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

49PP

JUN 18, 1996

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: The HED Chapter of the Reregistration Eligibility Decision Document (RED) for Profenofos (Case No. 2540; PC Code 111401)

FROM: Kathleen Martin, Chemist KM 6/14/96
Risk Characterization and Analysis Branch
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THRU: Michael Metzger, Chief
Risk Characterization and Analysis Branch
Health Effects Division (7509C) Michael L. Metzger

and

Stephanie Irene, Acting Director
Health Effects Division (7509C) Stephanie P. Irene 6/18/96

TO: Jay Ellenberger, Chief
Accelerated Reregistration Branch
Special Review and Reregistration Division (7508W)

Please find attached the Human Health Assessment for the Profenofos Reregistration Eligibility Decision Document (RED). This chapter includes the Hazard Assessment from Raymond Locke in TBI (Attachment I), the Occupational and Residential Exposure Assessment from Laura Morris in OREB (Attachment II), Product and Residue Chemistry Assessments from Catherine Eiden in CBRS (Attachment III), and the Dietary Risk Analysis from Brian Steinwand in SAB (Appendix IV).

Attachments

pc (without attachments): P. Deschamp, RCAB
C. Eiden, CBRS
R. Locke, TBI
L. Morris, OREB
B. Steinwand, SAB

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I. EXECUTIVE SUMMARY

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

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

Profenofos is a cholinesterase inhibitor. Because profenofos is applied to a food crop (i.e., cotton), EPA is concerned with potential risks from both dietary and occupational exposure.

II. SCIENCE ASSESSMENT

A. Physical Chemistry Assessment

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

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

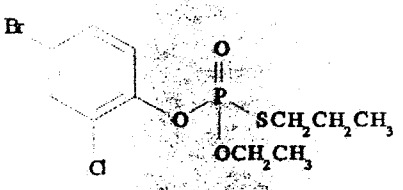
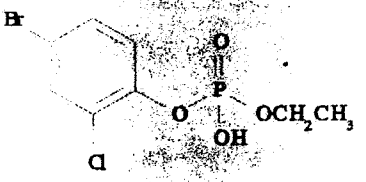
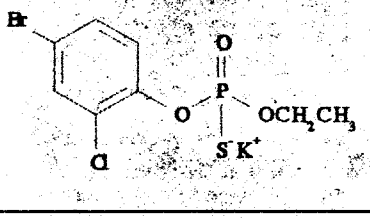
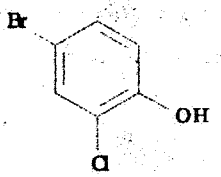
STRUCTURE	NAME
	Profenofos CGA-15324
	CGA-47196

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

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

1. Identification of Active Ingredient

Technical profenofos is a pale yellow liquid with a boiling point of 100°C (1.8 Pa) and a density of 1.46 g/cm^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 is: 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

A search of the Reference Files System (REFS) conducted on 8/1/95 identified a single profenofos manufacturing-use product under Shaughnessy No. 111401: the Ciba-Geigy Corporation 89%T (EPA Reg. No. 100-598). Only the Ciba-Geigy 89%T is subject to a reregistration eligibility decision.

3. Regulatory Background

The Profenofos Phase IV Review (dated 11/30/90 by C. Olinger) determined that Ciba-Geigy data submissions for 61 and 62 series requirements met the acceptance criteria for Phase V review; additional data were required concerning 63 series requirements. Analysis of the technical product for dioxin (i.e., 2,3,7,8-TCDD) contaminants was required during Phase V review. Dioxin data have been submitted. EPA concludes that this chemical

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is not formed or carried over from starting materials during the manufacture of technical profenofos, and that it does not need to be included on the Confidential Statement of Formulation.

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

4. Conclusions

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

B. Human Health Assessment

1. Hazard and Dose Response Assessment

At present, the available toxicological database for profenofos is adequate and will support a reregistration eligibility determination for the currently registered uses.

a. Acute Toxicity

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

Table 2. Acute Toxicity Values for Technical Profenofos[1]

TEST (Guideline)	RESULT [MRID]	TOXICITY CATEGORY
Oral LD_{50} in rat (81-1)	LD_{50} = Males: 492 (363-666) mg/kg Females: 809 (600-1090) mg/kg Combined: 630 mg/kg [MRID 41714801]	II
Oral LD_{50} in mouse (81-1)	LD_{50} = 298 (268-332) mg/kg [MRID 00105226]	II
Oral LD_{50} in rabbit (81-1)	LD_{50} = 300 mg/kg [MRID 00105228]	II
Dermal LD_{50} in rat (81-2)	LD_{50} = 1610 (1073-2415) mg/kg [MRID 00105231]	II
Dermal LD_{50}; in rabbit (81-2)	LD_{50} = Intact skin -- Males: 146.8 mg/kg Females: 143.4 mg/kg Abraded skin -- Males: 97.5 mg/kg Females: 15.9 mg/kg [MRID 00109427]	I
Inhalation LC_{50} in rat (81-3)	LC_{50} = 3.36 mg/L [MRID 0019428]	IV
Eye irritation in rabbit (81-4)	Minimal irritation, reversible within 7 days; no corneal opacity [MRID 00109429].	III
Dermal irritation in rabbit (81-5)	Moderately irritating at 72 hours; PIS = 3.3/8.0 [MRID 41714802]	III
Dermal sensitization in guinea pig (81-6)	Sensitization was induced [MRID 00109431].	--
Acute delayed neurotoxicity in hen (81-7)	No delayed neurotoxicity; NOEL = 52 mg/kg (20 mg a.i./kg); 100% mortality at next highest dose (104 mg/kg); LD_{50} = 127 mg/kg (56.3 mg a.i./kg) [MRID 00126485]	--
Acute oral neurotoxicity in rat (81-8)	NOEL for neurotoxicity = 95 mg/kg; multiple effects were seen in each sex at 190 mg/kg (LEL); NOEL for inhibition of cholinesterase activities in plasma and RBC <95 mg/kg (LDT) [MRIDs 42939801 and 42939802].	--

NOTE: [1]Technical profenofos was used in all these acute studies except for the acute delayed neurotoxicity in the hen (81-7). For this study, the formulation was used.

b. Subchronic Toxicity

Dermal Toxicity

In a repeated dose 21-day dermal toxicity study (MRID 41644501), profenofos technical (92% a.i.) was administered topically to the clipped dorsal trunk and flanks (intact skin) of HAR:PF/CF (NZW) BR albino rabbits

(5/sex/dose) as suspensions in U.S.P. purified water containing 0.5% Tween 80 at daily dose levels of 0, 0.05, 1.0, 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 (1.0 mg/kg/day) animals and high-dose (10.0 mg/kg/day) females.

After three weeks of treatment, red blood cell and serum cholinesterase (ChE) activities were statistically significantly ($p < 0.01$) decreased (range: 51-83% control values) only in high-dose (10 mg/kg/day) males and females. Brain ChE activity was also significantly decreased only in high-dose (10 mg/kg/day) males (70% control value) and females (85% control value). The LEL is 10 mg/kg/day, based on significant decreases in cholinesterase activities in red blood cells, serum, and brain. The NOEL is 1.0 mg/kg/day.

Oral Toxicity in Rodents

In a 90-day feeding study in rats (MRID 00105255), Charles River strain albino rats (28 days of age; 15/sex/group) were fed diets containing 0, 2, 20, or 200 ppm of CGA-15324 technical (corrected for purity: 94.8% a.i.), equivalent to 0, 0.2, 2.0, or 20.0 mg/kg/day, for 90 days. Five additional animals/sex/group in the control (0 ppm) and high-dose (200 ppm) groups were fed diets containing no CGA-15324 technical for four weeks of recovery after having received control (0 ppm) or high-dose diet (200 ppm) for the previous 90 days.

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 ppm) and high-dose (200 ppm) groups exposed for 90 days with no recovery period. Tissues from recovery animals were not examined microscopically. Weights of adrenals, brain, gonads, heart, kidneys, and livers were recorded for each animal and organ-to-brain and body-weight ratios determined. Standard hematology, clinical chemistry, and urinalysis studies were conducted, and cholinesterase

activities were determined in plasma, red blood cells, and brain. Ophthalmological examinations were conducted at study start and at termination.

CGA-15324 technical, at all doses tested, had no effect on any of the parameters monitored, except for inhibition of ChE activities. No compound-related effects on body weight, gross pathology, or organ histopathology were demonstrated in either male or female rats. ChE activities in plasma and red blood cells were inhibited (range: 12-98% control) in some animals in all groups treated with CGA-15324 technical, but these values returned to control values with four weeks of recovery. Brain ChE activity was inhibited (range: 56-65% control) in males only at 20 and 200 ppm, and in recovery animals at the high dose (200 ppm), returned to normal after four weeks of recovery. However, the Industrial BioTest (IBT) Validation Report indicates that the raw data (which are not available) indicate that brain ChE activity was significantly inhibited at 2 ppm (i.e., LDT), but returned to control values after the recovery period. The RBC and Plasma ChE NOEL is <2 ppm (LDT; 0.2 mg/kg/day; 2-32% inhibition) and the Brain ChE NOEL is <2 ppm (LDT; 0.2 mg/kg/day; "significant inhibition").

Oral Toxicity in Dogs

i. 13-Week Feeding Study

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

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

The only effect elicited by profenofos at any dose level tested consisted of inhibition of plasma, red blood cell, and brain cholinesterase (ChE) activities. Plasma ChE activity was depressed at least 40% in all profenofos treatment groups. Red blood cell ChE activity was depressed at least 10% in the mid- (20 ppm) and high-dose (200 ppm) groups. In males, brain cholinesterase was decreased (21% decrease) only at the high-dose (200 ppm) level, and in females only a slight decrease (5% decrease) occurred at this dose level only. In the recovery animals, plasma and brain ChE activities

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returned to pretest values, but the red blood cell ChE activity remained depressed at about 50% of pretest values (although some recovery was seen with respect to values at 90 days on test).

The systemic NOEL is >200 ppm (HDT; >5 mg/kg/day), based on lack of effects other than cholinesterase inhibition. The Plasma ChE NOEL is <2 ppm (LDT; <0.05 mg/kg/day), based on 52-58% inhibition at 2 ppm. The RBC ChE NOEL is 2 ppm (LDT; 0.05 mg/kg/day), based on 10-31% inhibition at 20 ppm. The Brain ChE NOEL is 20 ppm (0.5 mg/kg/day), based on a 21% decrease in brain ChE activity in males at 200 ppm.

ii. Six-Month Feeding Study

In a six-month feeding study (MRID 00081687), groups of Beagle dogs (7/sex/group) were administered diets containing profenofos technical (88.1-89.3% a.i.) at 0, 0.2, 2, 100, or 500 ppm for 182 consecutive days (26 weeks; six months). These dosage levels correspond to 0.0, 0.005, 0.05, 2.5, or 12.5 mg/kg/day, respectively. One animal/sex/group was maintained on laboratory chow diet containing no profenofos for a one-month recovery period following the six months of treatment.

Animals were examined daily for mortality, clinical signs of toxicity, and moribundity. Food consumption was monitored daily and weekly food efficiency values were calculated. Body weight and auditory response were determined weekly. Standard hematology, blood chemistry (including determination of plasma and red blood cell cholinesterase inhibition), and urinalysis determinations were conducted pretest and during weeks 4, 9, 13, 18, 22, and 26, and additionally at week 31 for recovery-group animals. Ophthalmological examinations were conducted pretest and after 26 week (and at 31 weeks for recovery-group animals). After 23 weeks of treatment, all animals from the control (0 ppm profenofos) and high-dose (500 ppm profenofos) 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 effect elicited by dietary administration of technical profenofos at any dose level tested was cholinesterase inhibition in brain (range: 0-11%), plasma (range: 0-79%), and red blood cells (range: 0-81%). One-month recovery only partially restored cholinesterase activities in plasma and red blood cells in males, but completely restored these

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activities in females. Brain cholinesterase was inhibited 5% only at the 2 ppm dose level in males; in females, inhibition was 8%, 10%, 11%, and 5% for the 0.2, 2.0, 100.0, or 500 ppm dietary profenofos levels, respectively. No recovery data were available for brain cholinesterase inhibition. The LEL is 2.0 ppm (0.05 mg/kg/day), based on cholinesterase inhibition (27-54%) in plasma in male and female dogs, and in RBC (1-81%) in male dogs only. The NOEL is 0.2 ppm (0.005 mg/kg/day).

c. Chronic Toxicity

In a chronic toxicity/oncogenicity study (MRID 00081685), groups of Fisher 344 rats (60/sex/group) were fed diets containing CGA-15324 technical (90.6% a.i.) at dose levels corrected for purity of 0, 0.3, 10.0, or 100.0 ppm for 105 weeks (two years). These dose levels approximately correspond to 0, 0.015, 0.50, or 5.0 mg/kg/day. Five animals/sex/group were added to the control (0 ppm) and high-dose (100 ppm) 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 ppm) or high-dose (100 ppm) diets for 52 weeks, and then only basal diet for an additional 11 weeks, with sacrifice at week 63.

Red blood cell and plasma cholinesterase (ChE) activities were determined in 10 animals/sex/group from all study groups at weeks 13, 26, and 52; these same determinations were made in 5 animals/sex/group in the control (0 ppm) and high-dose (100 ppm) recovery animals at weeks 57, 78, and 105. Brain ChE activity was determined in 5 animals/sex/group in the control and high-dose groups at 52 weeks, and in 10 animals/sex/group from all groups at week 105.

Treatment with CGA-15324 technical caused no effects, at any dose level tested, on survival with respect to control values at either 54 weeks (range: 83-99%) or 104 weeks (range: 72-90%). There were no biologically significant differences from control values noted in any treated group with respect to body weights or food consumption. In addition, CGA-15324 technical, at all doses tested, caused no effects on organ weights, organ/body weight or organ/brain weight ratios, hematological parameters, clinical chemistry and urinalysis values, or gross or microscopic pathology.

The only treatment-related effect observed was inhibition of red blood cell (RBC), plasma, and brain cholinesterase activities. Significant (>10%) inhibition of brain ChE occurred only in females in the 100 ppm group at 105 weeks only. This study was conducted at adequate dose levels, since at the highest dose tested (100 ppm), ChE activity was inhibited in red blood cells up to 69.4% and up to 62.4% in blood plasma. Higher dose levels

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would likely lead to unsatisfactory survival of test animals. The NOEL for chronic systemic effects is 0.3 ppm (LDT; 0.015 mg/kg/day), based on inhibition (>20%) of ChE activity in red blood cells and plasma at 10 ppm (i.e., the MDT; 0.5 mg/kg/day).

d. Carcinogenicity

i. Two-Year Carcinogenicity Study

In a two-year carcinogenicity study (MRID 00082901), groups of HaM/ICR Swiss, Charles River CD® mice (65/sex/group) were administered diets containing CGA-15324 technical at levels of 0, 1, 30, or 100 ppm (approximately corresponding to 0, 0.150, 4.50, or 15.0 mg/kg/day) for 85 weeks (males) or 97 weeks (females).

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

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

Cholinesterase (ChE) inhibition (>20%) occurred in plasma and red blood cells in both males and females at 53 weeks and at study termination at dose levels of 30 and 100 ppm, but not at 1 ppm. Adequate dose levels were used in this study, since at the highest dose tested (100 ppm), ChE activity was inhibited up to 74.2% in red blood cells, and up to 76.1% in blood plasma. Under the study conditions, technical profenofos did not demonstrate an oncogenic potential. The oncogenic NOEL is >100 ppm (HDT; 15.0 mg/kg/day).

ii. Chronic Toxicity/Oncogenicity Study

In a chronic toxicity/oncogenicity study (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 under 'chronic toxicity'). This study was conducted at adequate dose levels, since at the highest dose tested (100 ppm), ChE activity was inhibited in red

blood cells up to 69.4% and up to 62.4% in blood plasma. Higher dose levels would likely lead to unsatisfactory survival of test animals. Under the study conditions, profenofos did not demonstrate an oncogenic effect. Therefore, the oncogenic NOEL is >100 ppm
(HDT; 5.0 mg/kg/day).

e. Developmental Toxicity

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

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

Mean food consumption was markedly decreased (86% control value) during the treatment period in the pregnant females in the 60 mg/kg/day group 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 control were observed in any CGA-15324-treated group with respect to implantation ratio, embryolethality, fetal average body weight, or fetal skeletal abnormalities.

From these data, it is concluded that CGA-15324 at all doses tested caused no treatment-related developmental (teratogenic) effects. The Developmental NOEL is >60 mg/kg/day (HDT); the Maternal NOEL is 30 mg/kg/day (MDT), based on decreased food consumption and slightly decreased body weight at 60 mg/kg/day; and the Maternal LEL is 60 mg/kg/day (HDT), based on decreased food consumption and slightly decreased body weight.

Other available developmental toxicity studies on profenofos include an unacceptable study in rats (MRID 00109313) and supplementary studies in rabbits (MRIDs 00140827 and 00128870). On November 9, 1995, the Agency's Office of Pesticide Program Health Effects Division Reference Dose Peer Review Committee (i.e., RfD Peer Review Committee) concluded 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 will not be necessary, since they would not contribute meaningful additional information to the toxicological assessment of this chemical.

f. 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, 7.30, and 29.00 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 after 134-137 days of dietary treatment; P_0 parental females were necropsied at 183-186 days of age after 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 body weights and body weight changes, pup survival indices, external observations during lactation, or incidences of adverse observations during macroscopic examination of pups dying during lactation, culled on day 4, or weaned on day 21, or during histopathological examination of organs from high-dose (400 ppm diet) and control (0 ppm diet) P_0 and P_1 parental males and females.

The NOEL for parental systemic toxicity is 100 ppm (7.3 mg/kg/day; the MDT) and the LEL is 400 ppm (29 mg/kg/day; the 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 both males and females of both 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 100 ppm (7.3 mg/kg/day; the MDT) and the LEL is 400 ppm (29 mg/kg/day; the 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: $p \leq 0.01$) on days 14 and 21 of lactation.

g. Mutagenicity

In a bacterial/mammalian microsome reverse gene mutation assay (MRID 41866901), triplicate cultures of four Salmonella strains (TA100, TA1535, TA98, TA1537) and the WP2uvrA strain of Escherichia were exposed in independent replicate trials to concentrations of CGA-15324 technical (90.7% a.i.) up to the limit, 5000 μg/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 μg/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 μg/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 μg/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 dose producing 50% cytotoxicity (the HDT, 2.91 μg/mL).

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

h. Metabolism

In a metabolism study (MRID 42334301), the absorption, distribution, metabolism and elimination of profenofos were studied in groups of CD® rats administered a single oral dose of 1 or 100 mg/kg of (phenyl-UL-^{14}C)-labeled pesticide, and in 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 postexposure. Analysis of fecal material indicated that <4% of the parent compound or its metabolites are unabsorbed or excreted via the biliary system into the intestinal tract.

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

i. Neurotoxicity

i. Acute Neurotoxicity Study

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

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

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increased incidence of diarrhea, miosis, staining of the nose, abnormal gait, and increased ease of handling. Rats at 380 mg/kg also exhibited an increased incidence of salivation (females only), lacrimation, impaired respiration, soiled fur, ataxia, impaired righting reflex, impaired hindlimb extensor reflex (females only), flattened body position (females only), tremors, decreased arousal, decreased number of rears, dehydration, decreased core body temperature (females only), and decreased motor activity.

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

ii. Subchronic Neurotoxicity Study

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

The rats were assessed daily for clinical signs, FOB, and motor activity effects and plasma ChE and RBC AChE at 4, 8 and 13 weeks, and for neurohistopathological changes and brain AChE after 13 weeks. The study included acrylamide (16 mg/kg/day) and trimethyltin (3 mg/kg/day) as positive controls. No compound-related clinical signs, changes in the FOB parameters, nor motor activity were reported at any dose levels 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 (about up to 7% in males and 9% in females) in both sexes in the high dose group. The LEL for systemic toxicity is 36 mg/kg/day, based on slight decreases in body weight; the NOEL is 7.7 mg/kg/day. Profenofos inhibited ($p< 0.01$) plasma ChE (58-61% in females and 28 to 31% in males) and RBC AChE (54 to 74% in males and 51 to 56% in females) at 1.70 and 1.84 mg/kg/day at each assay interval.

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Progressively higher degrees of inhibition were noted at higher dose levels. Brain AChE became significantly inhibited (12% males and 20% females: $p < 0.01$) only at the high doses of 36 mg/kg/day for males and 37.9 mg/kg/day for females. The LEL for plasma ChE and RBC AChE is 1.70 mg/kg/day; no NOEL was established. The LEL for brain AChE is 36 mg/kg/day and the NOEL for brain AChE is 7.7 mg/kg/day.

iii. Acute Delayed Neurotoxicity Study

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

j. Epidemiological Information (U.S. EPA, 1996a)

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

IDS Data

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

PCC Data

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

exposed); four involved profenofos only and 11 were attributed to multiple chemicals.

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

2. Toxicological Endpoints for Risk Assessment

a. Reference Dose (RfD)

The RfD Peer Review Committee met on November 9, 1995 to discuss and evaluate the existing and/or recently submitted toxicology data in support of profenofos reregistration and to reassess the RfD for this chemical.

The Committee recommended that the RfD for this chemical remain unchanged; the RfD had been established based on the long-term (six-month) toxicity study in dogs (MRID 00081687) with a NOEL of 0.2 ppm (0.005 mg/kg/day). At the next higher dose level of 2 ppm (0.05 mg/kg/day). erythrocyte and plasma cholinesterase inhibition was observed. An Uncertainty Factor of 100 was applied to account for both the interspecies extrapolation and intraspecies variability. On this basis, the RfD was calculated to be 5×10^{-5} mg/kg/day (U.S. EPA, 1996b).

b. Carcinogenic Classification

The carcinogenic potential of profenofos was evaluated by the RfD Peer Review Committee on November 9, 1995. The Committee recommended that profenofos be classified as Group E (i.e., the chemical is 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).

c. Other Toxicological Endpoints

On January 16, 1996 the Agency's Office of Pesticide Program Health Effects Division Toxicity Endpoint Selection Committee (i.e., the TES Committee) met to discuss the toxicological endpoints to be used in the risk characterization of profenofos; they are summarized in Table 3. Because of the nature of selecting toxicological endpoints for risk assessment, particularly those for occupational and residential assessment, sometimes non-guideline, older, or less rigorous studies must be used. Such is the case for the acute dietary and inhalation toxicity endpoints. The studies examined for each of these endpoints is described below; the studies used for the short to intermediate-term occupational and chronic (noncancer) assessments are described in the "Hazard and Dose Response Assessment" section.

Acute Dietary Endpoint (MRID 43213302). In this non-guideline two-phase study, a NOEL for acute toxicity and the NOELs for cholinesterase inhibition in blood cells, plasma, and brains of male and female Crl:CD®BR VAF/Plus® rats were determined. In phase 1, groups of five males received a single oral dose of undiluted profenofos technical (89.2% a.i.) by gavage at dosage levels of 100, 200, 400, 600, or 800 mg/kg and groups of five female rats were similarly treated at dosage levels of 100, 200, 300, or 400 mg/kg.

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

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

In phase 2, 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.

Table 3. Toxicological Endpoints for Profenofos

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

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 and bled, and the brains flash-frozen, for determination of cholinesterase activities in red blood cells, plasma, and brain. All animals were subjected to gross necropsy, but no treatment-related findings were observed. The only clinical sign observed was soft feces. The NOEL for profenofos technical for plasma cholinesterase inhibition is 0.5 mg/kg in male rats and 0.1 mg/kg in female rats; the NOEL for inhibition of brain cholinesterase activity in both male and female rats is 25 mg/kg; and the NOEL for inhibition of red blood cell cholinesterase activity is 25 mg/kg for male rats and 0.5 mg/kg for female rats. It should be noted that in a 21-day dermal study (MRID 41644501) brain ChE was inhibited at the same dose level (10 mg/kg) as plasma and RBC cholinesterase.

Inhalation (MRID 00082079). In this 21-day inhalation toxicity study, 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 and then sacrificed. Complete clinical observations were made daily; ophthalmological and food consumption data were collected weekly. Hematologic, urinalysis, and blood chemistry data were collected at the end of

the 21-day treatment period and, in selected rats, at the end of the recovery period. Gross and microscopic pathology studies were conducted.

All rats of the high-dose group (0.449 mg/L) and one female of the mid-dose (0.219 mg/L) group died during the first week. Food intake of male rats of the mid-dose group decreased during the entire exposure period, while the weights of females of this group and all rats in the low-dose (0.068 mg/L) decreased during the first week of exposure only. Animals in the high-dose group lost weight until unscheduled death. Food intake and body weight gain of males in the mid-dose group, depressed during the exposure period, was comparable to controls by the end of the recovery period. Hematological and blood chemistry values of all treated animals were comparable to control values. However, the cholinesterase activities in plasma, red blood cells, and brain were significantly depressed (20% to 65% of control values) in all treated animals. Thus, a NOEL for cholinesterase inhibition was not determined in this study. The most common gross observation in treated animals was acute congestion of the nasal mucous membrane and some intermittent or purulent keratitis in all rats as the highest test concentration in animals that died on the 3rd to 5th test day, and this was confirmed by the microscopic histopathology. The LEL for ChE inhibition in brain, red blood cells, and plasma is 0.068 mg/L (LDT). The NOEL is <0.068 mg/L.

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

3. Exposure Assessment

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 applied aerially by helicopter and fixed-wing aircraft as well as being applied by a groundboom sprayer.

The only registered end-use product is Curacron 8E Insecticide-Miticide (EPA Reg. No. 100-669; 72.7% a.i.). Thus, the following exposure assessment is based on this single product.

EPA expects both dietary and occupational exposure from the use of profenofos (there are no residential uses). Dietary exposure is expected to be both acute and chronic (i.e., one day and over a long-term period of time). Occupational exposure is expected to occur over a short to intermediate term (i.e., from one day to several months).

a. Dietary Exposure

Regulatory 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 Review. 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 (3.0 ppm), eggs and the fat, meat, and meat byproducts of cattle, goats, hogs, horses, and sheep (0.05 ppm), and milk (0.01 ppm). Feed additive tolerances have been established for cottonseed hulls (6.0 ppm) and soapstock (15.0 ppm). The Pesticide Analytical Manual (PAM) Volume II lists two gas chromatography (GC) methods, Methods I and II, for the enforcement of tolerances (as currently expressed) for cottonseed and animal commodities, respectively. Codex maximum residue limits (MRLs) have been established for plant commodities and animal products and are expressed in terms of profenofos *per se*. Provided in the "Risk Management and Reregistration Decision" section of this document are the Codex MRLs (see Table 9).

Summary of Science Findings

i. GLN 171-3: Directions for Use

A REFs search conducted 8/1/95 identified one profenofos end-use product registered to Ciba-Geigy Corporation. The 8 lb/gal emulsifiable concentrate formulation (EC; EPA Reg. No. 100-669; Curacron® 8E Insecticide-Miticide; label accepted 2/10/94) is a restricted-use pesticide registered for multiple foliar spray applications, with 5- to 7-day retreatment

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intervals, to cotton at 0.25-1.0 lb a.i./application. Applications may be made alone, as a tank mix with other insecticides, or diluted with oil for ultra-low volume (ULV) application. When used alone or when tank mixed, the formulation may be applied using ground (minimum of 5 gal of water/A) or aerial (minimum of 1 gal of water/A) equipment; the established maximum seasonal rate is 6 lb a.i./A and the established preharvest interval (PHI) is 14 days. When diluted with once-refined vegetable oil for ULV application, application may by made in 1-2 qts. of finished spray/A or water may be added for application in a minimum of one gal of finished spray/A; a maximum of three applications may be made per growing season and the established PHI is 30 days. The label restricts the feeding of gin trash or foliage from treated cotton plants to livestock. The label specifies that fields treated with the 8 lb/gal EC formulation may be rotated to other crops.

Label amendments are required. 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."

Currently, the label allows aerial application in a minimum of 1 gal of water/A. Unless field residue data reflecting aerial applications in $\leq$1 gal of water/A with a 14-day PHI are available, the product label must be amended to specify that aerial applications be made in a minimum of 2 gal of water/A. Sufficient field residue data are available to support application using ground equipment with a 14-day PHI, and application using ULV equipment with a 30-day PHI.

ii. GLN 171-4 (a): Plant Metabolism

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

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

iii. GLN 171-4 (b): Animal Metabolism

The qualitative nature of the residue in animals is adequately understood based on the results of acceptable ruminant and poultry metabolism studies. The HED Metabolism Committee has determined that profenofos *per se* is the compound of toxicological concern in milk and livestock tissues. In ruminants, residues of profenofos were present in liver and fat, only, at 0.05 and 0.03 ppm, respectively.

The Metabolism Committee has also determined that 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 and eggs) even at exaggerated dosing levels. Thus, there is presently no need for tolerances for residues of profenofos in poultry tissues and eggs.

iv. GLN 171-4 (c) and (d): Residue Analytical Methods - Plants and Animals

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

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

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).

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v. GLN 171-4 (e): 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 demonstrating that 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 demonstrating that fortified residues of profenofos are stable for up to 12 months of frozen storage in beef muscle and liver, milk, and eggs.

vi. GLN 171-4 (k): Magnitude of the Residue in Plants

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 in light of the recent HED Metabolism Committee decision regarding the residues to be regulated, the Branch recommends that the established tolerances for cottonseed be lowered from 3.0 ppm to 2.0 ppm.

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

vii. GLN 171-4 (l): Magnitude of the Residue in Processed Food/Feed

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

Based on the HED Metabolism Committee decision regarding the residues to be regulated, the Agency concludes that a Section 409 tolerance for cottonseed hulls is not warranted. The expected residue level of profenofos in cottonseed hulls is less than the reassessed RAC tolerance (2.0 ppm). Therefore, the established feed additive tolerance of 6.0 ppm for cottonseed

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hulls should be revoked. The established feed additive tolerance of 15.0 ppm for soapstock should also be revoked since this commodity is no longer considered a significant feed item (Pesticide Assessment Guidelines Subdivision O, Table II; September 1995).

viii. GLN 171-4 (j): Magnitude of the Residue in Meat, Milk, Poultry, and Eggs

There are no registered direct animal 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 and animal metabolism studies, and in light of the HED Metabolism Committee decision regarding residues to be regulated, the Agency has reassessed the established tolerances for animal commodities.

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

ix. GLN 171-4 (f, g, and h): Nature and Magnitude of the Residue in Water, Fish and Irrigated Crops

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

x. GLN 171-4 (i): Magnitude of the Residue in Food-Handling Establishments

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

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xi. GLNs 165-1 and 165-2: Confined/Field Rotational Crops

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

xii. Residue Information (for dietary risk assessment)

Tolerances for profenofos are published in 40 CFR 180.404 and 186.4975. Tolerances had been established in/on cottonseed (3.0 ppm), eggs, and the fat, meat, and meat byproducts of cattle, goats, hogs, horses, and sheep (0.05 ppm), and milk (0.01 ppm). The established tolerances on animal commodities are adequate but should be redefined in terms of profenofos *per se*.

Anticipated residues are based on cottonseed processing and livestock feeding studies (U.S. EPA, 1996e). For cottonseed, the % crop treated is factored into the Anticipated Residue Contribution (ARC). For this analysis, 10% crop treated was used.

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

b. Occupational Exposure

An occupational and/or residential exposure assessment is required for an active ingredient if: (1) certain toxicological criteria are triggered; and (2) there is potential exposure to handlers (mixers, loaders, applicators, etc.) during use or to persons entering treated sites after application is complete.

In the case of profenofos, EPA has determined that there is a toxicological concern and there is potential exposure to mixers, loaders, applicators, or other handlers during activities that would occur under the usual profenofos use scenarios. Also, there is potential exposure to persons

reentering sites that have been treated with profenofos. Therefore, the Agency has assessed application and post-application exposure to profenofos.

At this time all products containing profenofos are intended primarily for occupational use (i.e., no residential exposure is expected). Thus, this exposure assessment is limited to occupational uses only. Further, EPA expects that, based on the use patterns, exposure to profenofos will occur for a short to intermediate duration; chronic exposure is not expected (i.e., there is not a continuous six month exposure period). Finally, the Agency expects exposure to occur via the dermal and inhalation routes.

i. Application Exposure

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

> *"Assessment of Worker Exposure for the Profenofos EC Formulation Using the Pesticide Handlers Exposure Database"*
> *(EPA MRID 426288-01)*
>
> PHED Version 1.01 was used to estimate the dermal and inhalation exposure resulting from the use of the emulsifiable concentrate formulation of profenofos. The study investigated mixer/loader, aerial applicator and groundboom applicator exposure. The results indicated that the mixer/loaders for aerial applications had a daily dose of 63 μg/kg/day. For pilots (aerial applicators) the daily dose was determined to be 73 μg/kg/day. For groundboom applicators, the daily dermal dose was estimated to be 48 μg/kg/day.

Since the registrants submitted their PHED analysis, a new version of PHED has been developed (i.e., Version 1.1). So, for this risk assessment, EPA reassessed profenofos mixer/loader/applicator exposure using the new version. EPA's exposure estimates are quite different from those provided by the registrant. These differences are attributed to: (1) the registrant's submission is based on PHED V1.01 while EPA's assessment is based on PHED V1.1; (2) the registrant and EPA used slightly different assumptions (i.e., number of acres treated/day, etc.); and, (3) the registrant used different clothing scenarios.

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

Potential dermal and inhalation baseline unit exposures (which are derived from PHED V1.1), along with their corresponding calculated daily exposures, are presented in Table 4. Baseline unit exposure is the PHED exposure estimate with just the clothing scenario that was provided in the PHED data base (i.e., the baseline clothing).

Please note that dermal exposure is several orders of magnitude greater than inhalation exposure. For the aerial scenarios (i.e., 1a, 3, and 5), "typical" (typ) and "maximum" (max) daily exposure values are presented, due to the nature of the "Daily Acres Treated" estimates. Typical and maximum "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:

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

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

ii. Post-Application Exposure

Based on the use patterns of profenofos, EPA has determined that there is potential exposure to persons entering treated sites after application is complete. Such exposure is possible for agricultural workers, such as harvesters, hoers and scouts.

The registrant submitted post-application exposure data in support of the profenofos data requirements requested during Phase 4 of the reregistration process. Two foliar dissipation studies (i.e., Study 1 and Study 2 below) and one worker reentry study (i.e., Study 3 below) using profenofos were conducted. The purpose of these studies was to determine foliar dislodgeable residue (FDR) dissipation and worker exposure to cotton treated with profenofos.

Table 4. Profenofos Baseline Unit Exposures and Daily Exposures (Short and Intermediate-Term)

EXPOSURE SCENARIO (Number)	BASELINE DERMAL UNIT EXPOSURE (mg/lb a.i.)[a]	BASELINE INHALATION UNIT EXPOSURE (mg/lb a.i.)[b]	APPLICATION RATE (lb a.i./A)[c]	DAILY ACRES TREATED[d]	DAILY DERMAL EXPOSURE (mg/day)[e]	DAILY INHALATION EXPOSURE (mg/day)[f]	DAILY TOTAL EXPOSURE (mg/day)[g]
Mixer/Loader Exposure							
Mixing/Loading Liquid Formulations for Aerial Equipment (1a)	2.9	1.2×10^{-3}	1	Typ: 350 Max: 800	Typ: 1015 Max: 2320	Typ: 0.42 Max: 0.96	Typ: 1015 Max: 2321
Mixing/Loading Liquid Formulations for Groundboom Equipment (1b)				80	232	0.096	232.1
Applicator Exposure							
Applying the Liquid Formulation Using a Helicopter (enclosed cockpit) (2)	2×10^{-3}	2×10^{-6}	1	350	0.7	0.0007	0.7
Applying the Liquid Formulation Using a Fixed-Wing Aircraft (enclosed cockpit) (3)	5×10^{-3}	7×10^{-5}	1	Typ: 350 Max: 800	Typ: 1.75 Max: 4	Typ: 0.02 Max: 0.056	Typ: 1.77 Max: 4.06
Applying the Liquid Formulation Using a Groundboom Sprayer (4)	1×10^{-2}	7×10^{-4}	1	80	0.8	0.056	0.856
Flagger Exposure							
Flagging During Aerial Application of Liquids (5)	1×10^{-2}	3×10^{-4}	1	Typ: 350 Max: 800	Typ: 3.5 Max: 8	Typ: 0.105 Max: 0.24	Typ: 3.61 Max: 8.24

NOTES:

[a]Baseline dermal unit exposure (from PHED V1.1) represents long pants, long sleeve shirts, no gloves, open mixing/loading, enclosed cockpit (no data available for open cockpits), open cab tractor.
[b]Baseline inhalation unit exposure (from PHED V1.1) represents no respirator.
[c]Application rate based on values found in EPA label Reg. No. 100-669.
[d]Acres treated values are from EPA estimates of acreage that could be treated in a single day for each exposure scenario of concern.
[e]Daily dermal exposure (mg/day) = Unit Exposure (mg/lb a.i.) * Application Rate (lb a.i./A) * Acres treated/day.
[f]Daily inhalation exposure (mg/day) = Unit Exposure (mg/lb a.i.) * Application Rate (lb a.i./A) * Acres treated/day.
[g]Total daily exposure (mg/day) = Daily dermal exposure (mg/day) + Daily inhalation exposure (mg/day).

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

The test site was in Burlington County, TX. Curacron® 8E was applied to cotton at an application rate of 1.0 lb a.i./A. In total, six applications were made for a total of 6.0 lb a.i./A. The applications were made on July 8, 13, 18, 23, 28 and August 2, 1991. Application was made with a tractor-drawn groundboom sprayer. The first samples were collected after the sixth (i.e., final) application, day after treatment (DAT) 0 after sprays had dried. On DAT 0 the mean residues were 1.950 $\mu g/cm^2$ and by DAT 35 the residues were 0.010 $\mu g/cm^2$.

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 a.i./A. In total, six applications were made for a total of 6.0 lb a.i./A. The applications were made on July 24, 29, August 3, 8, 13, and 19, 1991. Application was made with a commercial cotton sprayer. The first samples were collected after the sixth (i.e., final) application, day after treatment (DAT) 0 after sprays had dried. On DAT 0 the mean residues were 1.40 $\mu g/cm^2$ 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 FDR test site was in Cheraw, SC. Curacron® 8E was applied to cotton at an application rate of 1.0 lb a.i./A. In total, six applications were made for a total of 6.0 lb a.i./A. The applications were made on August 11, 18, 25, and 31 and September 6, and 11, 1992. Application was made with a tractor-drawn groundboom sprayer. The first samples were collected after the sixth (i.e., final) application, days after treatment (DAT) 0 after sprays have dried. On DAT 0 the mean residues were 2.70 $\mu g/cm^2$ and by DAT 35 the residues were 0.010 $\mu g/cm^2$.

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

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

In addition to these three FDR 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 which had been previously treated with profenofos. There were two days of reentry activities for each site. Five volunteers worked at each site on both reentry days. Three of the workers acted as scouts (looking for insects) while the remaining two workers hoed around cotton plants. Dermal exposure was measured using face/neck swipes, hand washes and whole body dosimeters. The outer dosimeter was coveralls, while the inner dosimeter was one-piece cotton underwear. Inhalation monitoring was also conducted using personal sampling pumps. The sample collector was composed of a Chromosorb 102 air sorbent tube. There was a preloaded filter cassette attached to the end of the Chromosorb tube to capture particulate matter.

On DAT 0, the scouts were exposed to 1174.5 μg/day (inner dosimeter plus inhalation data), while on DAT 1, the scouts were exposed to 763.7 μg/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 μg/day (inner dosimeter plus inhalation data), while on DAT 1, the hoers were exposed to 365.4 μg/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).

4. Risk Characterization

EPA expects both dietary and occupational exposure and risks from the use of profenofos (there are no residential uses). Dietary exposure occurs via the oral route while occupational exposure occurs via the dermal and inhalation routes.

Dietary exposure is expected to occur over an acute through chronic period. To characterize the acute dietary risk, EPA calculates a margin-of-exposure (MOE), which is the ratio of the toxicity (i.e., NOEL) to exposure. To characterize chronic risk, EPA calculates the percent of the RfD (i.e., %RfD) used.

Occupational exposure is expected to occur over a short to intermediate term. Because of the selected toxicity endpoints, the Agency is characterizing the applicator risks by MOE, that is, by the ratio of the NOEL to the exposure estimates. For reentry workers, EPA is characterizing the risk by establishing the restricted entry interval (REI).

a. Dietary Risk

i. Acute Dietary Risk

The acute Dietary Risk Evaluation System (DRES) analysis estimates the distribution of single-day exposures for the overall U.S. population and certain subgroups. It includes all published uses of profenofos, even those commodities that are being recommended for revocation (U.S. EPA, 1996c). The analysis evaluates individual food consumption as reported by respondents in the USDA 1977-1978 Nationwide Food Consumption Survey and accumulates exposure to the chemical for each commodity.

The MOE is calculated by dividing the acute dietary NOEL (i.e., 0.5 mg/kg/day) by the high-end exposure (see Table 1 of Appendix 4 for the exposure estimates). Provided in Table 5 are the MOEs for the overall U.S. population along with four subgroups: Infants (< 1 year), Children (1-6 years), Females (13+ years), and Males (13+ years).

ii. Chronic Dietary Risk

A DRES chronic exposure analysis was performed using anticipated residues for the general population and 22 subgroups; a summary of the ARCs is provided in Tables 2 and 3 of Appendix 4. Provided in Table 5 are the %RfD values for the U.S. general population, non-nursing infants (< 1 year old), and children (1-6 years). Please note that this chronic analysis for profenofos is not a worst case estimate of dietary exposure; it includes some residues at anticipated levels.

Table 5. Acute and Chronic Dietary Risk Evaluation for Profenofos

POPULATION SUBGROUP	MOE (Acute)	%RfD* (Chronic - noncancer)
General U.S. Population	333	7.7
Infants (< 1 year)	250	21.0
Children (1-6 years)	250	18.1
Females (13+ years)	500	--
Males (13+ years)	500	--

NOTE:

* The %RfD includes some residues at TMRC.

Conclusion

Generally, acute dietary MOEs greater than 100 tend to cause no dietary concern when the data are compared to a toxicological endpoint from an animal study (such is the case for profenofos). According to Table 5, the lowest MOE is 250. Thus, EPA is not concerned with acute dietary risks from exposure to profenofos residues in food.

As shown in Table 5, much less than 100% of the RfD is occupied by the dietary uses recommended through reregistration. Thus, chronic dietary exposure is not of concern to the Agency.

b. Occupational Risk

i. Applicators

Provided in Table 6, among other things, are the MOEs (total) for the profenofos application scenarios. The "Daily Total Dose" includes the contributions from both the dermal and inhalation exposure components. The Daily Inhalation Dose is not presented in the Table because it makes such a small contribution to the 'Daily Total Dose.' Because the short and intermediate term toxicity studies were dermal, it is not appropriate to apply a dermal absorption factor in the daily dose calculations.

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

EXPOSURE SCENARIO (Number)	MOE CALCULATION USING BASELINE EXPOSURE			MOE CALCULATIONS CONSIDERING RISK MITIGATION MEASURES							
				ADDITIONAL PPE[d]				ENGINEERING CONTROLS[e]			
	Daily Dermal Dose[a] (mg/kg/day)	Daily Total Dose[b] (mg/kg/day)	Baseline MOE[c] (Total)	Dermal Unit Exposure (mg/lb a.i.)	Inhalation Unit Exposure (mg/lb a.i.)	Daily Total Dose[b] (mg/kg/day)	PPE MOE[c] (Total)	Dermal Unit Exposure (mg/lb a.i.)	Inhalation Unit Exposure (mg/lb a.i.)	Daily Total Dose[b] (mg/kg/day)	Engineering MOE[c] (Total)
Mixer/Loader Risk											
Mixing/Loading Liquid Formulations for Aerial Equipment (1a)	Typ: 14.5 Max: 33.2	Typ: 14.5 Max: 33.2	Typ: 0.07 Max: 0.03	0.024	2.4x10-4	Typ: 0.12 Max: 0.28	Typ: 8 Max: 4	0.007	8.0x10-5	Typ: 0.035 Max: 0.081	Typ: 29 Max: 12
Mixing/Loading Liquid Formulations for Groundboom Equipment (1b)	3.3	3.3	0.3	0.024	2.4x10-4	0.027	37	0.007	8.0x10-5	0.008	125
Applicator Risk											
Applying the Liquid Formulation Using a Helicopter (enclosed cockpit) (2)	0.01	0.01	100	No data	No data	No data	No data	No data	No data	No data	No data
Applying the Liquid Formulation Using a Fixed-Wing Aircraft (enclosed cockpit) (3)	Typ: 0.025 Max: 0.057	Typ: 0.025 Max: 0.058	Typ: 40 Max: 17	No data	No data	No data	No data	No data	No data	No data	No data
Applying the Liquid Formulation Using a Groundboom Sprayer (4)	0.011	0.012	82	0.01	7.0x10-4	0.012	83	0.004	4.0x10-5	0.0046	217
Flagger Risk											
Flagging During Aerial Application of Liquids (5)	Typ: 0.05 Max: 0.11	Typ: 0.05 Max: 0.12	Typ: 20 Max: 8	0.0065	6.0x10-5	Typ: 0.033 Max: 0.07	Typ: 31 Max: 14	0.0002	6.0x10-6	Typ: 0.001 Max: 0.002	Typ: 1,000 Max: 500

NOTES FOR TABLE 6:

aDaily Dermal Dose = Daily Dermal Exposure/70 kg; where Daily Dermal Exposure is obtained from Table 4.

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

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

dAdditional PPE (unit exposures from PHED V1.1)

Scenario 1a: Double layer of clothing and chemical resistant gloves.
Scenario 1b: Double layer of clothing and chemical resistant gloves.
Scenario 2: No data.
Scenario 3: No data.
Scenario 4: Double layer of clothing and chemical resistant gloves.
Scenario 5: Double layer of clothing and chemical resistant gloves.

eEngineering Controls (unit exposures from PHED V1.1)

Scenario 1a: Closed system, single layer clothing and no gloves.
Scenario 1b: Closed system, single layer clothing and no gloves.
Scenario 2: No data.
Scenario 3: No data.
Scenario 4: Closed-cab single layer clothing and no gloves.
Scenario 5: Closed-cab single layer clothing and no gloves.

The daily dose is calculated using the following formula:

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

The MOEs are calculated using the following formula:

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

"MOE (total)" means that the exposure values used in the calculations reflect combined dermal and inhalation exposures. As noted earlier, dermal exposure is much greater than inhalation exposure.

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

Provided in Table 6 are the MOEs calculated from Baseline and Risk Mitigation unit exposures (combined dermal and inhalation).

Because a toxicological endpoint was derived for inhalation toxicity, EPA has calculated the individual MOEs for inhalation exposure. These are listed in Table 7.

Table 7. Inhalation MOEs for Profenofos

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

NOTES (for Table 7):

[a]Daily Inhalation Dose = daily inhalation exposure/70 kg; where daily inhalation exposure is obtained from Table 4.
[b]MOE = LEL (9.7 mg/kg/day)/daily inhalation dose (where the inhalation LEL is 0.068 mg/L; [0.068 mg/L * 1,000 l/m^3 * 10 m^3/day]/70 kg = 9.7 mg/kg/day)

Conclusion

EPA generally considers an MOE of 100 to be protective of human health. The calculations of short-term and intermediate term risks indicate that the MOEs are more than 100 for aerial applicators using helicopters with enclosed-cockpit (while wearing long sleeve shirts, long pants and no gloves). For the other scenarios, when additional personal protective was added (in an effort to mitigate the risks), the resulting MOEs were still less than 100. However, with the addition of engineering controls such as closed mixing systems and enclosed cabs, the MOEs are more than 100 for the following scenarios:

- (1b) Mixing/loading liquids for groundboom application (closed-system);
- (4) Applying liquids with a groundboom sprayer (enclosed-cab): and
- (5) Flagging for Liquid Application (enclosed-cab).

(3)

Despite the utilization of several mitigation measures, MOEs for short-term risk and intermediate-term risk are less than 100 for:

- (1a) Mixing/loading liquids for aerial application (closed-system); and,
- (3) Applying liquids with a fixed wing air-craft (enclosed-cockpit).

As shown in Table 7, all the inhalation only MOEs are well over 100. Thus, the Agency is not concerned with potential risks from inhalation exposure to profenofos.

ii. Post-Application

The REI is established, in general, based upon the number of days following application that must elapse before the MOEs for occupational workers exceed 100.

Conclusion

When more than one use-site was used to gather post-application exposure data, the average number of days following application when the MOE exceed 100 was estimated among sites. The average is based on the average FDR data, not an average of MOEs at the various sites (see Tables 4-7 of U.S. EPA 1996f for reentry interval calculations for scouts and hoers). EPA has estimated that under the present assumptions and use-rates, the following REIs would apply for occupational exposures to profenofos:

- For scouts the REI would be at least 8 days; and
- For hoers the REI would be at least 4 days.

c. Additional Occupational Exposure Studies

i. Handler Studies

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

(3)

ii. Post-Application Studies

Additional post-application studies are not required.

IV. RISK MANAGEMENT AND REREGISTRATION DECISION

A. Dietary

1. Tolerance Reassessment Summary

a. Tolerances Listed Under 40 CFR 180.404

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

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

Ruminant metabolism and feeding studies indicate that the established tolerances for the fat, meat, and meat byproducts of cattle, goats, hogs, horses, and sheep (0.05 ppm), and for milk (0.01 ppm) are adequate.

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

b. Tolerances To Be Proposed Under 40 CFR 180.404

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

c. Tolerances Listed Under 40 CFR 186.4975

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

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

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

2. Codex Harmonization

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

(3)

Table 8. 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.
Goats, fat	0.05	0.05	
Goats, mbyp	0.05	0.05	
Goats, meat	0.05	0.05	
Hogs, fat	0.05	0.05	
Hogs, mbyp	0.05	0.05	
Hogs, meat	0.05	0.05	
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.
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 Pesticide Assessment Guidelines Subdivision O, Table II (September 1995).
Tolerances Listed Under 40 CFR 186.4975:			
Cottonseed hulls	6.0	Revoke	Not warranted based on the results of an acceptable cottonseed processing study and the revision to the tolerance expression.
Soapstock	15.0	Revoke	No longer considered a feed item by the Agency (Pesticide Assessment Guidelines Subdivision O, Table II; September 1995).

NOTES:

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

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

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

NOTES:

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

[b]April 1994 FAO panel: proposed at 0.1 ppm (new).

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

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

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

[f]April 1994 FAO panel: proposed at 5 ppm (new).

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

B. Occupational

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

- (1a) Mixing/loading liquids for aerial application (closed-system); and,
- (3) Applying liquids with a fixed wing air-craft (enclosed-cockpit).

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

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

V. ACTIONS REQUIRED BY REGISTRANTS [To be completed, pending a meeting with the registrants.]

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. 1996c. Memorandum from B. Steinwand to M. Metzger. "Dietary Exposure Analysis for Profenofos in Support of the Reregistration Eligibility Document." May 9, 1996.

U.S. EPA. 1996f. Memorandum from L. Morris to M. Metzger. "Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document for Profenofos." March 29. 1996

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

U.S. EPA. 1996d. Memorandum from R. Locke to P. Deschamp. "Profenofos: Toxicology Chapter for the RED." January 30. 1996.

U.S. EPA. 1996e. Memorandum from C. Eiden to M. Metzger. "Profenofos. List B Reregistration Case 3540. Chemical No. 111401. Product and Residue Chemistry Chapters for the Reregistration Eligibility Decision: Amendment. CBRS No. 17094. DP Barcode D224887.

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Appendix 1 - Product Chemistry Data Summary

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Appendix 4 - Memorandum from B. Steinwand to M. Metzger. "Dietary Exposure Analysis for Profenofos in Support of the Reregistration Eligibility Document." May 9, 1996 (U.S. EPA. 1996d).

APPENDIX 1

Product Chemistry Data Summary

Case No. 2540
Chemical No. 111401

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

PRODUCT CHEMISTRY DATA SUMMARY

Guideline Number	Requirement	Are Data Requirements Fulfilled? [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 [f], 42854201 [g]
63-12	pH	Y	42030301 [c], 42731401 [e]
63-13	Stability	Y	40445003 [f], 42854201 [g], 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? [1]	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 [8]
171-4 (k): Magnitude of the Residue in Plants			
- Cottonseed and gin byproducts	3.0 (cottonseed) [§180.404]	No [9]	**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	

Appendix 2 *(continued)*

GLN: Data Requirements	Current Tolerances, ppm [40 CFR]	Must Additional Data Be Submitted?	References [1]
171-4 (g): Nature and Magnitude of the Residue in Fish	N/A	N/A	
171-4 (h): Nature and Magnitude of the Residue in Irrigated Crops	N/A	N/A	
171-4 (i): Magnitude of the Residue in Food-Handling Establishments	N/A	N/A	
165-1: Rotational Crops (Confined)	--	Yes [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.

(4)

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:** "Best Available" grades: Hands, dermal, and inhalation acceptable grades. Hands = 53 replicates; Dermal = 25 to 122 replicates; Inhalation = 85 replicates. High confidence in dermal data; high confidence in inhalation data. **PPE:** "Best Available" grades: Hands and dermal acceptable grades. Hands = 59 replicates; Dermal = 25 to 122 replicates. High confidence in dermal and inhalation data. **Engineering Controls:** "Best Available" grades: Dermal and inhalation acceptable grades. Dermal = 16 to 22 replicates; Inhalation = 27 replicates. High confidence in dermal and inhalation data. PHED data used for baseline, no protection factors (PFs) were necessary. 50% PF was used for coveralls (PPE)
Applicator Exposure		
Aerial equipment -- helicopter enclosed cab (liquids) (2)	350 acres	**Baseline/Engineering Controls:** "Best Available" grades: dermal grades A,B,C; inhalation grades "acceptable". Dermal = 2 to 3 replicates; Inhalation = 3 replicates. Low confidence in dermal and inhalation data. PHED data used for baseline, no PFs were necessary.
Aerial equipment--fixed wing enclosed cab (liquids) (3)	350 to 800 acres	**Baseline/Engineering Controls:** "Best Available" grades: Hands acceptable grades, dermal and inhalation grades A,B,C. Hands = 34 replicates; Dermal = 24 to 48 replicates; Inhalation = 23 replicates. Medium confidence in dermal and inhalation data. PHED data used for baseline, no PFs were necessary.

EXPOSURE SCENARIO (Number)	STANDARD ASSUMPTIONS[a] (8-hr work day)	COMMENTS[b]
Groundboom (4)	80 acres	**Baseline:** "Best Available" grades: Hands, dermal, and inhalation acceptable grades. Hands = 29 replicates; Dermal = 32 to 42 replicates; Inhalation = 22 replicates. High confidence in dermal and inhalation data. **PPE:** "Best Available" grades: Dermal and inhalation acceptable grades. Dermal = 32 to 42 replicates; inhalation = 22 replicates. Medium confidence in dermal data; high confidence in inhalation data. **Engineering Controls:** "Best Available" grades: Dermal = ABC grades; Inhalation = acceptable grades. Dermal = 20 to 31 replicates; Inhalation = 16 replicates PHED data used for baseline, no PFs were necessary. 50% PF was added for coveralls for PPE.
Flagger		
Liquids (5)	350-800 acres	**Baseline:** "Best Available" grades: Hands, dermal, and inhalation acceptable grades. Hands = 16 replicates; Dermal = 16 to 18 replicates; Inhalation = 18 replicates. High confidence in dermal and inhalation data. **PPE:** "Best Available" grades: Dermal, and inhalation acceptable grades. Hands = 16 replicates; Dermal = 16 to 18 replicates; Inhalation = 18 replicates. High confidence in dermal and Low confidence for inhalation data. **Engineering Controls:** "Best Available" grades: Dermal, and inhalation acceptable grades. Dermal = 16 to 18 replicates; Inhalation = 18 replicates. High confidence in dermal and inhalation data. PHED data used for baseline, no PFs were necessary. 50% PF for addition of coveralls PPE. 98% PF added 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).
[b]"Best Available" grades are defined by OREB Standard Operating Procedure for meeting Subdivision U Guidelines. Best available grades are assigned as follows: matrices with grades A and B data and a minimum of 15 replicates; if not available, then grades A, B, and C data and a minimum of 15 replicates; if not available, then all data regardless of the quality and number of replicates.