) occupational 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) RfD. An Uncertainty Factor of 100 is applied to account for interspecies extrapolation and intraspecies variability. *Dermal exposure estimates should assume 50% absorption.* Risk is expressed as a Margin of Exposure.

*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/$m^3$ (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, RBC's, 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 LOEL for cholinesterase inhibition in brain, RBC's, and plasma is 0.068 mg/L (LDT). The NOEL was not established. 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 9.7 mg/kg/day is used, based on the LOEL of 0.068 mg/L which demonstrated inhibition of cholinesterase activities in RBC's, plasma, and the brain (NOEL not determined).

Table 3. Summary of Toxicological Endpoints for Profenofos

| TYPE OF EXPOSURE (duration and route) | ENDPOINT (AND DOSE) |
|---|---|
| Acute Dietary (one day) | aPAD of 0.005 mg/kg [NOEL 0.5 mg/kg / inhibition of cholinesterase activities in plasma (males) and RBC's (females) in a non-guideline acute oral toxicity study in rats (MRID 43213302)]. UF: 100 |
| Chronic Dietary | cPAD of 0.00005 mg/kg/day [NOEL 0.005 mg/kg/day / inhibition of cholinesterase activity in plasma and RBC's in a six-month dog study (MRID 00081687)] UF: 100 |
| Short-Term Occupational or Residential (one to seven days) | NOEL of 1.0 mg/kg/day [NOEL for significant decreases in cholinesterase activities in RBC's, serum, and brain in a 21-day dermal toxicity study in rabbit (MRID 41644501)]. UF: 100 |
| Intermediate-Term Occupational or Residential (one week to several months) | |
| Long-Term Occupational or Residential (several months to lifetime) | NOEL of 0.005 mg/kg/day [NOEL for inhibition of cholinesterase activities in plasma and RBC's in a six-month feeding study in dogs (MRID 00081687)]. UF: 100 (No long term occupational exposure is expected). |
| Inhalation (any duration) | LOEL of 9.7 mg/kg/day. These doses were calculated for route-to-route extrapolation based on the LOEL of 0.068 mg/L [the lowest dose used in a 21-day inhalation toxicity study in rat (MRID 00082079)], which inhibited brain, RBC, and plasma cholinesterase activities. UF: 300 |

## 3. Aggregate Exposure and Risk Assessment

### a. Exposure From 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 and aircraft. The single registered end-use product is Curacron 8E Insecticide-Miticide (EPA Reg. No. 100-669; 72.7% a.i.). The Agency expects dietary exposure resulting from the use of profenofos since cottonseed is processed into cottonseed oil. An indirect exposure to humans may also be due to the use of cottonseed meal, by-products and gin “trash” as ruminant feed items. As determined by HIARC, 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. 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 12).

*Summary of Science Findings*

*Directions for Use*

The Agency's Reference Files System Database identifies one profenofos end-use product, which is now registered to Novartis Crop Protection, Inc. 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 ai/application. Applications may be made with profenofos alone or as a tank mix with other pesticides. Applications 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 (see below). The label specifies a maximum seasonal rate of 6 lb ai/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.

**Required Label Amendments.** Current labeling 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.

*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. HED's 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.

*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 Assessment Review 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.

*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 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.

*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).

*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.

*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.

*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 Assessment Review Committee decision (7/28/95) regarding the residues to be regulated, the Agency concludes that a separate 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.

*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 Assessment Review 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, 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 Assessment Review Committee concluded there is no reasonable expectation of finite residues of profenofos in poultry tissues and eggs. HED has since evaluated the need for hog tolerances and has concluded there is no reasonable expectation of finite residues of profenofos in hog tissues (C. Olinger, 6/99). The established 40 CFR 180.404 tolerances for eggs and poultry fat, meat, and meat byproducts, hog fat, meat, and meat

by-products 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 and hog tissues and eggs may be required.

*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.

*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.

*Confined Accumulation in Rotational Crops*

A confined rotational crop study has been submitted by the Registrant and is under review by the Agency. Once the required confined rotational crop study has been evaluated, the need for limited and/or extensive field rotational crop studies will be examined, and the appropriate plantback interval restrictions will be determined.

*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. Chronic 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 profenofosPAD for chronic dietary exposure. 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 feeding studies) to estimate anticipated residues.

The Biological and Economic Analysis Division (BEAD) estimates (I. Yusuf and T. Kiely, 4/19/99) that the use of profenofos averages 5% of total acres planted to cotton. The estimated maximum percentage of acres treated in a given year is twice that or 10%. Percent crop treated estimates are derived from federal and private market survey data. Typically the Agency uses the weighted average for the chronic risk assessments and the estimated maximum for acute assessments.

**Chronic Anticipated Residues.** Previous estimates of chronic dietary risk have been based on anticipated residue estimates (C. Olinger, 9/12/90; C. Eiden, 4/11/96; and J. Garbus, 10/21/97). The chronic anticipated residues have been revised in accordance with Agency policy using the most recent usage information (I. Yusuf and T. Kiely, 4/19/99). Processing studies conducted at one and two times the maximum application rate have indicated that residues in refined cottonseed oil are less than the limit of quantitation (LOQ) of 0.05 ppm. Therefore the anticipated residue is 0.0013 ppm, calculated by multiplying ½ the LOQ, or 0.025 ppm by the weighted average of percent crop treated.

To calculate the anticipated residues for livestock commodities, the Agency initially adjusted the maximum dietary burden for the weighted average of the percent crop treated, resulting in a dietary burden of 0.65 ppm. Residues in all livestock commodities were less than the limit of quantitation at feeding levels ranging from 0.25 to 25 ppm. The anticipated residue was calculated by multiplying the limit of quantitation by the relative ratio of the anticipated dietary burden to the highest feeding level where residues were less than the limit of quantitation (0.01 for milk and 0.05 for meat). The resulting anticipated residue is 0.0013 for meat and meat by-products, and 0.00026 ppm for milk.

**Acute Anticipated Residues.** Anticipated residues were also estimated for the acute dietary risk analysis. Because cottonseed is a highly blended commodity, there will likely be blending of treated oil with untreated oil; thus, the anticipated residue is treated as a point estimate in the acute analysis. The anticipated residue for oil was calculated in a similar manner as was done in the chronic analysis, except that the estimated maximum percent of crop treated was used instead of the weighted average. The anticipated residue used in the acute analysis is 0.0025 ppm.

Livestock commodities were assumed to have residues at 1/2 the LOQ, and that all livestock commodities bear such residues. This is an overestimate, since BEAD has determined that the maximum percent cotton treated in a given year is 10%.

*Residues for Acute Risk Estimates*

| Food Code | Crop Grp | Food Name | RESIDUE (ppm) | RDF # | Adj.Factors #1 | Adj.Factors #2 |
|---|---|---|---|---|---|---|
| 323 | M | Beef-dried | 0.025000 | 0 | 1.920 | 1.000 |
| 324 | M | Beef-fat w/o bones | 0.025000 | 0 | 1.000 | 1.000 |
| 325 | M | Beef-kidney | 0.025000 | 0 | 1.000 | 1.000 |
| 327 | M | Beef-lean (fat/free) w/o bones | 0.025000 | 0 | 1.000 | 1.000 |
| 326 | M | Beef-liver | 0.025000 | 0 | 1.000 | 1.000 |
| 321 | M | Beef-meat byproducts | 0.025000 | 0 | 1.000 | 1.000 |
| 322 | M | Beef-other organ meats | 0.025000 | 0 | 1.000 | 1.000 |
| 290 | O | Cottonseed-oil | 0.002500 | 0 | 1.000 | 1.000 |
| 330 | M | Goat-fat w/o bone | 0.025000 | 0 | 1.000 | 1.000 |
| 331 | M | Goat-kidney | 0.025000 | 0 | 1.000 | 1.000 |
| 333 | M | Goat-lean (fat/free) w/o bone | 0.025000 | 0 | 1.000 | 1.000 |
| 332 | M | Goat-liver | 0.025000 | 0 | 1.000 | 1.000 |
| 328 | M | Goat-meat byproducts | 0.025000 | 0 | 1.000 | 1.000 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 329 | M | Goat-other organ meats | 0.025000 | 0 | 1.000 | 1.000 |
| 398 | D | Milk-based water | 0.005000 | 0 | 1.000 | 1.000 |
| 319 | D | Milk-fat solids | 0.005000 | 0 | 1.000 | 1.000 |
| 318 | D | Milk-nonfat solids | 0.005000 | 0 | 1.000 | 1.000 |
| 320 | D | Milk sugar (lactose) | 0.005000 | 0 | 1.000 | 1.000 |
| 338 | M | Sheep-fat w/o bone | 0.025000 | 0 | 1.000 | 1.000 |
| 339 | M | Sheep-kidney | 0.025000 | 0 | 1.000 | 1.000 |
| 341 | M | Sheep-lean (fat free) w/o bone | 0.025000 | 0 | 1.000 | 1.000 |
| 340 | M | Sheep-liver | 0.025000 | 0 | 1.000 | 1.000 |
| 336 | M | Sheep-meat byproducts | 0.025000 | 0 | 1.000 | 1.000 |
| 337 | M | Sheep-other organ meats | 0.025000 | 0 | 1.000 | 1.000 |

*Residues for Chronic Risk Estimates*

| Food Code | Crop Grp | Food Name | RESIDUE (ppm) | RDF # | Adj.Factors #1 | #2 |
|---|---|---|---|---|---|---|
| 323 | M | Beef-dried | 0.001300 | 0 | 1.920 | 1.000 |
| 324 | M | Beef-fat w/o bones | 0.001300 | 0 | 1.000 | 1.000 |
| 325 | M | Beef-kidney | 0.001300 | 0 | 1.000 | 1.000 |
| 327 | M | Beef-lean (fat/free) w/o bones | 0.001300 | 0 | 1.000 | 1.000 |
| 326 | M | Beef-liver | 0.001300 | 0 | 1.000 | 1.000 |
| 321 | M | Beef-meat byproducts | 0.001300 | 0 | 1.000 | 1.000 |
| 322 | M | Beef-other organ meats | 0.001300 | 0 | 1.000 | 1.000 |
| 290 | O | Cottonseed-oil | 0.001300 | 0 | 1.000 | 1.000 |
| 330 | M | Goat-fat w/o bone | 0.001300 | 0 | 1.000 | 1.000 |
| 331 | M | Goat-kidney | 0.001300 | 0 | 1.000 | 1.000 |
| 333 | M | Goat-lean (fat/free) w/o bone | 0.001300 | 0 | 1.000 | 1.000 |
| 332 | M | Goat-liver | 0.001300 | 0 | 1.000 | 1.000 |
| 328 | M | Goat-meat byproducts | 0.001300 | 0 | 1.000 | 1.000 |
| 329 | M | Goat-other organ meats | 0.001300 | 0 | 1.000 | 1.000 |
| 398 | D | Milk-based water | 0.000260 | 0 | 1.000 | 1.000 |
| 319 | D | Milk-fat solids | 0.000260 | 0 | 1.000 | 1.000 |
| 318 | D | Milk-nonfat solids | 0.000260 | 0 | 1.000 | 1.000 |
| 320 | D | Milk sugar (lactose) | 0.000260 | 0 | 1.000 | 1.000 |
| 338 | M | Sheep-fat w/o bone | 0.001300 | 0 | 1.000 | 1.000 |
| 339 | M | Sheep-kidney | 0.001300 | 0 | 1.000 | 1.000 |
| 341 | M | Sheep-lean (fat free) w/o bone | 0.001300 | 0 | 1.000 | 1.000 |
| 340 | M | Sheep-liver | 0.001300 | 0 | 1.000 | 1.000 |
| 336 | M | Sheep-meat byproducts | 0.001300 | 0 | 1.000 | 1.000 |
| 337 | M | Sheep-other organ meats | 0.001300 | 0 | 1.000 | 1.000 |

### b. Exposure From Drinking Water Sources

Maximum Contaminant Level (MCL) and/or Health Advisory Level (HAL) have not 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.

*Potential Groundwater 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).

*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 phosphorthioate. 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 $\mu$g/L and an *annualized* concentration 0.1 $\mu$g/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.

Chronic and acute DWLOCs were calculated based on the acute dietary and chronic (food) exposure and default body weights and water consumption figures. The Agency's default body weights and water consumption values used to calculate DWLOCs are as follows: 2L/70 kg

(adult male), 2L/60 kg (adult female), and 1L/10kg (child). The chronic and acute DWLOCs, were calculated separately using the equation:

DWLOCacute/chronic = [acute/chronic water exposure (mg/kg/day) x (body weight)]
[consumption (L) x 10-3 mg/ g]

where acute water exposure (mg/kg/day) = [aPAD - acute food (mg/kg/day)] or where chronic water exposure (mg/kg/day) = [cPAD - chronic food (mg/kg/day)]. Estimates of acute exposure from food were based on the 95th percentile of exposure.

As shown in Table 4, the drinking water estimated concentrations in surface water (peak of 0.1 ppb and average annual of 6 ppb) are below HED's DWLOCs for profenofos. HED concludes that based on the available information, modeled residues of profenofos in drinking water do not indicate an unacceptable contribution to chronic or acute dietary exposure at this time.

Table 4. Drinking Water Levels of Comparison for Acute and Chronic Dietary Exposure

| Population Subgroup | PAD (mg/kg/day) | Food Exposure (mg/kg/day) | Water Exposure (mg/kg/day) | DWLOC ($\mu$g/L) | PRZM EXAMS ($\mu$g/L) |
|---|---|---|---|---|---|
| **Acute Exposure** | | | | | |
| Adult Male | 0.005 | 0.000114 | 0.004886 | 171 | 6 |
| Adult Female | 0.005 | 0.000108 | 0.004892 | 146 | 6 |
| Infants <1 yr | 0.005 | 0.000394 | 0.004606 | 46 | 6 |
| Children 1-6 | 0.005 | 0.000400 | 0.0046 | 46 | 6 |
| Children 7-12 | 0.005 | 0.000237 | 0.004763 | 48 | 6 |
| **Chronic Exposure** | | | | | |
| Adult Male | 0.00005 | 0.000003 | 0.000047 | 2 | 0.1 |
| Adult Female | 0.00005 | 0.000003 | 0.000047 | 1.41 | 0.1 |
| Infants <1 yr | 0.00005 | 0.000004 | 0.000046 | 0.46 | 0.1 |
| Children 1-6 | 0.00005 | 0.000009 | 0.000041 | 0.41 | 0.1 |
| Children 7-12 | 0.00005 | 0.000005 | 0.000045 | 1.57 | 0.1 |

### c. Exposure From Residential Sources

There are no profenofos uses in or around homes. Residential exposure is not a part of aggregate risk assessment for profenofos.

### d. Aggregate Risk Estimates

Based on the conclusions of the HED Peer Review Committee, dietary (food and water) risk for profenofos is assessed both for acute (one-day) exposure and chronic (one-year to an assumed life-time) exposure interval.

*DEEM™ and Food Consumption Data*

HED is currently using software developed by Novigen Sciences, Inc., named the *Dietary Exposure Evaluation Model* , or DEEM™ , to calculate acute and chronic dietary risk estimates for the general U.S. population and various population subgroups. The food consumption data used in the program is based on the *USDA Continuing Survey of Food Intake by Individuals* (CSFII). The Agency is currently using 1989-91 consumption data, which will be updated with USDA 1994-96 data, during the 1999 calendar year. The 1989-91 data is based on the reported consumption of 15,128 individuals over a 3 day interval, and in total represents 35,712 unique "person days" of data. Foods "as eaten" (such as cherry pie) are linked to Raw Agricultural Commodities (cherries/wheat/etc.) by the use of "recipe" translation files. Consumption data are averaged for the entire U.S. population, and within population subgroups such as "all infants" to support chronic risk assessment, but retained as individual consumption data points to support acute risk assessment (which is based on consumption distributions for either deterministic or probabilistic-type exposure estimates). As noted above, the DEEM™ software is capable of calculating probabilistic (Monte Carlo) type risk assessments when appropriate residue data are available. For chronic risk assessments, residue estimates for foods (apples) or food-forms (apple-juice) of interest are multiplied by the averaged consumption estimate of each food/food-form of each population group. Exposure estimates are expressed in mg/kg body weight/day and as a percent of the PAD. For acute risk assessments, one-day consumption data are summed and a food consumption distribution is calculated for each population group of interest. The consumption distribution can be multiplied by a residue point estimate for a deterministic exposure/risk assessment, or used with a residue distribution in a probabilistic (Monte Carlo) type risk assessment.

*Acute Dietary Risk Estimates*

The *Dietary Exposure Evaluation Model* (DEEM™) software, based on 1989-91USDA food consumption data, was used to estimate acute risk from *food* sources. The DEEM™ model was used to calculate acute dietary exposure estimates based on total *single-day* (rather than single-serving) consumption data.

Based on the residue and consumption data outlined above, the DEEM™ program estimates that the "U.S. population - all seasons" and all DEEM™ population subgroups "All infants" and "Children (1-6 years)" are exposed to profenofos at a level less than or equal to 8 percent of the acute PAD (0.005 mg/kg/day) at the 95$^{th}$ exposure percentile. Since the exposure estimates are considered upper-end, no further analysis is considered necessary at this time.

DEEM™ Acute Risk Estimates (1989-91 data)

| | 95th Percentile | | | 99th Percentile | | | 99.9th Percentile | |
|---|---|---|---|---|---|---|---|---|
| | Exposure | % aPAD | MOE | Exposure | % aPAD | MOE | Exposure | % aPAD | MOE |
| U.S. pop - all seasons: | 0.000199 | 3.97 | 2516 | 0.000350 | 6.99 | 1430 | 0.000553 | 11.06 | 904 |
| All infants (<1 year): | 0.000394 | 7.88 | 1269 | 0.000707 | 14.15 | 706 | 0.000920 | 18.40 | 543 |
| Children (1-6 years): | 0.000400 | 8.00 | 1250 | 0.000527 | 10.54 | 949 | 0.000756 | 15.12 | 661 |
| Children (7-12 years): | 0.000237 | 4.74 | 2111 | 0.000324 | 6.48 | 1542 | 0.000405 | 8.09 | 1235 |
| Females (13-50 years): | 0.000108 | 2.15 | 4649 | 0.000164 | 3.27 | 3055 | 0.000280 | 5.60 | 1785 |
| Males (20+ years): | 0.000114 | 2.27 | 4403 | 0.000164 | 3.29 | 3043 | 0.000262 | 5.25 | 1904 |

*Chronic Dietary Risk*

The *Dietary Exposure Evaluation Model* (DEEM™) software, based on 1989-91 USDA food consumption data, was used to estimate chronic risk from *food* sources. The DEEM™ model calculates chronic exposure estimates based on *averaged* consumption data for the average U.S. population and various population subgroups including infants and children. Chronic risk is expressed as a percent of the PAD (0.00005 mg/kg/day). Based on the residue and percent crop treated data outlined above, the DEEM™ program estimates that the "U.S. population - seasons" and all population subgroups, including "All infants" and "Children (1-6 years)" are exposed to profenofos at a level less than 20 percent of the chronic PAD.

DEEM™ Chronic Risk Estimates

Total exposure by population subgroup

| Population Subgroup | Total Exposure mg/kg body wt/day | Total Exposure Percent of PAD |
|---|---|---|
| U.S. Population (total) | 0.000003 | 6.3% |
| U.S. Population (spring season) | 0.000003 | 6.3% |
| U.S. Population (summer season) | 0.000003 | 6.2% |
| U.S. Population (autumn season) | 0.000003 | 6.5% |
| U.S. Population (winter season) | 0.000003 | 6.2% |
| Northeast region | 0.000003 | 6.1% |
| Midwest region | 0.000004 | 7.0% |
| Southern region | 0.000003 | 6.0% |
| Western region | 0.000003 | 6.2% |
| Hispanics | 0.000004 | 7.0% |
| Non-hispanic whites | 0.000003 | 6.3% |
| Non-hispanic blacks | 0.000003 | 5.7% |
| Non-hisp/non-white/non-black) | 0.000003 | 6.7% |
| All infants (< 1 year) | 0.000004 | 7.3% |
| Nursing infants | 0.000001 | 2.1% |
| Non-nursing infants | 0.000005 | 9.6% |
| Children 1-6 yrs | 0.000009 | 18.9% |
| Children 7-12 yrs | 0.000005 | 10.8% |
| Females 13-19(not preg or nursing) | 0.000003 | 5.4% |
| Females 20+ (not preg or nursing) | 0.000002 | 3.6% |
| Females 13-50 yrs | 0.000002 | 4.1% |
| Females 13+ (preg/not nursing) | 0.000003 | 5.7% |
| Females 13+ (nursing) | 0.000002 | 4.9% |
| Males 13-19 yrs | 0.000004 | 7.1% |
| Males 20+ yrs | 0.000002 | 4.3% |
| Seniors 55+ | 0.000002 | 3.7% |
| Pacific Region | 0.000003 | 6.0% |

*Aggregate Risk Conclusions*

**Acute.** The Agency considers estimated acute dietary exposure to profenofos to be less than a level of concern for the general U.S. population (or any population subgroup such as infants and children) if the estimated exposure does not equal or exceed 0.005 mg/kg/day (the acute PAD). Estimated acute dietary risk for profenofos in *food* does not exceed 8 percent of this aPAD, including children which are estimated to be the most highly exposed. Exposure due to *drinking water* contaminated at the modeled annualized or peak levels, added to the food source exposure estimate, does not exceed 100 percent of the aPAD (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 population subgroup from acute exposure to profenofos.

**Chronic.** The Agency considers chronic dietary exposure to profenofos to be less than a level of concern for the general U. S. population (or any population subgroup such as infants and children) if the estimated exposure does not equal or exceed 0.00005 mg/kg/day (the cPAD). Estimated chronic dietary risk for profenofos in *food* does not exceed 20 percent of this cPAD, including infants which are estimated to be the most highly exposed. Chronic exposure due to *drinking water* contaminated at the modeled annualized level, added to the food source exposure estimate, does not exceed 100 percent of the cPAD (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 population subgroup from chronic exposure to profenofos.

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

The following three sources of data provide information on incidents of exposure to profenofos. For a more detailed review see U.S. EPA, 1996a.

**Incident Data System (IDS).** There are IDS reports of incidents from various sources, including registrants, other health and environmental agencies and individual consumers, submitted to Office of Pesticide Programs (OPP) since 1992. Reports represent anecdotal reports or allegations only, unless otherwise stated.

Since 1992, there have been over 17,000 reports of incidents involving adverse effects to humans and approximately 9,000 reports involving domestic animals. Profenofos has been involved in seven human cases with minor symptoms and one lawsuit alleging death. One incident involving sick and dead cattle that ingested profenofos-treated grass was reported, but there were inconsistencies in the investigation and no cause of illness or death could be determined.

**Poison Control Centers**. As the result of Data Call-Ins issued in 1993, OPP received Poison Control Center data covering the years 1985 through 1992 for 28 organophosphate and carbamate chemicals. Additional data on all pesticide exposures was obtained for the years 1993-1996. Most of the national Poison Control Centers (PCCs) participate in a national data collection system, the Toxic Exposure Surveillance System which obtains data from about 70 centers at hospitals and universities.

Few cases of profenofos illness were reported by Poison Control Centers either during the 1985-1992 or the 1993-1996 time periods. From 1985 through 1992 there were three occupational cases and four non-occupational cases involving exposure to profenofos alone. From 1993 through 1996 there were two occupational and six non-occupational cases. Non-occupational cases are likely to involve bystanders or workers exposed to spray drift. Profenofos had a lower ratio of symptomatic cases per pounds reported in use than did other organophosphate or carbamate insecticides.

**California Environmental Protection Agency**. California has collected uniform data on suspected pesticide poisonings since 1982. Physicians are required, by statute, to report to their local health officer all occurrences of illness suspected of being related to exposure to pesticides. The majority of the incidents involve workers.

From 1982 through 1993 California reported two cases of handlers with systemic poisoning and four cases of fieldworkers who developed skin irritation or rash from exposure to residues. Likelihood of a causal relationship was deemed definite for the two handler cases and possible for the four fieldworkers. The ratio of systemic cases per 1,000 applications reported in California was about a third lower than the median for 29 alternative insecticides used in that State.

HED concludes there have been few reports of adverse health effects in humans and domestic animals as the result of the use of profenofos.

## 4. Occupational Exposure and Risk Assessment

An occupational risk assessment is required for profenofos since there is potential exposure to handlers during use (mixers/loaders/applicators), and to handlers/workers (scouts/hoers) entering treated sites postapplication.

At this time all products containing profenofos are intended *only* for use on cotton. The Agency expects that, based on the cotton use patterns, handler and postapplication worker exposure to profenofos will be short- to intermediate-term in duration (chronic exposure is *not* expected), and exposure will occur *via* both the dermal and inhalation routes for handlers and *via* the dermal routes for workers. Based on the profenofos toxicity endpoints and doses for risk assessment, the Agency is characterizing risk to: (1) mixers/loaders, applicators, and flaggers by the Margin of Exposure approach, (2) postapplication workers by the required duration of the restricted-entry interval (REI), and (3) crops advisors/scouts by the duration of the period during which personal protective equipment must be used.

### a. Handler Exposure

*Introduction*

During the Phase IV review (1/21/91 by W. Dang), EPA required the registrants to submit handler 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.

PHED was designed by a task force consisting of representatives from the U.S. EPA, Health Canada, the California Department of Pesticide Regulation, and member companies of the American Crop Protection Association. PHED is a generic database containing measured exposure data for workers involved in the handling or application of pesticides in the field (i.e., currently contains data for over 2000 monitored exposure events). The basic assumption underlying the system is that exposure to pesticide handlers can be calculated using the monitored data as exposure is primarily a function of the physical parameters of the handling and application process (e.g., packaging type, application method, and clothing scenario). PHED also contains algorithms that allow the user to complete surrogate task-based exposure assessments beginning with one of the four main data files contained in the system (i.e., mixer/loader, applicator, flagger, and mixer/loader/applicator).

Users can select data from each major PHED file and construct exposure scenarios that are representative of the use of the chemical. However, to add consistency to the risk assessment process, EPA in conjunction with the PHED Task Force has evaluated all data within the system and developed a surrogate exposure table that contains a series of standard unit exposure values for various occupational exposure scenarios (*PHED Surrogate Exposure Guide of May, 1997*). These standard unit exposure values are the basis for this assessment. The standard exposure values (i.e., the unit exposure values included in the exposure and risk assessment tables) are based on the "best fit" values calculated by PHED. PHED calculates "best fit" exposure values by assessing the distributions of exposures for each body part included in datasets selected for the assessment (e.g., chest or forearm) and then calculates a composite exposure value representing the entire body. PHED categorizes distributions as normal, lognormal, or in an "other" category. Generally, most data contained in PHED are lognormally distributed or fall into the PHED "other" distribution category. If the distribution is lognormal, the geometric mean for the distribution is used in the calculation of the "best fit" exposure value. If the data are an "other" distribution, the median value of the dataset is used in the calculation of the "best fit" exposure value. As a result, the surrogate unit exposure values that serve as the basis for this assessment generally range from the geometric mean to the median of the selected dataset.

Occupational handler exposure assessments are completed using a baseline exposure scenario and, if required, increasing levels of risk mitigation (PPE and engineering controls) to achieve an appropriate margin of exposure or cancer risk. The baseline clothing/PPE ensemble for occupational exposure scenarios is generally an individual wearing long pants, a long-sleeved shirt, no chemical-resistant gloves (there are exceptions pertaining to the use of gloves and these are noted), and no respirator.

*Handler Exposure Estimates*

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 submission evaluated mixer/loader, aerial applicator, and groundboom applicator exposure. Assuming baseline attire plus chemical-resistant gloves, 400 acres treated per day, an application rate of 1.0 lb ai/acre, and a body weight of 60 kg, the results indicated that the mixer/loaders supporting aerial applications had a daily dose of 63 $\mu$g/kg/day, pilots (aerial applicators) had a daily dose of 73 $\mu$g/kg/day, and groundboom applicators had a daily dermal dose of 48 $\mu$g/kg/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, and flagger exposure using the new version of PHED. The resultant exposure estimates are different from those provided by the registrant. These differences are attributed to several different factors: (1) the registrant's submission is based on PHED V1.01, while EPA's assessment is based on PHED V1.1; (2) the registrant used lower quality data (i.e., A, B, and C quality) in their selection of PHED subsets; (3) the registrant and EPA used different assumptions (i.e., number of acres treated/day, etc.); (4) the registrant used different baseline attire and personal protective equipment scenarios. The registrant's calculation assumes that mixers and loaders are wearing chemical-resistant gloves in addition to baseline attire (long-sleeve shirt, long pants, shoes, and socks). EPA's risk assessment initially assumes that handlers are wearing baseline attire. When the margins of exposure are unacceptable at baseline attire, risks are also assessed for handlers wearing additional personal protective equipment, including gloves, double-layer body protection, and a respirator (if necessary), or for handlers using engineering controls. In the profenofos RED, the daily dermal dose for mixers/loaders supporting aerial applications of 350 acres per day and wearing gloves and double-layer body protection in addition to baseline attire is 0.086 mg/kg/day, which is similar to the registrant-calculated dose of 0.063 mg/kg/day for mixers/loader supporting aerial applications of 400 acres per day and wearing gloves in addition to baseline attire. EPA notes that the registrant's risk assessment for such mixers/loaders results in an MOE of approximately 16.

The Agency identifies four 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 spray using aircraft (enclosed cockpit); (3) applying spray using groundboom equipment; and (4) flagging during aerial spray applications.

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 long-sleeve shirt, long pants, shoes and socks.

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 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:

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

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

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

| Exposure Scenario (Number) | Daily Acres Treated[a] | Application Rate (lb ai/A)[b] | Baseline Dermal Unit Exposure (mg/lb ai)[c] | Baseline Daily Dermal Exposure (mg/day)d | Baseline Daily Dermal Dose (mg/kg/day)[e] | Baseline Dermal MOE [f] (UF =100) | Baseline Inhalation Unit Exposure (mg/lb ai)[g] | Baseline Daily Inhalation Exposure (mg/day)[h] | Baseline Daily Inhalation Dose (mg/kg/day)[i] | Baseline Inhalation MOE[j] (UF =300) |
|---|---|---|---|---|---|---|---|---|---|---|
| Mixer/Loader Exposure | | | | | | | | | | |
| Mixing/Loading Liquid Formulations for Aerial Equipment (1a) | Typ: 350 | 1 | 2.9 | Typ: 1015 | 15 | 0.07 | $1.2x10^{-3}$ | Typ: 0.42 | 0.006 | 1600 |
| | Max: 800 | | | Max: 2320 | 33 | 0.03 | | Max: 0.96 | 0.014 | 710 |
| Mixing/Loading Liquid Formulations for Groundboom Equipment (1b) | 80 | | | 232 | 3.3 | 0.3 | | 0.096 | 0.0014 | 7100 |
| Applicator Exposure | | | | | | | | | | |
| Applying Spray Using Aircraft (enclosed cockpit) (2) | Typ: 350 | 1 | See Eng. Controls | See Eng. Controls | See Eng. Controls | See Eng. Controls | See Eng. Controls | See Eng. Controls | See Eng. Controls | See Eng. Controls |
| | Max: 800 | | | | | | | | | |
| Applying Spray Using a Groundboom (3) | 80 | 1 | $1x10^{-2}$ | 0.8 | 0.011 | 88 | $7x10^{-4}$ | 0.056 | 0.0008 | 12,000 |
| **Flagger Exposure** | | | | | | | | | | |
| Flagging During Aerial Spray Applications (4) | Typ: 350 | 1 | $1x10^{-2}$ | Typ: 3.5 | 0.05 | 20 | $3x10^{-4}$ | Typ: 0.105 | 0.0015 | 6,500 |
| | Max: 800 | | | Max: 8 | 0.11 | 8.8 | | Max: 0.24 | 0.0034 | 2,800 |

NOTES:

[a]Acres treated values are from EPA estimates of acreage that could be treated in a single day for each exposure scenario of concern.

[b]Application rate based on values found in EPA label Reg. No. 100-669.

[c]Baseline dermal unit exposure (from PHED V1.1) represents long pants, long-sleeve shirts, no gloves, open mixing/loading, open cab tractor.

[d]Baseline daily dermal exposure (mg/day) = Unit Exposure (mg/lb ai) * Application Rate (lb ai/A) * Acres treated/day.

[e]Baseline daily dermal dose (mg/kg/day) = Daily dermal exposure (mg/day) / adult body weight (70 kg)

[f]Baseline dermal MOE = NOEL (1 mg/kg/day) / daily dermal dose; Uncertainty factor (UF) is 100, which means that MOEs 100 of not of concern.

[g]Baseline inhalation unit exposure (from PHED V1.1) represents no respirator.

[h]Baseline daily inhalation exposure (mg/day) = Unit Exposure (mg/lb ai) * Application Rate (lb ai/A) * Acres treated/day.

[i]Baseline daily inhalation dose = daily inhalation exposure (mg/day) / adult body weight (70 kg)

[j]Baseline inhalation MOE = LOEL (9.7 mg/kg/day) / baseline daily inhalation dose; Uncertainty factor (UF) is 300, which means that MOEs 300 of not of concern.

**b. Postapplication 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 postapplication profenofos exposure data in response to the data requested by the Agency during Phase 4 of the reregistration process. Postapplication data submitted by the registrant was for workers performing hoeing tasks, based on the presumption that most cotton is mechanically harvested. Since EPA has no data upon which to assess postapplication exposures and risks to workers engaged in hand harvesting cotton, the Agency will limit harvesting of profenofos-treated cotton to mechanical harvesting only. Two foliar dissipation (dislodgeable residue) studies (Study 1 and Study 2 below) and one worker reentry study (Study 3 below) using profenofos were submitted.

*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 ai/A. In total, six applications were made for a total of 6.0 lb ai/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 $\mu g/cm^2$ and by DAT 35 the residues were 0.01 $\mu g/cm^2$.

*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 ai/A. In total, six applications were made for a total of 6.0 lb ai/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 $\mu g/cm^2$ and by DAT 35 the residues were 0.0088 $\mu g/cm^2$.

*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 ai/A. In total, six applications were made for a total of 6.0 lb ai/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 $\mu g/cm^2$ and by DAT 35 the residues were 0.01 $\mu g/cm^2$. The second DFR test site was in McFarland, NC. Curacron® 8E was applied to cotton at an application rate of 1.0 lb ai/A. In total, six applications

were made for a total of 6.0 lb ai/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, DAT 0 after sprays have dried. On DAT 0, the mean residues were 2.13 $\mu$g/cm$^2$ and by DAT 35 the residues were 0.056 $\mu$g/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 ai/A. In total, six applications were made for a total of 6.0 lb ai/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, DAT 0 after sprays have dried. On DAT 0, the mean residues were 2.63 $\mu$g/cm$^2$ and by DAT 35 the residues were 0.056 $\mu$g/cm$^2$.

In addition to these three DFR studies, a worker reentry 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 that 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 consisting of a chambray-shirt-like top and jean-like bottoms, 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 $\mu$g/day (inner dosimeter plus inhalation data), while on DAT 1, the scouts were exposed to 763.7 $\mu$g/day. The resulting average transfer coefficient for scouts is 765 cm$^2$/hr (888 cm$^2$/hr on DAT 0 and 642 cm$^2$/hr on DAT 1). On DAT 0, the hoers were exposed to 859.9 $\mu$g/day (inner dosimeter plus inhalation data), while on DAT 1, the hoers were exposed to 365.4 $\mu$g/day. The resulting average transfer coefficient for hoers is 479 cm$^2$/hr (650 cm$^2$/hr on DAT 0 and 307 cm$^2$/hr on DAT 1).

**c Occupational Risk Estimates**

*Handlers*

Provided in Table 6 are Margin of Exposure estimates for the profenofos handler scenarios. The endpoint for assessing dermal risks is a NOEL of 1 mg/kg/day. The endpoint for assessing inhalation risk is an LOEL of 9.7 mg/kg/day. This was derived from an inhalation LOEL of 0.068 mg/L [0.068 mg/L x 1,000 l/m$^3$ x 10 m$^3$/day]/70 kg = 9.7 mg/kg/day).

The daily dose is calculated using the following formula:

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

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

| EXPOSURE SCENARIO (Number) | MOE CALCULATIONS CONSIDERING RISK MITIGATION MEASURES | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ADDITIONAL PPE | | | | | | ENGINEERING CONTROLS | | | | | | |
| | Dermal Unit Exposure[a] (mg/lb ai) | Dermal Daily Dose[b] (mg/day) | Dermal MOE[c] (UF =100) | Inhalation Unit Exposure[d] (mg/lb ai) | Inhalation Daily Dose[e] (mg/day) | Inhalation MOE[f] (UF =300) | Dermal Unit Exposure[g] (mg/lb ai) | Dermal Daily Dose[h] (mg/day) | Dermal MOE[i] (UF =100) | Inhalation Unit Exposure[j] (mg/lb ai) | Inhalation Daily Dose[k] (mg/day) | Inhalation MOE[l] (UF =300) | Engineering Controls Aggregate[m] (UF 1) |
| **Mixer/Loader Risk** | | | | | | | | | | | | | |
| Mixing/Loading Liquid Formulations for Aerial Equipment (1a) | 0.017 | 0.085 | 12 (typ) | 2.4x10-4 | 0.0012 | 8100 (typ) | 0.0086 | 0.043 | 23 (typ) | 8.0x10-5 | 0.00040 (max) | 24,000 (typ) | 0.2 (typ) |
| | | 0.19 | 5.1 (max) | | 0.0027 | 3500 (max) | | 0.098 | 10 (max) | | 0.00091 | 11,000 (max) | 0.1 (max) |
| Mixing/Loading Liquid Formulations for Groundboom Equipment (1b) | | 0.019 | 51 | | 0.00027 | 35,000 | | 0.0098 | 100 | | 0.000091 | 110,000 | 1.0 |
| **Applicator Risk** | | | | | | | | | | | | | |
| Applying Spray Using Aircraft (enclosed cockpit) (2) | See Eng. Controls | See Eng. Controls | See Eng. Controls | See Eng. Controls | See Eng. Controls | See Eng. Controls | 5x10-3 | 0.025 | 40 (typ) | 7x10-5 | 0.00035 | 28,000 (typ) | 0.4 (typ) |
| | | | | | | | | 0.057 | 18 (max) | | 0.00080 | 12,000 (max) | 0.2 (max) |
| Applying Spray Using a Groundboom (3) | 0.01 | 0.011 | 88 | 7.0x10-4 | 0.00080 | 12,000 | 0.005 | 0.0057 | 180 | 4.0x10-5 | 0.000046 | 210,000 | 1.7 |
| **Flagger Risk** | | | | | | | | | | | | | |
| Flagging During Aerial Spray Application (4) | 0.01 | 0.05 | 20 (typ) | 7.0x10-5 | 0.00035 | 28,000 (typ) | 0.0002 | 0.0010 | 1000 (typ) | 7.0x10-6 | 0.000035 | 280,000 (typ) | 9.9 (typ) |
| | | 0.11 | 8.8 (max) | | 0.00080 | 12,000 (max ) | | 0.0023 | 440 (max) | | 0.000080 | 120,000 (max) | 4.3 (max) |

NOTES FOR TABLE 6:

PPE dermal unit exposure (from PHED V1.1) represents double layer of clothing and chemical resistant gloves for scenarios 1 and 3; double layers and no gloves for scenario 4; no data for scenario 3.

[b] PPE daily dermal dose (mg/kg/day) = PPE unit exposure (mg/lb ai) * application rate (lb ai/A) * acres treated/day / adult body weight (70 kg)

[c] PPE dermal MOE = NOEL (1 mg/kg/day) / PPE daily dermal dose; Uncertainty factor (UF) is 100, which means that an MOE 100 is not of concern

[d] PPE inhalation unit exposure (from PHED V1.1) represents dust/mist respirator (80% protection factor) for all scenarios, except scenario 3 which is baseline -- no respirator.

[e] PPE daily inhalation dose = PPE unit exposure (mg/lb ai) * application rate (lb ai/A) * acres treated/day / adult body weight (70 kg)

[f] PPE inhalation MOE = LOEL (9.7 mg/kg/day) / additional PPE daily inhalation dose; Uncertainty factor (UF) is 300, which means that an MOE 300 is not of concern.

[g] Engineering Controls dermal unit exposure (from PHED V1.1) represents engineering controls (closed system for mixing/loading, enclosed cab for ground applicators and flaggers, enclosed cockpit for aerial applicators) plus single layer of clothing plus chemical-resistant gloves for scenario 1, and single layer of clothing and no gloves for scenarios 2, 3, and 4.

[h] Engineering Controls daily dermal dose (mg/kg/day) = Engineering Control Unit Exposure (mg/lb ai) * Application Rate (lb ai/A) * Acres treated/day / adult body weight (70 kg).

[l] Engineering Controls dermal MOE = NOEL (1 mg/kg/day) / Engineering Controls daily dermal dose; Uncertainty factor (UF) is 100, which means that an MOE 100 is not of concern.

[j] Engineering Controls inhalation unit exposure (from PHED V1.1) represents engineering controls (closed system for mixing/loading, enclosed cab for ground applicators and flaggers, enclosed cockpit for aerial applicators) plus no respirator.

[k] Engineering Controls daily inhalation dose = Engineering Control Unit Exposure (mg/lb ai) * Application Rate (lb ai/A) * Acres treated/day / adult body weight (70 kg).

[l] Engineering Controls inhalation MOE = LOEL (9.7 mg/kg/day) / Engineering Controls daily inhalation dose; Uncertainty factor (UF) is 300, which means that an MOE 300 is not of concern.

[m] Engineering Controls Aggregate Dermal + Inhalation Risk = 1 / (100/dermal MOE + 300/inhalation MOE). Aggregate Risk Index (ADI) method used to aggregate dermal and inhalation MOEs due to dissimilar UF. Acceptable ARI 1.

The MOEs are calculated using the following formula:

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

**Risk from Aggregating Dermal and Inhalation Exposure**. Because the same toxicity endpoint (i.e., cholinesterase inhibition) is applicable to both inhalation and dermal risks, it is appropriate to add these risks together to obtain a total risk for occupational exposure. Since individual risks for dermal scenarios are of concern (i.e., MOE <100) by themselves until engineering controls are evaluated, only the engineering control risks will be aggregated to assess whether the risks posed by both routes together remain acceptable. MOEs can only be combined if they have a common UF. If the MOE/UF ratios for each route are treated as fractions, they can be adjusted to a common denominator of 1. This is accomplished by dividing each MOE by its UF to yield a **Risk Index** (**RI**). The RIs can then be combined to yield an **Aggregate Risk Index (ARI)**: The formula used to aggregate the risks is as follows:

$$AggregateRisk = \frac{1}{\frac{1}{MOE_{dermal}} + \frac{1}{MOE_{inhalation}}}$$

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, socks, 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, enclosed cockpit/cab). 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 Risk Mitigation unit exposures and, for engineering controls scenarios, aggregate risks (combined dermal and inhalation) are shown.

For profenofos, the Agency considers a Margin of Exposure of 100 (or greater) to be adequate protection concerning handler dermal risk and a Margin of Exposure of 300 (or greater) to be adequate protection concerning handler inhalation risk. The additional uncertainty factor of 3 for inhalation risks reflects the uncertainty from the use of a lowest observable effect level (LOEL) rather than a no observable effect level (NOEL). Despite the utilization of additional mitigation measures (added PPE and engineering controls), MOE estimates for short-term risk and intermediate-term handler dermal risk are less than 100 for two exposure scenarios: (1) mixing/loading liquids for aerial application, based on an assumption of a closed system for mixing/loading and 350 acres application/day at the maximum label rate (the PHED

based exposure estimate provides a MOE estimate of 23 and the data for this scenario is described as *high confidence*), and (2) applying spray with aircraft, based on an assumption of engineering controls (enclosed cockpit) and the application of 350 acres/day at the maximum label rate (the PHED based exposure estimates provides a MOE estimate of 40 and the data for this scenario is described as *medium confidence*). Information received from the registrant persuaded the Agency that the estimate of 350 acres per day was a reasonable assumption for aerial applications of profenofos; therefore the Agency considered only the scenarios using the 350 acres per day.

The estimated MOEs for inhalation *only* exposure are well over 300 and are not a significant issue for reregistration.

*Postapplication*

Postapplication risks are mitigated for workers using a restricted-entry interval (REI). In general, the REI is established 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 while wearing baseline attire (i.e., long-sleeve shirt, long pants, shoes, and socks). Under the Worker Protection Standard for Agricultural Pesticides (WPS) -- 40 CFR Part 170, entry to perform routine hand labor tasks is prohibited during the REI and PPE can not be considered as a risk reduction measure in establishing the REI. REI calculations for profenofos are based on the averaged residue measurements from foliar dislodgeable residue (DFR) studies conducted in several geographical areas -- Texas, California, South Carolina, and North Carolina. Exposure monitoring of hoers was conducted in field studies in North and South Carolina (see Tables 9-10 for reentry interval calculations for hoers).

Postapplication risks are mitigated for crop advisors/scouts using entry restrictions, not restricted-entry intervals. Because under the Worker Protection Standard for Agricultural Pesticides -- 40 CFR Part 170, crop advisors/scouts are defined as handlers, the Agency can permit such persons to enter treated areas to perform scouting tasks, provided they are using required PPE. Postapplication requirements for crop advisors/scouts for profenofos are based on the averaged residue measurements from dislodgeable foliar residue (DFR) studies conducted in several geographical areas -- Texas, California, South Carolina, and North Carolina. Exposure monitoring of scouts was conducted in field studies in North and South Carolina (see Tables 7-8 for entry restriction calculations for scouts and crop advisors).

Using registrant-submitted data, EPA calculates that under the present assumptions and use-rates, the following entry restrictions would apply for occupational exposures to profenofos: for hoers, the REI would be at least 4 days following application (MOE = 110 on day 4 following application); and for crop advisors/scouts, the entry restriction would be at least 8 days following application (MOE = 108 on day 8 following application).

## Table 7: Scout/Crop Advisor Best Fit DFRs and Exposure

| Best Fit DFRs ($\mu$g/cm$^2$)[a] | | | | | | | Exposure (mg/day)[b] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DAT | Texas | California | South Carolina 1 | North Carolina | South Carolina 2 | *Average* | Texas | California | South Carolina 1 | North Carolina | South Carolina 2 | *Average* |
| 0 | 0.2249 | 0.4237 | 0.2592 | 0.1417 | 0.2603 | *0.2620* | 1.3765 | 2.5932 | 1.5864 | 0.8670 | 1.5931 | *1.6032* |
| 1 | 0.1992 | 0.3737 | 0.2287 | 0.1305 | 0.2361 | *0.2337* | 1.2194 | 2.2868 | 1.3998 | 0.7987 | 1.4451 | *1.4300* |
| 2 | 0.1765 | 0.3295 | 0.2018 | 0.1202 | 0.2142 | *0.2084* | 1.0802 | 2.0166 | 1.2352 | 0.7357 | 1.3108 | *1.2757* |
| 3 | 0.1564 | 0.2906 | 0.1781 | 0.1107 | 0.1943 | *0.1860* | 0.9569 | 1.7783 | 1.0899 | 0.6777 | 1.1890 | *1.1384* |
| 4 | 0.1385 | 0.2562 | 0.1571 | 0.1020 | 0.1762 | *0.1660* | 0.8477 | 1.5682 | 0.9617 | 0.6243 | 1.0786 | *1.0161* |
| 5 | 0.1227 | 0.2260 | 0.1387 | 0.0940 | 0.1599 | *0.1482* | 0.7509 | 1.3829 | 0.8486 | 0.5751 | 0.9784 | *0.9072* |
| 6 | 0.1087 | 0.1993 | 0.1224 | 0.0866 | 0.1450 | *0.1324* | 0.6652 | 1.2195 | 0.7488 | 0.5298 | 0.8875 | *0.8102* |
| 7 | 0.0963 | 0.1757 | 0.1080 | 0.0797 | 0.1315 | *0.1183* | 0.5893 | 1.0754 | 0.6607 | 0.4880 | 0.8051 | *0.7237* |
| 8 | 0.0835 | 0.1550 | 0.0953 | 0.0735 | 0.1193 | *0.1057* | 0.5220 | 0.9484 | 0.5830 | 0.4495 | 0.7303 | *0.6466* |
| 9 | 0.0756 | 0.1367 | 0.0841 | 0.0677 | 0.1082 | *0.0944* | 0.4624 | 0.8363 | 0.5144 | 0.4141 | 0.6624 | *0.5779* |
| 10 | 0.0669 | 0.1205 | 0.0742 | 0.0623 | 0.0982 | *0.0844* | 0.4097 | 0.7375 | 0.4539 | 0.3815 | 0.6009 | *0.5167* |
| 11 | 0.0593 | 0.1063 | 0.0654 | 0.0574 | 0.0891 | *0.0755* | 0.3629 | 0.6504 | 0.4005 | 0.3514 | 0.5451 | *0.4621* |

a Best Fit DFR ($\mu$g/cm$^2$) = foliar dislodgeable residue: double sided leaves.

b Exposure (mg/day) = [(Best Fit DFR x Transfer Coefficient (765 cm$^2$/hr))/1000 (conversion)] x 8 hrs.

## Table 8: Scout/Crop Advisor Daily Dose and MOEs

| Dose (mg/kg)[a] | | | | | | | MOE[b] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DAT | Texas | California | South Carolina 1 | North Carolina | South Carolina 2 | *Average* | Texas | California | South Carolina 1 | North Carolina | South Carolina 2 | *Average* |
| 0 | 0.0197 | 0.0370 | 0.0227 | 0.0124 | 0.0228 | *0.0229* | 51 | 27 | 44 | 81 | 44 | *44* |
| 1 | 0.0174 | 0.0327 | 0.0200 | 0.0114 | 0.0206 | *0.0204* | 57 | 31 | 50 | 88 | 48 | *49* |
| 2 | 0.0154 | 0.0288 | 0.0176 | 0.0105 | 0.0187 | *0.0182* | 64 | 35 | 57 | 95 | 53 | *55* |
| 3 | 0.0137 | 0.0254 | 0.0156 | 0.0097 | 0.0170 | *0.0163* | 73 | 39 | 64 | 103 | 59 | *61* |
| 4 | 0.0121 | 0.0224 | 0.0137 | 0.0089 | 0.0154 | *0.0145* | 83 | 45 | 73 | 112 | 65 | *69* |
| 5 | 0.0107 | 0.0198 | 0.0121 | 0.0082 | 0.0140 | *0.0130* | 93 | 51 | 82 | 122 | 72 | *77* |
| 6 | 0.0095 | 0.0174 | 0.0107 | 0.0076 | 0.0127 | *0.0116* | 105 | 57 | 93 | 132 | 79 | *86* |
| 7 | 0.0084 | 0.0154 | 0.0094 | 0.0070 | 0.0115 | *0.0103* | 119 | 65 | 106 | 143 | 87 | *97* |
| 8 | 0.0075 | 0.0135 | 0.0083 | 0.0064 | 0.0104 | *0.0092* | 134 | 74 | 120 | 156 | 96 | *108* |
| 9 | 0.0066 | 0.0119 | 0.0073 | 0.0059 | 0.0095 | *0.0083* | 151 | 84 | 136 | 169 | 106 | *121* |
| 10 | 0.0059 | 0.0105 | 0.0065 | 0.0054 | 0.0086 | *0.0074* | 171 | 95 | 154 | 184 | 116 | *135* |
| 11 | 0.0052 | 0.0093 | 0.0057 | 0.0050 | 0.0078 | *0.0066* | 193 | 108 | 175 | 199 | 128 | *151* |

a Dose (mg/kg/day) = Exposure/70 kg.

b MOE = NOEL (1 mg/kg/day)/Dose (mg/kg/day).

## Table 9: Hoer Best Fit DFRs and Exposure

| Best Fit DFRs ($\mu$g/cm$^2$)[a] | | | | | | | Exposure (mg/day)[b] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DAT | Texas | California | South Carolina 1 | North Carolina | South Carolina 2 | *Average* | Texas | California | South Carolina 1 | North Carolina | South Carolina 2 | *Average* |
| 0 | 0.2249 | 0.4237 | 0.2592 | 0.1417 | 0.2603 | *0.2620* | 0.8619 | 1.6237 | 0.9933 | 0.5429 | 0.9975 | *1.0039* |
| 1 | 0.1992 | 0.3737 | 0.2287 | 0.1305 | 0.2361 | *0.2337* | 0.7635 | 1.4319 | 0.8765 | 0.5001 | 0.9048 | *0.8954* |
| 2 | 0.1765 | 0.3295 | 0.2018 | 0.1202 | 0.2142 | *0.2084* | 0.6764 | 1.2627 | 0.7734 | 0.4607 | 0.8208 | *0.7988* |
| 3 | 0.1564 | 0.2906 | 0.1781 | 0.1107 | 0.1943 | *0.1860* | 0.5992 | 1.1135 | 0.6824 | 0.4243 | 0.7445 | *0.7128* |
| 4 | 0.1385 | 0.2562 | 0.1571 | 0.1020 | 0.1762 | *0.1660* | 0.5308 | 0.9819 | 0.6022 | 0.3909 | 0.6754 | *0.6362* |
| 5 | 0.1227 | 0.2260 | 0.1387 | 0.0940 | 0.1599 | *0.1482* | 0.4702 | 0.8659 | 0.5313 | 0.3601 | 0.6126 | *0.5680* |
| 6 | 0.1087 | 0.1993 | 0.1224 | 0.0866 | 0.1450 | *0.1324* | 0.4165 | 0.7636 | 0.4688 | 0.3317 | 0.5557 | *0.5073* |
| 7 | 0.0963 | 0.1757 | 0.1080 | 0.0797 | 0.1315 | *0.1183* | 0.3690 | 0.6734 | 0.4137 | 0.3056 | 0.5041 | *0.4531* |

a Best Fit DFR ($\mu$g/cm$^2$) = foliar dislodgeable residue: double sided leaves.

b Exposure (mg/day) = [(Best Fit DFR x Transfer Coefficient (479 cm$^2$/hr))/1000 (conversion)] x 8 hrs.

## Table 10: Hoer Daily Dose and MOEs

| Dose (mg/kg)[a] | | | | | | | MOE[b] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DAT | Texas | California | South Carolina 1 | North Carolina | South Carolina 2 | *Average* | Texas | California | South Carolina 1 | North Carolina | South Carolina 2 | *Average* |
| 0 | 0.0123 | 0.0232 | 0.0142 | 0.0078 | 0.0142 | *0.0143* | 81 | 43 | 70 | 129 | 70 | *70* |
| 1 | 0.0109 | 0.0205 | 0.0125 | 0.0071 | 0.0129 | *0.0128* | 91 | 49 | 80 | 140 | 77 | *78* |
| 2 | 0.0097 | 0.0180 | 0.0110 | 0.0066 | 0.0117 | *0.0114* | 103 | 55 | 91 | 152 | 85 | *87* |
| 3 | 0.0086 | 0.0159 | 0.0097 | 0.0061 | 0.0106 | *0.0102* | 117 | 63 | 103 | 165 | 94 | *98* |
| 4 | 0.0076 | 0.0140 | 0.0086 | 0.0056 | 0.0096 | *0.0091* | 132 | 71 | 116 | 179 | 104 | *110* |
| 5 | 0.0067 | 0.0124 | 0.0076 | 0.0051 | 0.0088 | *0.0081* | 149 | 81 | 132 | 194 | 114 | *123* |
| 6 | 0.0060 | 0.0109 | 0.0067 | 0.0047 | 0.0079 | *0.0072* | 168 | 92 | 149 | 211 | 126 | *138* |
| 7 | 0.0053 | 0.0096 | 0.0059 | 0.0044 | 0.0072 | *0.0065* | 190 | 104 | 169 | 229 | 139 | *154* |

a Dose (mg/kg/day) = Exposure/70 kg.

b MOE = NOEL (1 mg/kg/day)/Dose (mg/kg/day

## III. RISK MANAGEMENT AND REREGISTRATION DECISION

### A. Dietary

#### 1. Tolerance Reassessment Summary/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, 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. HED has since evaluated the need for hog tolerances and has concluded there is no reasonable expectation of finite residues of profenofos in hog tissues (C. Olinger, 6/99). The established 40 CFR 180.404 tolerances for eggs and poultry fat, meat, and meat byproducts, hog fat, meat, and meat by-products 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 and hog tissues and eggs may be required.

##### a. 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.

##### b. 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. A summary of profenofos tolerance reassessments is presented in Table 11.

## 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 12.

The following conclusions can be made regarding efforts to harmonize the U.S. tolerances with the Codex MRLs with respect to MRL/tolerance level: (1) compatibility between the U.S. tolerance and Codex MRL exists for milk; (2) incompatibility of the U.S. tolerance and Codex MRL for cottonseed remains because of differences in agricultural practices; and (3) 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 12).

## B. Occupational

This section will be addressed in the future.

Table 11. Tolerance Reassessment Summary for Profenofos

| COMMODITY | CURRENT TOLERANCE (ppm)[a] | TOLERANCE REASSESSMENT (ppm)[b] | COMMENT/ *[Correct Commodity Definition]* |
|---|---|---|---|
| Tolerances Listed Under 40 CFR 180.404: | | | |
| Cattle, fat | 0.05 | 0.05 | |
| Cattle, mbyp | 0.05 | 0.05 | |
| 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. [Category 40 CFR 180.6(a)(3)] |
| Goats, fat | 0.05 | 0.05 | |
| Goats, mbyp | 0.05 | 0.05 | |
| Goats, meat | 0.05 | 0.05 | |
| Hogs, fat | 0.05 | Revoke | Feeding studies indicate that tolerances are not needed for hog commodities. [Category 40 CFR 180.6(a)(3)] |
| Hogs, mbyp | 0.05 | Revoke | |
| Hogs, meat | 0.05 | Revoke | |
| Horses, fat | 0.05 | 0.05 | |
| Horses, mbyp | 0.05 | 0.05 | |
| 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. [Category 40 CFR 180.6(a)(3)] |
| Poultry, mbyp | 0.05 | Revoke | |
| Poultry, meat | 0.05 | Revoke | |
| Sheep, fat | 0.05 | 0.05 | |
| Sheep, mbyp | 0.05 | 0.05 | |
| 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 860 Residue Chemistry Guidelines,860.1000, Table 1 (August 1996). |
| 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 (860 Residue Chemistry Guidelines, 860.1000, Table 1; August 1996). |

NOTES:

[a]Defined as profenofos and its metabolites converted to 4-bromo-2-chlorophenol and calculated as profenofos.
[b]Defined as profenofos *per se*.

Table 12. Codex MRLs and Applicable U.S. Tolerances

| CODEX | | REASSESSED U.S. TOLERANCE (ppm) | RECOMMENDATION AND COMMENTS |
|---|---|---|---|
| COMMODITY (as defined) | MRL[a] (mg/kg) | | |
| Brussels sprouts | 0.5[c] | -- | |
| Cabbages, head | 1 | -- | |
| Cauliflower | 0.5[d] | -- | |
| Cottonseed | 2 | 2 | |
| Cottonseed oil, edible | 0.05* | -- | |
| Common bean (pods and/or immature seed | 0.1 | -- | |
| Eggs | 0.02* | Revoke | |
| Meat | 0.05* | 0.05 | |
| Milks | 0.01* | 0.01 | |
| Oranges, sweet, sour | 1[e] | -- | |
| Peppers, chili | 5[f] | -- | |
| Peppers, sweet | 0.5 | -- | |
| Potato | 0.05* | -- | |
| Soya bean oil, refined | 0.05* | -- | |
| Soya bean (dry) | 0.05* | -- | |
| Sugar beet | 0.05* | -- | |
| Tomato | 2 | -- | |

NOTES:
[a]All MRLs received CXL status in 1997. It is schedule for re-evaluation in 2004.

Compatibility between the U.S. tolerance and Codex MRL exists for milk, meat and cottonseed with regard to residue definition and numerical value. 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 12).

## 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. Dobozy 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. 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.

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

NOTES:

[a] Y = Yes; N = No; N/A = Not Applicable.
[b] **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.
[c] CBRS No. 8674, D169433, 12/29/92, F. Toghrol.
[d] Data are not required because the TGAI is a liquid at room temperature.
[e] CBRS No.11808, D190824, 5/24/93, L. Cheng.
[f] CBRS No. 12323, D193633, 9/1/93, K. Dockter.
[g] CBRS No. 12749, D196268, 12/16/93, F. Toghrol.

# APPENDIX 2

## Residue Chemistry Science Assessments for Reregistration of Profenofos

| GLN: Data Requirements | Current Tolerances, ppm [40 CFR] | Must Additional Data Be Submitted? | References [1] |
|---|---|---|---|
| 171-3: Directions for Use | N/A = Not Applicable | Yes [2] | |
| 171-4 (a): Plant Metabolism | N/A | No | **00045036**, **00045037**, 43186801 [3] |
| 171-4 (b): Animal Metabolism | N/A | No | **00046063**, **00046064**, **00046085**, **00048056**, 43301901 [4], 43301902 [5] |
| 171-4 (c/d): Residue Analytical Methods | | | |
| - Plant commodities | N/A | No | **00086645**, **00105244**, 43203501 [3] |
| - Animal commodities | N/A | No | **00105243**, 43354801 [4,5] |
| 171-4 (e): Storage Stability | N/A | No | 42535202 [6], 42928401-42928409 [7], 43430101 [5] |
| 171-4 (k): Magnitude of the Residue in Plants | | | |
| - Cottonseed and gin byproducts | 3.0 (cottonseed) [§180.404] | No [8] | **00045035**, **00045038**, **00046060**, **00105217**, **00106649**, 42535201 [6], 92148055 [9] |
| 171-4 (l): Magnitude of the Residues in Processed Food/Feed | | | |
| - Cottonseed processed commodities | 6.0 (cottonseed hulls); 15.0 (soapstock) [§186.4975] | No [10] | **00046060**, **00105217**, **00106649**, 92148057 [11] |
| 171-4 (j): Magnitude of the Residue in Meat, Milk, Poultry, and Eggs | | | |
| - Milk and the Fat, Meat, and Meat Byproducts of Cattle, Goats, Hogs, Horses, and Sheep | 0.01 (milk); 0.05 (fat, meat, meat byproducts) [§180.404] | No | **00046061**, **00046062**, **00046065**, **00046067**, **00048057**, **00105217**, **00106649**, 92148050-92148051 [12] |
| - Eggs and the Fat, Meat, and Meat Byproducts of Poultry | 0.05 (eggs, fat, meat, meat byproducts) [§180.404] | No [13] | **00046061**, **00046063**, **00046064**, **00046067**, **00048056**, **00105217**, **00106649**, 92148052-92148053 [12] |
| 171-4 (f): Nature and Magnitude of the Residue in Water | N/A | N/A | |
| 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 | |

Appendix 2 *(continued)*

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

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 ≤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).

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[a] (8-hr work day) | COMMENTS[b] |
|---|---|---|
| Mixer/Loader Exposure | | |
| Mixing Liquid (1a and b) | 80 acres groundboom, and 350 to 800 acres aerial | **Baseline:** Hands, dermal, and inhalation data are grades A and B. Hands = 53 replicates; Dermal = 72 to 122 replicates; Inhalation = 85 replicates. High confidence in dermal and inhalation. PHED data used for baseline, no protection factors (PFs) were necessary.<br><br>**PPE:** Hands data are grades A and B. Hands = 59 replicates; High confidence in hands data. 80% protection factor on baseline inhalation data for addition of dust/mist respirator. 50% protection factor on dermal (non-hands) baseline data for addition of second layer body protection.<br><br>**Engineering Controls:** Hands, dermal and inhalation data are grades A and B. Hands = 31 replicates; Dermal = 16 to 22 replicates; Inhalation = 27 replicates. High confidence in dermal and inhalation data. PHED data used, no protection factors were necessary. |
| Applicator Exposure | | |
| Aerial spray equipment--enclosed cab (2) | 350 to 800 acres | **Baseline:** No data<br><br>**PPE:** No data<br><br>**Engineering Controls**: Hands data are grades A and B; dermal and inhalation data are grades A,B,C. Hands = 34 replicates; Dermal = 24 to 48 replicates; Inhalation = 23 replicates. Medium confidence in dermal and inhalation data. PHED data used, no protection factors were necessary. |

| EXPOSURE SCENARIO (Number) | STANDARD ASSUMPTIONs[a] (8-hr work day) | COMMENTS[b] |
|---|---|---|
| Groundboom (3) | 80 acres | **Baseline:** Hands, dermal, and inhalation data are grades A and B. Hands = 29 replicates; Dermal = 23 to 42 replicates; Inhalation = 22 replicates. High confidence in dermal and inhalation data. PHED data used for baseline, no protection factors were necessary.<br><br>**PPE:** Hands data are grades A, B, and C. Hands = 21 replicates. Medium confidence in hands data. 80% protection factor on baseline inhalation data for addition of dust/mist respirator. 50% protection factor on dermal (non-hands) baseline data for addition of second layer body protection.<br><br>**Engineering Controls:** Hands and dermal data are grades A, B, and C; inhalation data are grades A and B. = acceptable grades. Hands = 16; Dermal = 20 to 31 replicates; Inhalation = 16 replicates. PHED data used, no protection factors were necessary. |
| Flagger | | |
| Liquids (4) | 350-800 acres | **Baseline:** Hands, dermal, and inhalation data are grades A and B. Hands = 30 replicates; Dermal = 18 to 28 replicates; Inhalation = 28 replicates. High confidence in dermal and inhalation data. PHED data used for baseline, no protection factors were necessary.<br><br>**PPE:** No data; 80% protection factor on baseline inhalation data for addition of dust/mist respirator; 50% protection factor on dermal (non-hands) baseline data for addition of second layer body protection.<br><br>**Engineering Controls:** No data; 98% protection factor added to dermal and hands for enclosed cab. |

NOTES:

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