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

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

DATE: 19-OCT-2016

SUBJECT: AMENDMENT TO: **Profenofos:** Human Health Draft Risk Assessment (DRA) for Registration Review.

PC Code: 111401
Decision No.: 520865
Petition No.: NA
Risk Assessment Type: Single Chemical/Aggregate
TXR No.: NA
MRID No.: NA

DP Barcode: D435471
Registration No.: 180-669
Regulatory Action: Registration Review
Case No.: 2540
CAS No.: 41198-08-7
40 CFR: §180.404

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A human health draft risk assessment for registration review was conducted for the organophosphate (OP) profenofos [*O*-(4-bromo-2-chlorophenyl)*O*-ethyl-*S*-propyl phosphorothioate] on 15-SEP-2015 (Memo, M. Perron, *et al.*; D414150). Since this assessment, the registrant has requested the following: cancellation of the sole technical and end-use product (EPA Registration Number 180-669) registered for profenofos in the U.S. and conversion of the established tolerances for residues in/on cotton commodities to tolerances without a U.S. registration. The registrant confirmed that Mexico is the only country that has a profenofos registered product where there could be potential for import (Letter and electronic correspondence from C. Levey of Syngenta to C. Scheltema of PRD/HED; 28-SEP-2016 and 15-JUL-2016). This document is an update to the previous assessment.

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1.0 Executive Summary

Background

Profenofos is an organophosphate (OP) insecticide-miticide used for insect and mite control on cotton. There is only one end-use product label registered with profenofos as the active ingredient (ai) (EPA Reg. #100-669; Curacron® 8E Insecticide-Miticide). This product is formulated as an emulsifiable concentrate (EC), containing 73% ai or 8 lb ai/gallon. The petitioner is now requesting cancellation of the sole technical and end-use product (EPA Registration Number 180-669) registered for profenofos in the U.S. and conversion of the established tolerances for residues in/on cotton commodities to tolerances without a U.S. registration.

Based on the updated use pattern for profenofos, exposure to profenofos can occur only in food. Drinking water and occupational exposures are not expected to occur since profenofos will no longer be applied in the U.S.

Hazard Assessment

Profenofos is a member of the OP class of pesticides. Like other OPs, the initiating event in the mode of action (MOA)/adverse-outcome pathway (AOP) for profenofos involves inhibition of the enzyme acetylcholinesterase (AChE) via phosphorylation of the serine residue at the active site of the enzyme. This inhibition leads to accumulation of acetylcholine and ultimately to neurotoxicity in the central and/or peripheral nervous system. For profenofos, AChE inhibition is the most sensitive endpoint in the toxicology database in multiple species, durations, lifestages, and routes. Profenofos does not require metabolic activation to an oxon metabolite to inhibit AChE (i.e., the parent compound is the active form inhibiting AChE). OPs also exhibit a phenomenon known as steady-state AChE inhibition. After repeated dosing at the same dose level, the degree of inhibition comes into equilibrium with the production of new, uninhibited enzyme. Therefore, steady-state exposure assessments of 21 days and longer were conducted instead of the traditional chronic or long-term assessments.

The toxicology database for profenofos is considered adequate for risk assessment. There are acceptable studies available for toxicity endpoint selection. Profenofos has high-quality dose-response data across multiple lifestages, durations, and routes for both red blood cell (RBC) and brain AChE inhibition. Dermal and inhalation studies allow for route-specific evaluation. Clinical signs of neurotoxicity can be found throughout the database following acute exposures at doses much higher than those causing inhibition of AChE. None of the submitted studies in the toxicology database for profenofos suggest increased sensitivity to profenofos based on AChE inhibition; however, the Food Quality Protection Act (FQPA) Safety Factor (SF) has been retained for infants, children, youths, and women of childbearing age for all exposure scenarios due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4). Interspecies (10X) and intraspecies (10X) uncertainty factors were also applied. As a result, a total uncertainty factor of 1000X was applied for all dietary exposure scenarios, except dietary exposures for the adult population subgroup 50-99 years old where the FQPA SF does not apply (total uncertainty factor = 100X).

Profenofos is classified as a "Group E Chemical – evidence of non-carcinogenicity for humans" based on lack of evidence of carcinogenicity in rats and mice. A quantitative cancer risk assessment is not required.

Dietary (Food Only) Exposure and Risk

The existing residue chemistry database for profenofos is adequate for risk assessment purposes. As the petitioner is now supporting a tolerance without a U.S. registration only, drinking water estimates were not included in the dietary exposure and risk assessment. Drinking water exposures are not expected since profenofos will not be applied in the U.S.

The acute and steady-state analyses demonstrate that the profenofos uses will not result in dietary (food only) risk estimates that exceed HED's LOC for any of the regulated population subgroups, including those comprised of infants and children.

Residential (Non-Occupational) Exposure and Risk

There were no registered residential uses of profenofos prior to the registrant's request for cancellation and profenofos is being supported as a tolerance without a U.S. registration on cotton only; therefore, a quantitative residential handler and post-application assessment is not germane to this action.

Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.archives.gov/federal-register/executive-orders/pdf/12898.pdf.

Profenofos is being supported as a tolerance without a U.S. registration on cotton only; therefore, a discussion of spray drift, occupational exposure and risk, and human studies is not germane to this action.

2.0 HED Recommendations

2.1 Data Deficiencies

There are no data deficiencies for the Registration Review eligibility of profenofos.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

Profenofos is adequately recovered using the Food and Drug Administration (FDA) protocol multiresidue methods (MRMs) D and E (PAM Volume 1, Sections 302, 303 and 304). The plant and livestock data collection methods for profenofos were 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. 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).

2.2.2 International Harmonization

U.S. permanent tolerances are summarized in Appendix E along with International Maximum Residue Limits (MRLs) established by Codex Alimentarius Commission. Mexico adopts the U.S. tolerances and/or Codex MRLs for its export purposes. Canada has not established MRLs for profenofos. Codex has a maximum residue limit (MRL) for "cotton seed" at 3 ppm. For purposes of harmonization, HED recommends increasing the existing U.S. cotton, undelinted seed tolerance of 2.0 ppm to 3.0 ppm.

2.2.3 Revisions to Established Tolerances

Adequate field trial data have been submitted and reviewed for cotton undelinted seed and cotton gin byproducts. Field trials reflected use of the registered EC formulation at the maximum registered use patterns. Permanent tolerances are established for profenofos residues under 40 CFR §180.404 in/on cotton, undelinted seed at 2.0 ppm; cotton gin byproducts at 55.0 ppm; milk at 0.01 ppm; and the fat, meat, and meat byproducts of cattle, goat, horse, and sheep at 0.05 ppm. Codex has a MRL for "cotton seed" at 3 ppm. For purposes of harmonization, HED recommends increasing the existing U.S. cotton, undelinted seed tolerance of 2.0 ppm to 3.0 ppm. Furthermore, HED concludes that the residue chemistry data support conversion of the tolerance for residues of profenofos in/on cotton, undelinted seed to a tolerance without U.S. registration. As cotton gin byproducts are not imported into the United States, the established tolerance of 55.0 ppm is no longer necessary; therefore, the established tolerance should be revoked.

HED concludes that, based on the recalculated more balanced diet (MBD) for ruminants, there is no reasonable expectation of finite residues of profenofos in livestock commodities (Category 3 of 40 CFR §180.6(a)) (Memo, S. Levy, 05-OCT-2016; D435814). The established tolerances for residues of profenofos in/on milk at 0.01 ppm; and the fat, meat, and meat byproducts of cattle, goat, horse, and sheep at 0.05 ppm should be revoked (40 CFR §180.404).

The tolerance expression for profenofos has been reviewed and should be updated as follows based on HED's Interim Guidance on Tolerance Expressions (S. Knizner, 5/27/09).

> "Tolerances are established for residues of the insecticide profenofos, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only profenofos (*O*-(4-bromo-2-chlorophenyl)-*O*-ethyl *S*-propyl phosphorothioate) in or on the commodities:"

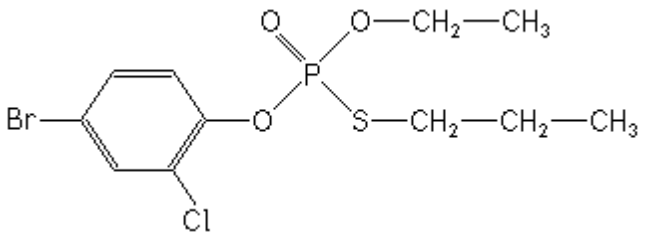
Table 2.2.3.1. Tolerance Summary for Profenofos.			
Commodity	Established Tolerance (ppm)	HED-Recommended Tolerance (ppm)	Comments (*correct commodity definition*)
Cattle, fat	0.05	Revoke	Category 3 of 40 CFR §180.6(a))
Cattle, meat	0.05	Revoke	Category 3 of 40 CFR §180.6(a))
Cattle, meat byproducts	0.05	Revoke	Category 3 of 40 CFR §180.6(a))
Cotton, gin byproducts	55.0	Revoke	Cotton gin byproducts are not imported into the United States.
Cotton, undelinted seed	2.0	3.0	Increase in tolerance level for purposes of harmonization.
Goat, fat	0.05	Revoke	Category 3 of 40 CFR §180.6(a))
Goat, meat	0.05	Revoke	Category 3 of 40 CFR §180.6(a))
Goat, meat byproducts	0.05	Revoke	Category 3 of 40 CFR §180.6(a))
Horse, fat	0.05	Revoke	Category 3 of 40 CFR §180.6(a))
Horse, meat	0.05	Revoke	Category 3 of 40 CFR §180.6(a))
Horse, meat byproducts	0.05	Revoke	Category 3 of 40 CFR §180.6(a))
Milk	0.01	Revoke	Category 3 of 40 CFR §180.6(a))
Sheep, fat	0.05	Revoke	Category 3 of 40 CFR §180.6(a))
Sheep, meat	0.05	Revoke	Category 3 of 40 CFR §180.6(a))
Sheep, meat byproducts	0.05	Revoke	Category 3 of 40 CFR §180.6(a))

2.3 Label Recommendations

No label recommendations have been identified. Current tolerances need to be updated as discussed in Section 2.2.3.

3.0 Introduction

3.1 Chemical Identity

Table 3.1.1. Test Compound Nomenclature.	
Compound	
Common Name	Profenofos
Chemical Class	Organophosphate, OP
Molecular Formula	$C_{11}H_{15}BrClO_3PS$
Molecular Weight	373.65 g/mole
IUPAC Name	(*RS*)-(*O*-4-bromo-2-chlorophenyl *O*-ethyl *S*-propyl phosphorothioate)
CAS Name	*O*-(4-bromo-2-chlorophenyl) *O*-ethyl *S*-propyl phosphorothioate
CAS Registry Number	41198-08-7
PC Code	111401

3.2 Physical/Chemical Characteristics

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 molecular weight is 373.65 g/Mole. 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 soluble in organic solvents (acetone, ethanol, toluene, n-octanol, and n-hexane) at 25°C. It has a log octanol-water partition coefficient of 4.83. Profenofos is stable under neutral and slightly acidic conditions, and is unstable under alkaline conditions. It has a low vapor pressure (9.001 x 10^{-7} mm Hg). A summary of physical/chemical properties for profenofos can be found in Appendix D.

3.3 Pesticide Use Pattern

In the previous risk assessment, one end-use product label registered with profenofos as the ai (EPA Reg. #100-669; Curacron® 8E Insecticide-Miticide) was evaluated. Since this assessment, the registrant has requested the following: cancellation of the sole technical and end-use product (EPA Registration Number 180-669) registered for profenofos in the U.S. and conversion of the established tolerances for residues in/on cotton commodities to tolerances without a U.S. registration. The registrant confirmed that Mexico is the only country that has a profenofos registered product where there could be potential for import (Letter and electronic correspondence from C. Levey of Syngenta to C. Scheltema of PRD/HED; 28-SEP-2016 and 15-JUL-2016). Table 3.3.1 is a summary of the use pattern for use in Mexico.

Table 3.3.1. Summary of Use Directions for Profenofos.

Formulation	Maximum Application Rate	Max No. Applications per Season	Max Seasonal Application Rate	Use Directions and Limitations[1]
Emulsifiable Concentrate 73%ai 8 lb ai/gal Curacron® 8E Insecticide-Miticide	0.5 pt product/A 0.5 lb ai/A	Based on max single rate and max seasonal rate, up to 10 applications per season (not specified on label).	5 pt/A/season 5 lb ai/A/season	• REI = 48 hours. • Repeat applications at 5-7 days intervals as needed. • Apply in minimum of 5 gallons/A. • PHI = 14 days.

[1] REI = restricted-entry interval, PHI= pre-harvest interval.

3.4 Anticipated Exposure Pathways

Based on the updated use pattern, exposure to profenofos can occur only in food (from cottonseed oil). Drinking water, residential, and occupational exposures are not expected to occur since profenofos will no longer be applied in the U.S.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (http://www.archives.gov/federal-register/executive-orders/pdf/12898.pdf). As a part of every

pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the National Health and Nutrition Survey/What We Eat in America (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

Profenofos is a member of the OP class of pesticides. Like other OPs, the initiating event in the MOA/AOP for profenofos involves inhibition of the enzyme AChE via phosphorylation of the serine residue at the active site of the enzyme. This inhibition leads to accumulation of acetylcholine and ultimately to neurotoxicity in the central and/or peripheral nervous system (see Figure 1). For profenofos, AChE inhibition is the most sensitive endpoint in the toxicology database in multiple species, durations, lifestages, and routes. AChE inhibition is the focus of this hazard characterization; the availability of reliable AChE inhibition dose response data is one of the key determinants in evaluating the toxicology database.

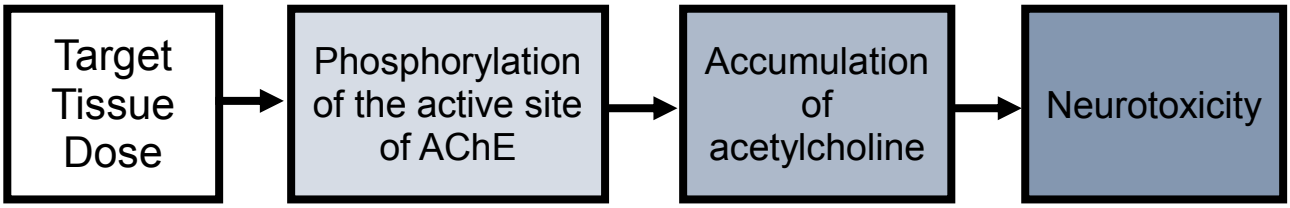


Figure 1. AOP for OPs.

4.1 Toxicology Studies Available for Analysis

The toxicology database for profenofos is complete for risk assessment. The acceptable profenofos studies available for risk assessment include:

- subchronic oral toxicity studies in rats and dogs;
- chronic oral toxicity studies in rats and dogs;
- carcinogenicity studies in rats and mice;
- developmental studies in rats and rabbits;
- multigenerational reproduction toxicity study in rats;
- acute and subchronic neurotoxicity studies in rats;
- acute and repeated comparative cholinesterase assays (CCA) in juvenile and adult rats;
- acute delayed neurotoxicity study in hens;

- subchronic dermal toxicity study in rabbits;
- subchronic inhalation toxicity study in rats;
- mutagenicity and genotoxicity studies;
- metabolism studies in rats and monkeys;
- immunotoxicity study in mice;
- developmental neurotoxicity (DNT) study with AChE measurements in non-pregnant females, pregnant females, fetuses, and juvenile rats.

4.2 Absorption, Distribution, Metabolism, & Excretion (ADME)

Some OPs require metabolic activation to the oxon metabolite; however, for profenofos, the parent compound is responsible for AChE inhibition activity (see chemical structure in Table 3.1.1). Generally, absorption and distribution are rapid with extensive metabolism and no accumulation in the tissues for OPs.

In a rat metabolism study (MRID 42334301), recovery of radioactivity for combined fecal and urine samples ranged from 97-108% of the administered dose, with >97% of the radioactivity excreted in the urine within 48 hours. Less than 0.2% of the radioactivity was expired as volatiles. Insignificant amounts of radioactivity were retained in tissues after 7 days post-exposure. Analysis of fecal material indicated that <4% of the parent compound or its metabolites remain unabsorbed or are excreted via the biliary system into the intestinal tract. Profenofos 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-55960), *O*-ethyl-*O*-(2-chloro-4-bromo-phenyl)-phosphate (CGA-47196), and thiophosphoric acid *O*-(4-bromo-2-chloro-phenyl) ester *O´*-ethyl ester (CGA-65867). There were no apparent dose or sex-related differences in the absorption, distribution, metabolism, or excretion of profenofos.

In a metabolism/pharmacokinetic study with rhesus monkeys, young adult males were administered a single oral dose via capsule at 2.4 mg/animal (approximately 0.5 mg/kg). The test material was rapidly absorbed with significant concentrations measured in the blood and plasma by the first blood measurement (30 minutes post-dose). The time to reach maximum concentration in the blood (T_{max}) was reached by 1 hour post-dose and rapidly declined thereafter. The terminal phase elimination half-life ($t_{1/2}$) was estimated to be 4 hours in this study. Approximately 68% of the administered dose was recovered in the excreta (urine, feces, and cage wash after 168 hours) with the majority recovered in the urine (49%). Excretion was nearly complete by 24 hours following treatment. CGA-55163 was identified as the major urinary metabolite, which is the glucuronide conjugate of the phenol analog (CGA-55960).

4.2.1 Dermal Absorption

There are no dermal penetration studies available for profenofos. Previously, a route-specific dermal toxicity study was used to assess dermal exposure scenarios; therefore, a dermal absorption factor was not needed (Memo, M. Perron, *et al.*; 15-SEP-2015; D414150). Based on the updated use pattern, dermal exposures are no longer expected since profenofos will no longer be applied in the U.S.

4.3 Toxicological Effects

Profenofos has high-quality dose-response data across multiple lifestages, durations, and routes for both RBC and brain AChE inhibition. In the case of profenofos, RBC AChE inhibition was more sensitive than brain AChE inhibition and provides the basis for human health risk extrapolations. Using AChE inhibition as the critical endpoint for risk assessment protects for other cholinergic effects, such as clinical signs, which are seen at doses much higher than those causing inhibition of AChE. Clinical signs indicative of neurotoxicity seen following a single oral dose included compulsive licking, abnormal gait, salivation, lacrimation, impaired respiration, ataxia, impaired reflexes, tremors, and decreased arousal, rearing, and motor activity. In general, these clinical signs of toxicity were observed at doses approximately 100-200X higher than the AChE inhibition used as the basis for the acute oral point of departure (POD). There were no clinical signs noted in repeated exposure studies; however, body weight decrements were noted in several studies.

Many of the studies have been evaluated using benchmark dose (BMD) modeling techniques. Based on BMD modeling results (M. Perron; 15-SEP-2015; TXR# 0057250 and Appendix C), RBC AChE inhibition is remarkably similar across oral studies for adult rats. Available studies with adult animals show similar findings in gavage and dietary studies. Studies via the dermal and inhalation routes allow for route-specific evaluation; however, data from these route-specific studies were not amenable to BMD modeling (see Section 4.5.1). In acute and repeated studies, AChE inhibition in juvenile rats was seen at or above dose levels eliciting inhibition in adults. In the DNT studies, the adults were found to have considerable AChE inhibition at relatively low doses, while little or no inhibition was seen in fetuses and young juvenile rats except at the highest doses tested. As a result, no dose response was observed and BMD estimates were not calculated. Pregnant females were also not found to be more sensitive than non-pregnant females.

Profenofos is classified as acutely toxic via the oral (Toxicity Category II) and dermal routes (Toxicity Category I or II) and classified as having low acute toxicity via the inhalation route (Toxicity Category IV). It was found to be a minimal eye irritant and moderate dermal irritant (Toxicity Category III). It was also found to be a dermal sensitizer.

4.3.1 Critical Durations of Exposure

One of the key elements in risk assessment is the appropriate integration of temporality between the exposure and hazard assessments. One advantage of an AOP understanding is that human health risk assessments can be refined to focus on the most relevant durations of exposure. The following text provides an analysis of the temporal pattern of AChE inhibition from acute (single) and repeated-dosing studies in laboratory animals for profenofos. This analysis provides the basis for determining which exposure durations are appropriate for assessing human health risk. Table 4.3.1.1 provides a summary of the selected results from experimental toxicology studies with profenofos.

Table 4.3.1.1. Profenofos BMD_{10} and $BMDL_{10}$ Results (mg/kg/day) for RBC AChE Inhibition Over Time in Adult Rats.

Days of Dosing	Males		Females	
	BMD_{10}	$BMDL_{10}$	BMD_{10}	$BMDL_{10}$
1[a]	13.49	11.24	3.17	1.99
10[b]	NMF	NMF	0.38	0.17
35[c]	NA	NA	0.32	0.19
90[d]	0.33	0.29	0.66	0.54
91[e]	0.14	0.12	0.13	0.12
364[e]	0.17	0.15	0.22	0.18

BMD_{10} = estimated dose where AChE is inhibited by 10% compared to background.
$BMDL_{10}$ = lower confidence bound on the BMD_{10}.
NMF = no model fit.
NA = not applicable.
[a] MRID 46025406 – acute CCA study in rats(gavage).
[b] MRID 46025403– repeat CCA study in rats (gavage).
[c] MRID 46025401 – DNT study in rats (dietary).
[d] MRID 00105255 – subchronic oral toxicity study in rats (dietary).
[e] MRID 00081685 – combined chronic/carcinogenicity study in rats (dietary) – interim (91 days) and terminal measurements (364 days).

As shown in Table 4.3.1.1, the acute BMD values are the largest in the table, whereas BMD values from repeated dosing exposures are remarkably similar. OPs exhibit a phenomenon known as steady-state AChE inhibition. After repeated dosing at the same dose level, the degree of inhibition comes into equilibrium with the production of new, uninhibited enzyme. At this point, the amount of AChE inhibition at a given dose remains consistent across duration. In general, OPs reach steady-state within 2-3 weeks, but this can vary among OPs. In the case of profenofos, the results in Table 4.3.1.1 show a clear pattern of steady-state reached by 10 days of exposure. In addition to the consistency across durations, the data across multiple studies in rats are similar. Given the results in Table 4.3.1.1 (and Appendix C) for profenofos, acute (single-day) and steady-state durations are appropriate for human health risk assessment. As such, the endpoint selection discussed below focuses on acute (single-day) effects and steady-state effects.

Although there are data at a shorter time period than 21 days (i.e., 10 days), exposure assessments of 21 days and longer will be conducted for all routes of exposure (i.e., oral, dermal and inhalation) for all single chemical OP assessments. Although the durations of the toxicity and exposure assessments may differ, an exact match is not necessary and would suggest a level of precision that the toxicity data do not support. Given this, the 21-day and longer exposure assessment is scientifically supportable and also provides consistency with the OP cumulative risk assessment (OP Cumulative Risk Assessment (CRA); 2002, 2006) and across the single chemical risk assessment for the OPs.

4.4 Literature Review on Neurodevelopment Effects

For the OPs, historically the Agency has used inhibition of AChE as the POD for human health risk assessment; at present time, this policy continues. This science policy is based on decades of work which shows that AChE inhibition is the initial event in the pathway to acute cholinergic neurotoxicity. The use of AChE inhibition data for deriving PODs was supported by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP; 2008, 2012) for chlorpyrifos as the most robust source of dose-response data for extrapolating risk and is the source of data for PODs for profenofos. A detailed review of the epidemiological studies used in this review can be found either in the 2014 chlorpyrifos revised draft human health risk

assessment (D. Drew; 29-DEC-2014; D424485) or in the 2015 literature review for other organophosphates (OPP/USEPA; 15-SEP-2015; D331251).

Newer lines of research on OPs in the areas of potential AOPs, *in vivo* animal studies, and notably epidemiological studies in mothers and children, have raised some uncertainty about the Agency's risk assessment approach with regard to the potential for neurodevelopmental effects in fetuses and children. Many of these studies have been the subject of review by the Agency over the last several years as part of efforts to develop a risk assessment for chlorpyrifos (D. Drew; 29-DEC-2014; D424485). Initially, the Agency focused on studies from three U.S. cohorts: 1) The Mothers and Newborn Study of North Manhattan and South Bronx performed by the Columbia Children's Center for Environmental Health (CCCEH) at Columbia University; 2) the Mt. Sinai Inner-City Toxicants, Child Growth and Development Study or the "Mt. Sinai Child Growth and Development Study"; and 3) the Center for Health Assessment of Mothers and Children of Salinas Valley (CHAMACOS) conducted by researchers at University of California Berkeley. The Agency has evaluated these studies and sought external peer review (FIFRA SAP reviews in 2008 and 2012; federal panel, 2013[1]) and concludes they are of high quality. In the three U.S. epidemiology cohort studies, mother-infant pairs were recruited for the purpose of studying the potential health effects of environmental exposures during pregnancy on subsequent child development. Each of these cohorts evaluated the association between prenatal chlorpyrifos and/or OP exposure (with adverse neurodevelopmental outcomes in children through age 7 years). For the 2014 chlorpyrifos revised human health risk assessment (D. Drew; 29-DEC-2014; D424485), EPA included epidemiologic research results from these three U.S. prospective birth cohort studies but primarily focused on the results of CCCEH since this cohort has published studies on the association between cord blood levels of chlorpyrifos and neurodevelopmental outcomes. The Agency retained the FQPA 10X SF in the 2014 chlorpyrifos revised risk assessment, in large part, based on the findings of these studies.

In the 2015 updated literature review (OPP/USEPA; 15-SEP-2015; D331251), the Agency conducted a systematic review expanding the scope of the 2012/2014 review focused on U.S. cohort studies with particular emphasis on chlorpyrifos. The expanded 2015 review includes consideration of the epidemiological data on any OP pesticide, study designs beyond prospective cohort studies, and non-U.S. based studies. The updated literature review identified seven studies which were relevant (Bouchard *et al*., 2010; Fortenberry *et al*., 2014; Furlong *et al*., 2014; Guodong *et al*., 2012; Oulhote and Bouchard, 2013; Zhang *et al*., 2014; Shelton *et al*., 2014). These seven studies have been evaluated in context with studies from the 2012/2014 review (D. Drew; 29-DEC-2014; D424485). Only a brief summary is provided below.

The OP exposure being assessed in many of these studies used concentrations of urinary dialkyl phosphate metabolites (DAPs) as the urinary biomarker. Total DAPs is a non-specific measure of OP exposure and is the sum of six separate molecules - three dimethyl alkylphosphate (DMAP) molecules of DMP, DMTP, DMDTP, and three diethyl alkylphosphate (DEAP) molecules of DEP, DETP, and DEDTP. Each metabolite is a breakdown product from multiple OPs (Table 4.4.1; CDC, 2008)[2]. Specifically, DMP, DMTP, and DMDTP are associated with 18, 13, and 5 OPs, whereas DEP, DETP, and DEDTP are associated with 10, 10, and 4 OPs, respectively. Thus, using urinary DAPs alone as an exposure measure, it is not possible to separate the exposure and associated effects for single, specific OPs.

[1] http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0170
[2] http://www.cdc.gov/nchs/data/nhanes/nhanes_03_04/l26opd_c_met_organophosphorus_pesticides.pdf

Table 4.4.1. CDC Table of Organophosphate Pesticides and Their Dialkyl Phosphate Metabolites (2008).

Pesticide	DMP	DMTP	DMDTP	DEP	DETP	DEDTP
Azinphos methyl	X	X	X			
Chlorethoxyphos				X	X	
Chlorpyrifos				X	X	
Chlorpyrifos methyl	X	X				
Coumaphos				X	X	
Dichlorvos (DDVP)	X					
Diazinon				X	X	
Dicrotophos	X					
Dimethoate	X	X	X			
Disulfoton				X	X	X
Ethion				X	X	X
Fenitrothion	X	X				
Fenthion	X	X				
Isazaphos-methyl	X	X				
Malathion	X	X	X			
Methidathion	X	X	X			
Methyl parathion	X	X				
Naled	X					
Oxydemeton-methyl	X	X				
Parathion				X	X	
Phorate				X	X	X
Phosmet	X	X	X			
Pirimiphos-methyl	X	X				
Sulfotepp				X	X	
Temephos	X	X				
Terbufos				X	X	X
Tetrachlorviphos	X					
Trichlorfon	X					

DMP = dimethylphosphate; DEP = diethylphosphate; DMTP = dimethylthiophosphate; DMDTP = dimethyldithiophosphate; DETP = diethylthiophosphate; DEDTP = diethyldithiophosphate.

For studies which measured urinary 3,5,6-trichloro-2-pyridinol (TCPy) (e.g., Fortenberry *et al*., 2014; Eskenazi *et al*., 2007; Whyatt *et al*., 2009), this metabolite can be derived from chlorpyrifos, chlorpyrifos-methyl, and the herbicide triclopyr. TCPy is also the primary environmental degradate of chlorpyrifos, chlorpyrifos-methyl, and triclopyr; thus exposure can be found directly on food treated with these pesticides. CCCEH studies have largely used chlorpyrifos measured in cord blood as the specific biomarker (e.g., Lovasi *et al*., 2010; Whyatt *et al*., 2004; Rauh *et al*., 2011). The CHARGE study (Shelton et al, 2015) did not measure biomarkers but instead used geospatial analysis to focus on the residential proximity to OP exposure using data from the California Department of Pesticide Regulation, with five OPs accounting for a total of 73% of the pesticide applied near residential settings (chlorpyrifos, acephate, diazinon, bensulide, and dimethoate).

Similarly, DAPs can be found directly on food following OP applications (Zhang *et al*., 2008; Chen *et al*., 2012). Specifically, studies have shown that DAPs may form as environmental degradates from abiotic hydrolysis, photolysis, and plant metabolism (Zhang *et al*., 2008; Chen *et al*., 2012; Racke *et al*., 1994). Furthermore, since these DAPs are excreted more rapidly and extensively than the parent OPs (Zhang *et al*., 2008; Forsberg *et al*., 2008), direct exposure to DAPs may lead to an overestimate of OP exposure when using urinary DAPs as a biomarker of

OP exposure. The Agency recognizes that this is a source of uncertainty when using DAPs for assessing OP exposure and will continue to monitor this issue in future assessments.

With respect to neurological effects near birth, the CHAMACOS and Mt. Sinai cohorts measured neurological effects at birth, and observed a putative association with total DEAP, total DMAP, and total DAP exposure (Engel *et al*., 2007; Young *et al*., 2005). Similarly, a Chinese study (Zhang *et al*., 2014) reported statistically significant associations between total DEAPs, total DMAPs, and total DAPs from prenatal OP pesticide exposure and neonatal neurodevelopment assessed 3 days after birth. However, another cross-sectional Chinese study, Guodong *et al*. (2012), observed no association with urinary DAPs and a developmental quotient score for 23-25 month old children.

The 3 U.S. cohorts (CCCEH, Mt. Sinai, CHAMACOS) each reported evidence of impaired mental and psychomotor development, albeit not consistent by age at time of testing (ranging from 6 month to 36 months across the three cohorts). Attentional problems and ADHD were reported by three prospective cohorts [Rauh *et al*., 2006; Eskenazi *et al*., 2007; Marks *et al*., 2010; and Fortenberry *et al*. (2014)] investigators with additional support from a case control study, Bouchard et al. (2010). The exposure metric varied among these studies. Specifically, Fortenberry *et al*. (2014) found suggestive evidence of an association with TCPy and ADHD in boys whereas statistically significant associations were observed by Rauh *et al*. (2006) with chlorpyrifos exposure and ADHD. Eskenazi *et al*. (2007) reported associations with total DMAPs and total DAPs and ADHD; Marks *et al*. (2010) reported associations with total DEAP, DMAP, and total DAP exposure and ADHD. In a national cross-sectional study of Canadian children, using 2007-2009 data for children age 6-11 years (Oulhote and Bouchard, 2013), there were no overall statistically significant associations observed between child urinary DEAP,

DMAP, or total DAP metabolite levels and parentally reported behavioral problems. In contrast, Bouchard *et al*. (2010), looking at U.S. children age 8-15 years in the 2000-2004 National Health and Nutrition Examination Survey (NHANES), observed a positive association between attention and behavior problems and total DAPs and DMAPs, but not DEAPs. As part of their analysis, Oulhote and Bouchard (2013) noted that their outcome assessment for behavioral problems may not have been as sensitive as Bouchard *et al*. (2010), which may in part account for the difference in the observed results from these studies.

In addition, the three U.S. cohorts and the CHARGE study have reported suggestive or positive associations between OP exposure and autism spectrum disorders (Rauh *et al*., 2006; Shelton *et al*., 2014; Eskenazi *et al*., 2007; Furlong et al., 2014). Specifically, Furlong et al (2014) documented suggestive evidence of an association between total DEAP exposure and reciprocal social responsiveness among blacks and boys. Eskenazi *et al*. (2007) reported a statistically significant association between pervasive developmental disorder (PDD) and total DAP exposure, whereas Eskenazi *et al*. (2010) reported non-significant, but suggestive, increased odds of PDD of 2.0 (0.8 to 5.1; p=0.14). Rauh *et al*. (2006) documented a significant association between PDD and specifically chlorpyrifos exposure. Both PDD and reciprocal social responsiveness are related to the autism spectrum disorder. Using a different exposure assessment method (geospatial analysis and residential proximity to total OP exposure), Shelton et al (2014) also showed statistically significant associations between total OP exposure and ASD. While these studies vary in the magnitude of the overall strength of association, they have consistently observed a positive association between OP exposure and ASD. Finally, CCCEH, Mt. Sinai, CHAMACOS have reported an inverse relation between the respective prenatal

measures of chlorpyrifos and intelligence measures at age 7 years (Rauh *et al*., 2011; Engel *et al*., 2011; Bouchard *et al*., 2011).

Across the epidemiology database of studies, the maternal urine, cord blood, and other (meconium) measures provide evidence that exposure did occur to the fetus during gestation but the actual level of such exposure during the critical window(s) of susceptibility is not known. While significant uncertainties remain about the actual exposure levels experienced by mothers and infant participants in the children's health cohorts, it is unlikely that these exposures resulted in AChE inhibition. As part of the CHAMACOS study, Eskenazi et al. (2004) measured AChE activity and showed that no differences in AChE activity were observed. The biomarker data (chlorpyrifos) from the Columbia University studies are supported by the Agency's dose reconstruction analysis using the PBPK-PD model (D. Drew; 29-DEC-2014; D424485). Following the recommendation of the FIFRA SAP (2012), the Agency conducted a dose reconstruction analysis of residential uses available prior to 2000 for pregnant women and young children inside the home. The PBPK-PD model results indicate for the highest exposure considered (i.e., indoor broadcast use of a 1% chlorpyrifos formulation) <1% RBC AChE inhibition was produced in pregnant women. While uncertainty exists as to actual OP exposure at (unknown) critical windows of exposure, EPA believes it is unlikely individuals in the epidemiology studies experienced RBC AChE inhibition.

A review of the scientific literature on potential modes of action/adverse outcome pathways (MOA/AOP)[3] leading to effects on the developing brain was conducted for the 2012 FIFRA SAP meeting (USEPA, 2012) and updated for the December 2014 chlorpyrifos revised risk assessment (D. Drew; 29-DEC-2014; D424485). In short, multiple biologically plausible hypotheses and pathways are being pursued by researchers that include targets other than AChE inhibition, including cholinergic and non-cholinergic systems, signaling pathways, proteins, and others. However, no one pathway has sufficient data to be considered more credible than the others. The fact that there are, however, sparse AOP data to support the *in vitro* to *in vivo* extrapolation, or the extrapolation from biological perturbation to adverse consequence significantly limits their quantitative use in risk assessment. The SAP concurred with the Agency in 2008 and 2012 about the lack of definable key events in a MOA/AOP leading to developmental neurobehavioral effects. However, since the 2014 literature review, there are no substantive changes in the ability to define and quantitate steps in an MOA/AOP leading from exposure to effects on the developing brain. Published and submitted guideline DNT laboratory animal studies have been reviewed for OPs as part of the 2012/2014 review (D. Drew; 29-DEC-2014; D424485) and the updated 2015 review (OPP/USEPA; 15-SEP-2015; D331251). Neurobehavioral alterations in laboratory animals were often reported, albeit at AChE inhibiting doses, but there was generally a lack of consistency in terms of pattern, timing, or dose-response for these effects, and a number of studies were of lower quality. However, this information does provide evidence of long-lasting neurodevelopmental disorders in rats and mice following gestational exposure.

At this time, a MOA(s)/AOP(s) has/have not been established for neurodevelopmental outcomes. This growing body of literature does demonstrate, however, that OPs are biologically active on a number of processes that affect the developing brain. Moreover, there is a large body of *in vivo* laboratory studies which show long-term behavioral effects from early life exposure, albeit at doses which cause AChE inhibition. EPA considers the results of the toxicological studies

[3] Mode of action (MOA) and adverse outcome pathways (AOPs) describe a set of measureable key events that make up the biological processes leading to an adverse outcome and the causal linkages between such events.

relevant to the human population, as qualitatively supported by the results of epidemiology studies. The Agency acknowledges the lack of established MOA/AOP pathway and uncertainties associated lack of ability to make strong causal linkages and unknown window(s) of susceptibility. These uncertainties do not undermine or reduce the confidence in the findings of the epidemiology studies. The epidemiology studies reviewed in the 2012/2014 and 2015 literature reviews represent different investigators, locations, points in time, exposure assessment procedures, and outcome measurements. Despite all these differences in study design, with the exception of two negative studies in the 2015 literature review (Guodong *et al*., 2012; Oulhote and Bouchard, 2013), authors have identified associations with neurodevelopmental outcomes associated with OP exposure across four cohorts and twelve study citations. Specifically, there is evidence of delays in mental development in infants (24-36 months), attention problems, and autism spectrum disorder in early childhood, and intelligence decrements in school age children who were exposed to OPs during gestation. Investigators reported strong measures of statistical association across several of these evaluations (odds ratios 2-4 fold increased in some instances), and observed evidence of exposures-response trends in some instances; e.g., intelligence measures.

As section 408(b)(2)(C) of the FFDCA instructs EPA, in making its "reasonable certainty of no harm" finding, that in "the case of threshold effects, an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and postnatal toxicity and completeness of data with respect to exposure and toxicity to infants and children." Section 408 (b)(2)(C) further states that "the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children." Given the totality of the evidence, there is sufficient uncertainty in the human dose-response relationship for neurodevelopmental effects which prevents the Agency from reducing or removing the statutory 10X FQPA SF. For the profenofos DRA, a value of 10X has been applied. Similarly, a database uncertainty factor of 10X will be retained for occupational risk assessments. The Agency will continue to evaluate the epidemiology studies and pursue approaches for quantitative or semi-quantitative comparisons between doses which elicit AChE inhibition and those which are associated with neurodevelopmental outcomes prior to a revised human health risk assessment.

4.5 Safety Factor for Infants and Children (FQPA SF)[4]

As noted above, the lack of an established MOA/AOP makes quantitative use of the epidemiology studies in risk assessment challenging, particularly with respect to determining dose-response, critical duration of exposure, and window(s) of susceptibility. However, exposure levels in the range measured in the epidemiology studies are likely low enough that they are unlikely to result in AChE inhibition. Epidemiology studies consistently identified associations with neurodevelopmental outcomes associated with OP exposure such as delays in mental development in infants (24-36 months), attention problems, and autism spectrum disorder in early childhood, and intelligence decrements in school age children. Therefore, there is a need to protect children from exposures that may cause these effects; this need prevents the Agency from reducing or removing the statutory FQPA SF. **Thus, the FQPA 10X SF will be retained for profenofos for the population subgroups that include infants, children, youths, and women of childbearing age for all exposure scenarios.**

[4] HED's standard toxicological, exposure, and risk assessment approaches are consistent with the requirements of EPA's children's environmental health policy (https://www.epa.gov/children/epas-policy-evaluating-risk-children).

4.5.1 Completeness of the Toxicology Database

The existing toxicological database is complete and adequate for characterizing profenofos toxicity. Available profenofos studies for FQPA evaluation include developmental studies in the rat and rabbit, reproductive toxicity studies, comparative cholinesterase studies, and neurotoxicity studies (acute, subchronic, and developmental).

As discussed in Section 4.4, there is uncertainty in the human dose-response relationship for neurodevelopmental effects and this warrants retention of the FQPA SF for the population subgroups that include infants, children, youths, and women of childbearing age for all exposure scenarios.

4.5.2 Evidence of Neurotoxicity

Profenofos is an OP with an established neurotoxic AOP. Neurotoxicity is the most sensitive effect in all species, routes, and lifestages and is being used in deriving the PODs.

4.5.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

There is no evidence of increased quantitative or qualitative sensitivity/susceptibility to offspring following exposure to profenofos in submitted studies.

As discussed in Section 4.4, there is uncertainty in the human dose-response relationship for neurodevelopmental effects and this warrants retention of the FQPA SF for the population subgroups that include infants, children, youths, and women of childbearing age for all exposure scenarios.

4.5.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties with regard to the exposure databases. The acute dietary assessment incorporated tolerance level residues, default processing factors and 100 percent crop treated (PCT). Although data were used to partially refine the steady-state dietary exposure assessments, the assessments are not expected to underestimate dietary (food and water) exposures.

4.6 Toxicity Endpoint and Point of Departure Selections

4.6.1 Dose-Response Assessment

Table 4.5.4.1 summarizes the profenofos toxicity endpoints and PODs selected from an evaluation of the database. This endpoint selection was based on a weight of the evidence evaluation using the following considerations:

- *Relative sensitivity of the brain and RBC compartments*: For profenofos, across most studies, durations, lifestages, and routes, RBC is similarly or more sensitive than the brain. As such, OPP has utilized the RBC data in POD derivation.
- *Potentially susceptible populations (fetuses, juveniles, pregnancy*): The available AChE data across multiple lifestages (adults, pregnant adults, fetuses, juveniles) show no quantitative lifestage sensitivity for profenofos. After single dose exposures, females

were more sensitive than males based on RBC AChE inhibition. Consequently, data from females were used as the basis for POD derivation for acute dietary exposures.

- *Route of exposure:* It is preferred to match, to the degree possible, the route of exposure in the toxicity study with that of the exposure scenario(s) of interest. There are oral, dermal, and inhalation studies with profenofos which contain high-quality dose-response AChE data for endpoint selection.
- *Duration of exposure:* It is preferred to match, to the degree possible, the duration of toxicity study with that of the exposure duration of interest. There are single day and steady-state oral studies, but only steady-state dermal and inhalation studies are available.
- *Consistency across studies:* In cases where multiple datasets are available for a single duration, it is important to evaluate the extent to which data are consistent (or not) across studies. The profenofos database has striking consistency across studies, which allows the PODs to be derived from multiple critical studies, thereby increasing the confidence in such values.

Summary tables of BMD analyses can be found in Appendix C and the technical details of the analysis can be found in the BMD analysis memo (M. Perron; 15-SEP-2015; TXR# 0057250).

Consistent with risk assessments for other AChE-inhibiting compounds, OPP has used a benchmark response (BMR) level of 10% and has thus calculated BMD_{10} and $BMDL_{10}$ values (See Appendix B for summary of OPP's ChE policy). The BMD_{10} is the estimated dose where AChE is inhibited by 10% compared to background. The $BMDL_{10}$ is the lower confidence bound on the BMD_{10}. As a matter of science policy, the Agency uses the BMDL, not the BMD, for use as the POD (USEPA, 2012). All BMD/BMDL modeling for all individual datasets was completed using USEPA BMD Software to fit an exponential model to the data. BMD results from the OP CRA (2002, 2006) were included in the endpoint selection weight-of-evidence evaluation.

Acute Dietary (all populations)

A POD for the acute dietary (all populations) exposure scenario was derived from the results of a high-quality, well-conducted CCA rat study (MRID 46025406). A $BMDL_{10}$ of 1.99 mg/kg/day associated with RBC AChE inhibition following a single oral exposure in adult females (day 42) was selected as a suitable POD for the acute dietary (all populations) exposure scenario. The corresponding BMD_{10} was 3.17 mg/kg/day.

RBC AChE inhibition was selected for the POD since RBCs are a principal target for OP pesticides and the RBC AChE data were more sensitive than the brain AChE data. Data from the adult females represent the lowest BMD_{10} and $BMDL_{10}$ values obtained following a single dose compared to juveniles (both sexes) and adult males. This endpoint is considered protective of all populations, including children, since there was no quantitative lifestage sensitivity seen in the database.

An uncertainty factor of 1000X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 10X for FQPA SF due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4)) is applied to the $BMDL_{10}$ to obtain an aPAD of 0.00199 mg/kg/day for exposure scenarios with infants, children, youths, and women of childbearing age. The only population subgroup for which the FQPA SF is not retained is adults 50-99; therefore, the aPAD for this population subgroup is 0.0199 mg/kg/day.

Steady-State Dietary (all populations)

There is remarkable similarity in BMD estimates across multiple studies, durations, and compartments in studies 10 days and longer in adult rats (Table 4.3.1.1 and Appendix C). There was no evidence of increased quantitative susceptibility to offspring. AChE inhibition in juvenile rats was seen at or above dose levels eliciting inhibition in adults. In the DNT studies, little or no inhibition was seen in fetuses and young juvenile rats at doses causing considerable AChE inhibition in adult rats. Additionally, pregnant females were not found to be more sensitive.

Of the repeated-dosing studies, data from the rat combined chronic/carcinogenicity study (MRID 00081685) was found to be the most robust taking into consideration dose spacing and BMD model results. A $BMDL_{10}$ of 0.12 mg/kg/day associated with RBC AChE inhibition in male and female adult rats at the 13 week interim measurement was selected as a suitable POD for the steady-state dietary (all populations) exposure scenario. The corresponding BMD_{10} was 0.14 mg/kg/day and 0.13 mg/kg/day in males and females, respectively. Similar $BMDL_{10}$ values were obtained in the repeat CCA study, in non-pregnant females in the DNT studies, and at terminal measurements in the rat chronic/carcinogenicity study. Although lower values were obtained in the rat subchronic neurotoxicity and mouse carcinogenicity studies, poor dose spacing forced extrapolation to much lower doses in order to obtain BMD_{10} estimates. The subchronic oral dog study also provided a lower BMD estimate; however, there was large variability noted at all doses and inspection of the data found no AChE inhibition at the BMD_{10} estimates generated. As a result, the BMD estimates from these studies were not considered appropriate for endpoint selection.

An uncertainty factor of 1000X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 10X for FQPA SF due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4)) is applied to the $BMDL_{10}$ to obtain a ssPAD of 0.00012 mg/kg/day for exposure scenarios with infants, children, youths, and women of childbearing age. The only population subgroup for which the FQPA SF is not retained is adults 50-99; therefore, the ssPAD for this population subgroup is 0.0012 mg/kg/day.

Incidental oral, dermal, and inhalation endpoints were selected and described for the previous assessment (Memo, M. Perron, *et al.*; 15-SEP-2015; D414150); however, exposure is not expected via these routes since profenofos will no longer be applied in the U.S.

4.6.2 Recommendation for Combining Routes of Exposures for Risk Assessment

When there are potential occupational and residential exposures to a pesticide, the risk assessment must address exposures from three major sources (oral, dermal, and inhalation) and determine whether the individual exposures can be combined if they have the same toxicological effects. PODs for the incidental oral, dermal, and inhalation routes are all derived from RBC AChE inhibition. As a result, exposure from all routes can be combined.

4.6.3 Cancer Classification and Risk Assessment Recommendation

Profenofos is classified as a "Group E Chemical – evidence of non-carcinogenicity for humans" based on lack of evidence of carcinogenicity in rats and mice. Therefore, a quantitative cancer risk assessment is not required.

4.6.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.6.4.1. Summary of Toxicological Doses and Endpoints for Profenofos for Use in Dietary and Non-Occupational Human Health Risk Assessments.

Exposure/ Scenario	POD	UFs[a]	LOC	Study and Toxicological Effects
Acute Dietary (all populations except adults 50-99 years)	$BMDL_{10}$ = 1.99 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 10X	aRfD = 0.00199 aPAD = 0.00199	Acute CCA study in rats (MRID 46025406) BMD_{10} = 3.17 mg/kg/day. Inhibition of RBC AChE in adult female rats.
Acute Dietary (adults 50-99 years)	$BMDL_{10}$ = 1.99 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	aRfD = 0.0199 aPAD = 0.0199	Acute CCA study in rats (MRID 46025406) BMD_{10} = 3.17 mg/kg/day. Inhibition of RBC AChE in adult female rats.
Steady-State Dietary (all populations except adults 50-99 years)	$BMDL_{10}$ = 0.12 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 10X	ssRfD = 0.00012 ssPAD = 0.00012	Combined chronic oral toxicity/carcinogenicity study (MRID 00081685) BMD_{10} = 0.14/0.13 mg/kg/day (males/females). Inhibition of RBC AChE in adult rats at 13 week interim measurement.
Steady-State Dietary (adults 50-99 years)	$BMDL_{10}$ = 0.12 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	ssRfD = 0.0012 ssPAD = 0.0012	Combined chronic oral toxicity/carcinogenicity study (MRID 00081685) BMD_{10} = 0.14/0.13 mg/kg/day (males/females). Inhibition of RBC AChE in adult rats at 13 week interim measurement.
Incidental Oral Steady-State	$BMDL_{10}$ = 0.12 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 10X	Residential LOC for MOE <1000	Combined chronic oral toxicity/carcinogenicity study (MRID 00081685) BMD_{10} = 0.14/0.13 mg/kg/day (males/females). Inhibition of RBC AChE in adult rats at 13 week interim measurement.
Dermal Steady-State	NOAEL = 1 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 10X	Residential LOC for MOE <1000	21-day rabbit dermal toxicity (MRID 41644501) LOAEL = 10 mg/kg/day. Inhibition of RBC AChE in adult rabbits.
Cancer (oral, dermal, inhalation)	Classification: Group E Chemical – evidence of non-carcinogenicity for humans.			

Point of departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL =

no-observed adverse-effect level. LOAEL = lowest-observed adverse-effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, ss = steady-state). RfD = reference dose (a = acute, ss = steady-state). MOE = margin of exposure. LOC = level of concern. BMD = benchmark dose. BMDL = lower 95% confidence interval for benchmark dose.
[a] FQPA SF retained for infants, children, youths, and women of childbearing age for all exposure scenarios due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4). This includes all exposure scenarios, except the dietary exposure scenarios for the population subgroup adults 50-99 for which the FQPA SF has been reduced to 1X.

Table 4.6.4.2. Summary of Toxicological Doses and Endpoints for Profenofos for Use in Occupational Human Health Risk Assessments.

Exposure/ Scenario	POD	UFs	LOC	Study and Toxicological Effects
Dermal Steady-State	NOAEL = 1 mg/kg/day	UF_A = 10X UF_H = 10X UF_{DB} = 10X[b]	Occupational LOC for MOE <1000	21-day rabbit dermal toxicity (MRID 41644501) LOAEL = 10 mg/kg/day. Inhibition of RBC AChE in adult rabbits.
Inhalation Steady-State	LOAEL = 68 mg/m^3/day[a]	UF_A = 10X UF_H = 10X UF_{DB} = 30X[c]	Occupational LOC for MOE <3000	21-day inhalation rat study (MRID 00082079) LOAEL = 68 mg/m^3/day. Inhibition of RBC AChE in adult rats.
Cancer (oral, dermal, inhalation)	Classification: Group E Chemical – evidence of non-carcinogenicity for humans.			

Point of departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no-observed adverse-effect level. LOAEL = lowest-observed adverse-effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = database uncertainty factor for extrapolation from a LOAEL to NOAEL. MOE = margin of exposure. LOC = level of concern. BMD = benchmark dose. BMDL = lower 95% confidence interval for benchmark dose.
[a] Inhalation doses corresponding to the breathing rates of 8.3, 16.7, and 29 L/min were calculated as 2.90, 5.84, and 10.14 mg/kg/day, respectively, for occupational activities using a duration adjusted value of 51 mg/m^3.
[b] UF_{DB} for occupational dermal exposures = database uncertainty factor for uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4).
[c] UF_{DB} for occupational inhalation exposures = database uncertainty factor incorporating uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4) and the UF_L due to lack of a NOAEL in the subchronic inhalation toxicity study.

4.7 Endocrine Disruption

As required by FIFRA and the Federal Food, Drug, and Cosmetic Act (FFDCA), EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic, and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints that may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its reregistration decision for profenofos, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), profenofos is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[5] and includes some pesticides scheduled for Registration Review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors.

Profenofos is on List 2. List 2 represents the next set of chemicals for which EPA intends to issue test orders/data call-ins in the near future. For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website.[6]

5.0 Dietary Exposure and Risk Assessment

5.1 Metabolite/Degradate Residue Profile

5.1.1 Summary of Plant and Animal Metabolism Studies

The requirement for plant metabolism is fulfilled based on acceptable cotton metabolism studies depicting the metabolism of profenofos in cotton following foliar treatment. Profenofos is metabolized in cotton primarily to a glucosyl sulfate conjugate of 4-bromo-2-chlorophenol. Profenofos and the glucosyl sulfate conjugate of 4-bromo-2-chlorophenol are the predominant residues of profenofos in cotton. The results of the cotton metabolism study were presented to the HED Metabolism Committee (7/28/95) which concluded that profenofos per se is the residue of concern in cotton for tolerance enforcement and risk assessment purposes.

The requirements for livestock metabolism are fulfilled. Acceptable ruminant and poultry metabolism studies have been submitted and evaluated. The HED Metabolism Committee (7/28/95) concluded that profenofos per se is the compound of toxicological concern in milk and ruminant tissues. The Committee also concluded that there is no reasonable expectation of finite residues of profenofos in poultry tissues or eggs. Residues of profenofos were not present in any of the poultry tissues analyzed (meat, fat, or eggs), even at exaggerated dosing levels. Thus, there is presently no need to establish tolerances for residues of profenofos in poultry tissues or

[5] See http://www.epa.gov/endocrine-disruption/overview-second-list-chemicals-tier-1-screening-under-endocrine-disruptor for the final second list of chemicals.
[6] http://www.epa.gov/endo/

eggs. If new uses are registered that would result in a higher dietary burden, Category 3 may no longer apply (Results of Metabolism Committee, 28-JUL-1995; No DP#).

HED recalculated a more balanced diet (MBD) for ruminants. As there were no detectable residues in ruminant tissues or milk from the feeding study conducted at 0.1-11x the MDB, HED concludes that there is no reasonable expectation of finite residues of profenofos in ruminant commodities (Category 3 of 40 CFR §180.6(a)). Thus, there is presently no need to have the established tolerances for residues of profenofos in/on milk at 0.01 ppm; and the fat, meat, and meat byproducts of cattle, goat, horse, and sheep at 0.05 ppm. These tolerances should be revoked (40 CFR §180.404). If new uses are registered that would result in a higher dietary burden, Category 3 may no longer apply (Memo, S. Levy, 05-OCT-2016; D435814).

The requirement for a confined rotational crop study is fulfilled. An acceptable study was submitted that adequately demonstrates residues of concern are not likely to be found in appreciable concentrations in crops planted in as little as 30 days after treatment. The 30-day plantback interval (PBI) on the label is adequate.

5.1.2 Summary of Environmental Degradation

As the petitioner is now supporting a tolerance without a U.S. registration only, a discussion of environmental degradation is not germane to this petition.

5.1.3 Comparison of Metabolic Pathways

In plants, profenofos is metabolized primarily to a glucosyl sulfate conjugate of 4-bromo-2-chlorophenol. In goat and poultry tissues and in rats, residues consist primarily of 4-bromo-2-chlorophenol and its sulfate. None of the primary metabolites in either plant or goat and poultry tissues; e.g., 4-bromo-2-chlorophenol, 4-bromo-2-chlorophenol sulfate and 4-bromo-2-chlorophenol sulfate glucosyl conjugate, are AChE inhibitors. Furthermore, metabolism and feeding studies indicate that residues of profenofos are found in the milk, fat, and liver of ruminants, only. No profenofos is found in poultry tissues or eggs even at exaggerated feeding levels.

5.1.4 Residues of Concern Summary and Rationale

Table 5.1.4.1. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression.

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Profenofos *per se*	Profenofos *per se*
	Rotational Crop	Profenofos *per se*	Profenofos *per se*
Livestock	Ruminant	Not Applicable[1]	Not Applicable[1]
	Poultry	Not Applicable[1]	Not Applicable[1]
Drinking Water		Profenofos *per se*	Not Applicable

[1] CFR 180.6(a)(3) (Category 3). If new uses are registered that would result in a higher dietary burden, Category 3 may no longer apply (Results of Metabolism Committee, 28-JUL-1995; No DP# and Memo, S. Levy, 05-OCT-2016; D435814).

5.2 Food Residue Profile

HED has previously evaluated residue data depicting the magnitude of profenofos residues of concern in/on cottonseed and cotton gin byproducts. The application rates represent 1X the maximum registered rates and the minimum PHI of 14 days. Profenofos residues in/on treated cottonseed ranged from <0.05 ppm (nondetectable) to 1.1 ppm. Residues were observed to concentrate marginally 1.4X in cottonseed hulls, and no concentration of residues were observed in cottonseed meal and refined, bleached, and deodorized oil.

5.3 Water Residue Profile

As the petitioner is now supporting a tolerance without a U.S. registration only, a discussion of drinking water is not germane to this petition. Drinking water exposures are not expected since profenofos will not be applied in the U.S.

5.4 Dietary Risk Assessment

Profenofos acute and steady-state dietary exposure assessments were conducted using DEEM-FCID, Version 3.16, which incorporates consumption data from USDA's NHANES/WWEIA. This dietary survey was conducted from 2003 to 2008. The analyses were performed to support the Registration Review of profenofos.

5.4.1 Description of Residue Data Used in Dietary Assessment

The acute dietary exposure assessment was conducted using tolerance-level residues (HED's recommended 3.0 ppm for cottonseed for purposes of harmonization) and assumed 100 PCT.

As cottonseed oil is considered a blended commodity, the steady-state dietary exposure assessment assumed an average field trial value for cotton of 0.382 ppm (Memo, C. Eiden, 01-AUG-1995; D217739) and median cottonseed oil processing factor of 0.07X (Memo, C. Eiden, 01-AUG-1995; D217744).

5.4.2 Percent Crop Treated Used in Dietary Assessment

100 PCT was assumed for both the acute and steady-state assessments.

5.4.3 Acute Dietary Risk Assessment

The acute assessment is not considered to be a refined assessment as anticipated residues, monitoring data, PCT data, empirical processing factors, or cooking factors derived from literature studies were not incorporated. Tolerance level residues (HED's recommended 3.0 ppm for cottonseed for purposes of harmonization) and 100 PCT data were utilized.

The unrefined acute dietary (food only) exposure analysis is <100% aPAD at the 95th percentile of exposure for the general population and all population subgroups (Table 5.4.3.1). The risk to the U.S. population utilized 12% aPAD, and the highest exposure population subgroup was children 1-2 years old, which utilized 28% of the aPAD.

Table 5.4.3.1. Summary of Acute Dietary (Food only) Exposure and Risk for Profenofos[1].			
Population Subgroup	aPAD (mg/kg/day)[2]	95th Percentile	
		Exposure (mg/kg/day)	% aPAD
General U.S. Population	0.00199	0.000245	12
All Infants (<1 year old)		0.000126	6.4
Children 1-2 years old		**0.000549**	**28**
Children 3-5 years old		0.000528	27
Children 6-12 years old		0.000402	20
Youth 13-19 years old		0.000247	12
Adults 20-49 years old		0.000167	8.4
Adults 50-99 years old[2]		0.000132	<1.0
Females 13-49 years old		0.000170	8.6

[1] Highest exposure at the 95th percentile is in bold.
[2] Subpopulation adults 50-99 years old: aPAD = 0.0199 mg/kg/day.

5.4.4 Steady-State Dietary Risk Assessment

A partially-refined steady-state assessment was conducted in the DEEM acute module using the steady-state endpoint. The steady-state dietary exposure assessments assumed an average field trial value for cotton, median cottonseed oil processing factor, and 100 PCT. The steady-state assessment is not considered to be a highly refined assessment as monitoring data, empirical processing/cooking factors, and PCT were not utilized.

Table 5.4.4.1 shows the results for the steady-state assessment. At the 95th percentile of exposure (as no PCT was included), the risk from food is <100% ssPAD for all population subgroups. The risk to the U.S. population utilized 1.7% ssPAD, and the highest exposure population subgroup was children 3-5 years old, which utilized 3.6% of the ssPAD.

Table 5.4.4.1. Summary of Steady-State Dietary (Food only) Exposure and Risk for Profenofos[1].			
Population Subgroup	ssPAD (mg/kg/day)[2]	95th Percentile	
		Exposure (mg/kg/day)	% ssPAD
General U.S. Population	0.00012	0.000002	1.7
All Infants (<1 year old)		0.000001	<1.0
Children 1-2 years old		0.000004	3.5
Children 3-5 years old		**0.000004**	**3.6**
Children 6-12 years old		0.000003	2.6
Youth 13-19 years old		0.000002	1.7
Adults 20-49 years old		0.000001	1.1
Adults 50-99 years old[2]		0.000001	<1.0
Females 13-49 years old		0.000001	1.2

[1] Highest exposure at the 95th percentile is in bold.
[2] Subpopulation adults 50-99 years old: ssPAD = 0.0012 mg/kg/day.

5.4.5 Cancer Dietary Risk Assessment

Profenofos is classified as a Group E Chemical based on lack of evidence of carcinogenicity in rats and mice. Quantitative risk assessment for profenofos using the reference dose approach will adequately account for all chronic toxic effects, including carcinogenicity.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

Profenofos is being supported as a tolerance without a U.S. registration on cotton only. Therefore, a discussion of residential exposure is not germane to this action.

7.0 Residential Bystander Post-Application Inhalation Exposure

Profenofos is being supported as a tolerance without a U.S. registration on cotton only. Therefore, a discussion of residential bystander post-application inhalation exposures is not germane to this petition.

8.0 Spray Drift

Profenofos is being supported as a tolerance without a U.S. registration on cotton only; therefore, a discussion of spray drift is not germane to this petition.

9.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. For the updated use pattern, exposure to profenofos can occur only in food; therefore, aggregation was not conducted. Drinking water and residential exposures are not expected to occur since profenofos will no longer be applied in the U.S.

10.0 Cumulative Exposure/Risk Characterization

OPs, like profenofos, share the ability to inhibit AChE through phosphorylation of the serine residue on the enzyme leading to accumulation of acetylcholine and ultimately cholinergic neurotoxicity. This shared MOA/AOP is the basis for the OP common mechanism grouping per OPP's *Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity* (USEPA, 1999). The 2002 and 2006 CRAs used brain AChE inhibition in female rats as the source of dose response data for the relative potency factors and PODs for each OP, including profenofos. Prior to the completion of Registration Review, OPP will update the OP CRA on AChE inhibition to incorporate new toxicity and exposure information available since 2006.

As described in Section 4.4, OPP has retained the FQPA SF for OPs, including profenofos, due to uncertainties associated with neurodevelopmental effects in children and exposure to OPs. There is a lack of an established MOA/AOP for the neurodevelopment outcomes which precludes the Agency from formally establishing a common mechanism group per the *Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity* (USEPA, 1999) based on that outcome. Moreover, the lack of a recognized MOA/AOP and other uncertainties with exposure assessment in the epidemiology studies prevent the Agency from establishing a causal relationship between OP exposure and neurodevelopmental outcomes. The Agency will continue to evaluate the epidemiology studies associated with neurodevelopmental outcomes and OP exposure prior to the release of the revised DRA. During this period, the Agency will determine whether or not it is appropriate to apply the draft guidance document entitled, *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis* for the neurodevelopment outcomes.

11.0 Occupational Exposure/Risk Characterization

There is no occupational exposure/risk to U.S. workers from importation of treated cottonseed.

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RDI: RAB1 (10/05/16)
cc: S. Levy
S. J. Levy: S10953:PY-S:(703)305-0783:7509P:RAB1

Appendix A. Toxicology Profile

A.1 Toxicology Data Requirements

Study requirements (40 CFR 158.340) for profenofos are presented below. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Study		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Acute Eye Irritation	yes	yes
870.2500	Acute Dermal Irritation	yes	yes
870.2600	Skin Sensitization	yes	yes
870.3100	90-Day Oral Toxicity in Rodents	yes	yes
870.3150	90-Day Oral Toxicity in Nonrodents	yes	yes
870.3200	21/28-Day Dermal Toxicity	yes	yes
870.3250	90-Day Dermal Toxicity	no	--
870.3465	90-Day Inhalation Toxicity	yes	yes
870.3700a	Prenatal Developmental Toxicity (rodent)	yes	yes
870.3700b	Prenatal Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction and Fertility Effects	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes[1]
870.4100b	Chronic Toxicity (nonrodent)	yes	yes[2]
870.4200a	Carcinogenicity (rat)	yes	yes[1]
870.4200b	Carcinogenicity (mouse)	yes	yes
870.4300	Combined Chronic Toxicity/Carcinogenicity	yes	yes
870.5100	Mutagenicity—Bacterial Reverse Mutation Test	yes	yes
870.5300	Mutagenicity—Mammalian Cell Gene Mutation Test	yes	yes
870.5xxx	Mutagenicity— Structural Chromosomal Aberrations	yes	yes
870.5xxx	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100	Acute Delayed Neurotoxicity (hen)	yes	yes
870.6200a	Acute Neurotoxicity Screening Battery (rat)	yes	yes
870.6200b	90-Day Neurotoxicity Screening Battery (rat)	yes	yes
870.6300	Developmental Neurotoxicity	yes	yes
870.7485	Metabolism and Pharmacokinetics	yes	yes
870.7600	Dermal Penetration	no	--
870.7800	Immunotoxicity	yes	yes

[1] The combined chronic toxicity/carcinogenicity study satisfies the requirement of the study.
[2] Subchronic 90-day and 6-month studies are available; therefore, a longer term study is not required.

A.2. Toxicity Profiles

Table A.2.1. Acute Toxicity Profile for Technical Profenofos.

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral (rat)	41714801	LD50 = Males: 492 (363-666) mg/kg Females: 809 (600-1090) mg/kg Combined: 630 mg/kg	II
870.1100	Acute oral (mouse)	00105226	LD50 = 298 (268-332) mg/kg	II
870.1100	Acute oral (rabbit)	00105228	LD50 = 300 mg/kg	II
870.1200	Acute dermal (rat)	00105231	LD50 = 1610 (1073-2415) mg/kg	II
870.1200	Acute dermal (rabbit)	00109427	LD50 = Intact skin – Males: 146.8 mg/kg Females: 143.4 mg/kg Abraded skin- Males: 97.5 mg/kg Females: 15.9 mg/kg	I
870.1300	Acute inhalation (rat)	00109428	LC50 = 3.36 mg/L	IV
870.2400	Acute eye irritation (rabbit)	00109429	Minimal irritation, reversible within 7 days; no corneal opacity	III
870.2500	Acute dermal irritation (rabbit)	41714802	Moderately irritating at 72 hours	III
870.2600	Skin sensitization (guinea pig)	00109431	Sensitization was induced	-

Note: Studies have not been updated to reflect current HED policy. Endpoint selection was driven by BMD modeling of the AChE activity to obtain BMD_{10} and $BMDL_{10}$ values. As a result, updates to NOAEL/LOAEL values (or NOEL/LOEL values) in these studies would not ultimately impact current PODs or risk estimates. Consequently, the Agency did not find it necessary to update these studies at this time.

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile - Profenofos.

Guideline No.	Study Type	MRID No./Doses	Results
870.3100	90-Day Oral Toxicity in Rodents (rat)	00105255 0, 0.2, 2, or 20 mg/kg/day	NOEL = not established. LOEL 0.2 mg/kg/day based on RBC, plasma and brain AChE inhibition.
870.3150	Subchronic Oral Toxicity in Non-Rodent (dog) 90 days	00108016 0, 0.05, 0.5, or 5 mg/kg/day	Systemic NOEL = 5 mg/kg/day. Systemic LOEL = not established. Plasma AChE inhibition NOEL = not established. Plasma AChE inhibition LOEL = 0.05 mg/kg/day. RBC AChE inhibition NOEL = 0.05 mg/kg/day. RBC AChE inhibition LOEL = 0.5 mg/kg/day. Brain AChE inhibition NOEL = 0.5 mg/kg/day. Brain AChE inhibition LOEL = 5 mg/kg/day.
870.3150	Subchronic Oral Toxicity in Non-Rodent (dog) 6 months	00081687 0, 0.005, 0.05, 2.5, or 12.5 mg/kg/day	NOEL = 0.005 mg/kg/day. LOEL = 0.05 mg/kg/day based on AChE inhibition in plasma.

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile - Profenofos.			
Guideline No.	Study Type	MRID No./Doses	Results
870.3200	21-Day Dermal Toxicity (rat)	41644501 0, 0.05, 1, or 10 mg/kg/d Acceptable/guideline	NOEL = 1 mg/kg/day. LOEL = 10 mg/kg/day based on significant decreases in AChE in RBC, serum, and brain.
870.3700a	Prenatal Developmental in Rodent (rat)	00045031 0, 10, 30, or 60 mg/kg/day	Maternal NOEL = 30 mg/kg/day. Maternal LOEL = 60 mg/kg/day based on decreased food consumption and slightly decreased body weights. Developmental NOEL = 60 mg/kg/day. Developmental LOEL = not established.
870.3700b	Prenatal Developmental in Non-Rodent (rabbit)	00128870 0, 30, 60, 90, or 175 mg/kg/day	Maternal NOEL = 30 mg/kg/day. Maternal LOEL = 60 mg/kg/day based on decreased body weight gain. Developmental NOEL = 175 mg/kg/day. Developmental LOEL = not established.
870.3800	Reproduction and Fertility Effects (rat)	43213308, 43213309 0, 0.36, 7.3, or 29 mg/kg/day	Parental NOEL = 7.3 mg/kg/day. Parental LOEL = 29 mg/kg/day based on decreased body weight, body weight gain, and food consumption. Offspring NOEL = 7.3 mg/kg/day. Offspring LOEL = 29 mg/kg/day based on decreased pup body weight and body weight gain. Reproductive NOEL = 29 mg/kg/day. Reproductive LOEL = not established.
870.4100a	Chronic Toxicity (rat)	See 870.4300	See 870.4300
870.4200a	Carcinogenicity (rat)	See 870.4300	See 870.4300
870.4200b	Carcinogenicity (mouse)	00082901 0, 0.15, 4.5, or 15 mg/kg/day	NOEL = 0.15 mg/kg/day. LOEL = 4.5 mg/kg/day based on AChE inhibition in plasma and RBC. No evidence of carcinogenicity.
870.4300	Combined Chronic Toxicity/ Carcinogenicity (rat)	00081685 0, 0.015, 0.5, or 5 mg/kg/day	NOEL = 0.015 mg/kg/day. LOEL = 0.5 mg/kg/day based on AChE inhibition in RBC and plasma. No evidence of carcinogenicity.
870.5100	Bacterial reverse mutation	41866901	No increases in revertant colonies were observed in any strain up to 5000 µg/plate.
870.5375	*In vitro mammalian cytogenetics*	41945103	No aberrations reported up to cytotoxic levels (37.5 to 75 µg/mL).
870.5385	*In vivo* bone marrow cytogenetics (rat)	41945102	No induction of micronuclei up to a dose causing death (200 mg/kg).
870.5550	Unscheduled DNA synthesis (UDS) in mammalian cells	41945101	No increased grain count up to a dose producing 50% cytotoxicity (highest dose = 2.91 µg/mL).
870.6100	Acute Delayed Neurotoxicity (hen)	00126485	NOEL = 52 mg/kg. 100% mortality at next highest dose of 104 mg/kg LD_{50} = 56.3 mg/kg. No delayed neurotoxicity.

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile - Profenofos.			
Guideline No.	Study Type	MRID No./Doses	Results
870.6200a	Acute Neurotoxicity Screening Battery (rat)	42939801, 42939802 0, 95, 190, or 380 mg/kg	NOEL = not established. LOEL = 95 mg/kg based on AChE inhibition in plasma and RBC.
870.6200b	Subchronic Neurotoxicity Screening Battery (rat)	43213303, 43213304 0, 1.70/1.84, 7.7/8.4, or 36.0/37.9 mg/kg/day (M/F)	Systemic NOEL = 7.7 mg/kg/day. Systemic LOEL = 36 mg/kg/day based on slight decreases in body weight. Plasma and RBC AChE inhibition NOEL = not established. Plasma and RBC AChE inhibition NOEL = 1.7 mg/kg/day. Brain AChE inhibition NOEL = 7.7 mg/kg/day. Brain AChE inhibition NOEL = 36 mg/kg/day.
870.6300	Developmental Neurotoxicity (rat)	46025401, 46025402 0, 0.3, 5.1, or 50.6 mg/kg/day	Maternal Systemic NOAEL = 5.1 mg/kg/day. Maternal Systemic LOAEL = 50.6 mg/kg/day based on decreases in body weight, body weight gain, and food consumption. Maternal Cholinesterase NOAEL = 0.3 mg/kg/day. Maternal Cholinesterase LOAEL = 5.1 mg/kg/day based on AChE inhibition in RBC and brain. Offspring Systemic NOAEL = 5.1 mg/kg/day. Offspring Systemic LOAEL = 50.6 mg/kg/day based on decreases in body weight, body weight gain, and food consumption. Offspring Cholinesterase NOAEL = 0.3 mg/kg/day. Offspring Cholinesterase LOAEL = 5.1 mg/kg/day based on AChE inhibition in RBC, plasma, and brain.
870.7485	Metabolism and Pharmacokinetics Rat	42334301 -Single oral dose of 1 or 100 mg/kg of phenyl-UL-^{14}C-labeled profenofos - Pre-exposed to 1 mg/kg/day oral gavage of non-radiolabeled profenofos for 14 days before a single oral dose of 1 mg/kg ^{14}C-profenofos	Recovery of radioactivity ranged from 97%-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 radioactivity was expired as volatiles. Insignificant amounts were retained in any tissue after 7 days post-exposure. Analysis of fecal material indicated that <4% of the parent compound or its metabolites are unabsorbed or excreted via the biliary system into the intestinal tract. Profenofos 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-55960), CGA-47196, and CGA-65867. There were no apparent dose or sex-related differences in the absorption, distribution, metabolism, or excretion of profenofos.

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile - Profenofos.			
Guideline No.	Study Type	MRID No./Doses	Results
870.7485	Metabolism and Pharmacokinetics Young adult male monkeys	46224401 single oral dose via capsule at 2.4 mg/animal (approximately 0.5 mg/kg)	The test material was rapidly absorbed with significant concentrations measured in the blood and plasma by the first blood measurement (30 minutes post-dose). T_{max} was reached by 1 hour post-dose and rapidly declined thereafter. The terminal phase elimination half-life was estimated to be 4 hours in this study. Approximately 68% of the administered dose was recovered in the excreta (urine, feces, and cage wash after 168 hours) with the majority recovered in the urine (49%). Excretion was nearly complete by 24 hours following treatment. CGA-55163 was identified as the major urinary metabolite, which is the glucuronide conjugate of the phenol analog (CGA-55960).
870.7800	Immunotoxicity	48785801 0, 0.2, 6.4, or 67.6 mg/kg/day	Systemic NOAEL = 67.6 mg/kg/day. Systemic LOAEL = not established. Immunotoxicity NOAEL = 67.6 mg/kg/day. Immunotoxicity LOAEL = not established.
Special Studies			
	Acute Comparative Cholinesterase Study	46025405, 46025406 0, 1, 5, 25, or 100 mg/kg	RBC AChE inhibition NOAEL = 1 mg/kg/day. RBC AChE inhibition LOAEL = 5 mg/kg/day. Brain AChE inhibition NOAEL = 5 mg/kg/day. Brain AChE inhibition LOAEL = 25 mg/kg/day.
	Repeated Comparative Cholinesterase Study	46025403, 46025404 0, 0.5, 5, or 50 mg/kg/day	RBC AChE inhibition NOAEL = not established. RBC AChE inhibition LOAEL = 0.5 mg/kg/day. Brain AChE inhibition NOAEL = not established. Brain AChE inhibition LOAEL = 0.5 mg/kg/day.

Appendix B. Summary of OPP's Cholinesterase Policy & Use of BMD Modeling

OPP's ChE policy (USEPA, 2000[7]) describes the manner in which ChE data are used in human health risk assessment. The following text provides a brief summary of that document to provide context to points of departure selected.

AChE inhibition can be inhibited in the central or peripheral nervous tissue. Measurements of AChE or ChE inhibition in peripheral tissues (e.g., liver, diaphragm, heart, lung, etc.) are rare. As such, experimental laboratory studies generally measure brain (central) and blood (plasma and red blood cell, RBC) ChE. Blood measures do not represent the target tissue, *per se*, but are instead used as surrogate measures for peripheral toxicity in studies with laboratory animals or for peripheral and/or central toxicity in humans. In addition, RBC measures represent AChE, whereas plasma measures are predominately butyryl-ChE (BuChE). Thus, RBC AChE data may provide a better representation of the inhibition in target tissues. As part of the dose response assessment, evaluations of neurobehavior and clinical signs are performed to consider the dose response linkage between AChE inhibition and apical outcomes.

Refinements to OPP's use of ChE data have come in the implementation of BMD approaches in dose response assessment. Beginning with the OP CRA, OPP has increased its use of BMD modeling to derive PODs for AChE inhibiting compounds. Most often the decreasing exponential empirical model has been used.

OPP does have not a defined BMR for OPs. However, the 10% level has been used in the majority of dose response analyses conducted to date. This 10% level represents a 10% reduction in AChE activity (i.e., inhibition) compared to background (i.e., controls). Specifically, the BMD_{10} is the estimated dose where ChE is inhibited by 10% compared to background. The $BMDL_{10}$ is the lower confidence bound on the BMD_{10}.

The use of the 10% BMR is derived from a combination of statistical and biological considerations. A power analysis was conducted by ORD on over 100 brain AChE datasets across more than 25 OPs as part of the OP CRA (USEPA, 2002). This analysis demonstrated that 10% is a level that can be reliably measured in the majority of rat toxicity studies. In addition, the 10% level is generally at or near the limit of sensitivity for discerning a statistically significant decrease in ChE activity in the brain compartment and is a response level close to the background brain ChE level. With respect to biological considerations, a change in 10% brain AChE inhibition is protective for downstream clinical signs and apical neurotoxic outcomes. With respect to RBC AChE inhibition, these data tend to be more variable than brain AChE data. OPP begins its BMD analyses using the 10% BMR for RBC AChE inhibition but BMRs up to 20% could be considered on a case-by-case basis as long as such PODs are protective for brain AChE inhibition, potential peripheral inhibition, and clinical signs of neurotoxicity.

[7] USEPA (2000) Office of Pesticide Programs, US Environmental Protection Agency, Washington DC 20460. August 18, 2000 Office of Pesticide Programs Science Policy of The Use of Data on Cholinesterase Inhibition for Risk Assessments of Organophosphorous and Carbamate Pesticides.

Appendix C. Summary Tables of Benchmark Dose (BMD) Analyses

Toxicity studies with AChE data were analyzed using the most recent version of EPA's Benchmark Dose Software (Version 2.4). In Tables C.1-C.3, results have been summarized. Full results and technical details for these analyses can be found in the latest BMD analysis memo (M. Perron; 15-SEP-2015; TXR# 0057250).

Table C.1. Summary of BMD Results Following Acute Exposures to Profenofos.[1]

Study	Age	Compartment	Males		Females	
			BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Rat Acute Comparative Cholinesterase Assay - Gavage (MRID 46025406)	D12	RBC	NMF	NMF	13.68	9.31
		Brain	9.57	7.75	10.29	7.16
	D22	RBC	7.43	4.60	14.99	12.06
		Brain	20.2	14.4	31.12	14.92
	D42	RBC	13.49	11.24	3.17	1.99
		Brain	NMF	NMF	NMF	NMF
Rat Acute Non-Guideline Oral Study - Gavage (MRID 43213302)	Adult	RBC	26.1	3.46	8.78	4.45

BMD_{10} = benchmark dose where AChE is inhibited by 10% compared to background. $BMDL_{10}$ = lower 95% confidence interval for BMD_{10}. NMF = no statistical or visual model fit. D = day.

[1] The acute neurotoxicity study is not shown. The data were not found to be amenable to BMD modeling because rats were dosed too high (95-380 mg/kg) causing extrapolation to much lower doses to obtain BMD_{10} estimates.

Table C.2. Summary of BMD Results Following Repeated Exposures to Profenofos.

Study	Age	Compartment	Males		Females	
			BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Rat Studies						
Rat Repeat Comparative Cholinesterase Assay - Gavage (MRID 46025403)	D12 post-partum	RBC	0.69	0.51	0.49	0.24
		Brain	NMF	NMF	6.26	5.81
	D42 post-partum	RBC	NMF	NMF	0.38	0.17
		Brain	NMF	NMF	18.18	7.22
Rat Developmental Neurotoxicity Study – Dietary (MRID 46025401)	Fetus (GD22)	RBC	NDR	NDR	NDR	NDR
		Brain	NDR	NDR	NDR	NDR
	D5 post-partum	RBC	NDR	NDR	NDR	NDR
		Brain	NDR	NDR	37.09	16.16
	D12 post-partum	RBC	NDR	NDR	NDR	NDR
		Brain	NDR	NDR	NDR	NDR
	D22 post-partum	RBC	NDR	NDR	NDR	NDR
		Brain	NDR	NDR	NDR	NDR
	Pregnant Dams (GD22)	RBC	-	-	0.51	0.37
		Brain	-	-	46.31	7.63
	Non-pregnant females (D22 post-partum)	RBC	-	-	0.32	0.19
		Brain	-	-	42.57	5.19
Range-Finding Rat Developmental	Fetus (GD22)	RBC	NDR	NDR	22.38	12.31
		Brain	NDR	NDR	NDR	NDR

Table C.2. Summary of BMD Results Following Repeated Exposures to Profenofos.

Study	Age	Compartment	Males		Females	
			BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Neurotoxicity Study – Dietary (MRID 46025402)	D5 post-partum	RBC	NDR	NDR	NDR	NDR
		Brain	NDR	NDR	NDR	NDR
	D12 post-partum	RBC	NDR	NDR	94.6	40.5
		Brain	NDR	NDR	NDR	NDR
	D22 post-partum	RBC	15.51	12.34	NMF	NMF
		Brain	42.81	20.41	43.65	27.96
	Pregnant Dams (GD22)	RBC	-	-	1.78	1.09
		Brain	-	-	NDR	NDR
	Non-pregnant females (D22 post-partum)	RBC	-	-	0.53	0.31
		Brain	-	-	13.7	7.99
Subchronic Oral Rat – Dietary (MRID 00105255)	Adult	RBC	0.33	0.29	0.66	0.54
Rat Subchronic Neurotoxicity Study – Dietary (MRID 43213303)	Adult	RBC	0.12[a]	0.05[a]	0.23[a]	0.19[a]
13 Week Interim Measurement in Rat Chronic/Carcinogenicity Study– Dietary (MRID 00081685)	Adult	RBC	0.14	0.12	0.13	0.12
Terminal Measurement in Rat Chronic/Carcinogenicity Study– Dietary (MRID 00081685)	Adult	RBC	0.17	0.15	0.22	0.18
Dog Studies						
Subchronic Oral Dog – Dietary (MRID 00108016	Adult	RBC	NMF[b]	NMF[b]	NMF[b]	NMF[b]
Mouse Studies						
Mouse Carcinogenicity Study – Dietary (MRID 00081686)	Adult	RBC	0.21[a]	0.08[a]	0.78[a]	0.57[a]

[a] Poor dose spacing forced extrapolation to a much lower value to obtain BMD_{10} and $BMDL_{10}$ values.

[b] Large variability noted at all doses and ground truthing found no AChE inhibition in the raw data for the BMD_{10} values generated.

BMD_{10} = benchmark dose where AChE is inhibited by 10% compared to background. $BMDL_{10}$ = lower 95% confidence interval for BMD_{10}. NMF = no statistical or visual model fit. NDR = no dose response. D = day.

Table C.3. Summary of BMD Results for Route-Specific Studies.						
Study	Age	Compartment	Males		Females	
			BMD_{10}	$BMDL_{10}$	BMD_{10}	$BMDL_{10}$
Rabbit Dermal Toxicity Study (MRID 41644501)	Adult	RBC	NMF[a]	NMF[a]	NMF[a]	NMF[a]
Rat Inhalation Toxicity Study (MRID 00082079)	Adult	RBC	NMF[b]	NMF[b]	NMF[b]	NMF[b]

[a] Flat dose response with a decrease only at the highest dose tested and relatively large variability noted at all doses.
[b] Mortality at the highest dose tested left only 2 treatment groups for modeling and poor dose selection forced extrapolation to a much lower value from the lowest dose to obtain a BMD_{10} and $BMDL_{10}$ values.
BMD_{10} = benchmark dose where AChE is inhibited by 10% compared to background. $BMDL_{10}$ = lower 95% confidence interval for BMD_{10}. NMF = no statistical or visual model fit.

Appendix D. Physical/Chemical Properties

Table D.1. Physicochemical Properties of Technical Grade Profenofos.		
Parameter	Value	Reference
Melting Point/Range	N/A	MRID 42030301, 42854201
pH	3-5	
Specific Gravity	1.46 g/cm^3 at 20ºC	
Solvent Solubility (at 25ºC)	Completely miscible in ethanol, acetone, toluene, n-octanol, and n-hexane	
Vapor Pressure (20ºC)	9.001×10^{-7} mm Hg	
Dissociation Constant (pK_a)	N/A	
Octanol/Water Partition Coefficient (Log[K_{OW}])	4.83	

Appendix E. International Residue Limits

Table E.1. Summary of U.S. and International Tolerances and Maximum Residue Limits (MRLs) for Profenofos.

Commodity	Tolerances or MRLs (ppm)			
	U.S.	**Canada**	**Mexico**[1]	**Codex**[2]
Residue Definition:				
40CFR180.404 profenofos (O-(4-bromo-2-chlorophenyl)-O-ethyl-S-propyl phosphorothioate)		None		Profenofos
Cattle, fat	0.05			
Cattle, meat	0.05			0.05 (*) meat (from mammals other than marine mammals)
Cattle, meat byproducts	0.05			0.05 (*) edible offal (mammalian)
Cotton, gin byproducts	55.0			
Cotton, undelinted seed	2.0			3 cotton seed
Goat, fat	0.05			
Goat, meat	0.05			0.05 (*) meat (from mammals other than marine mammals)
Goat, meat byproducts	0.05			0.05 (*) edible offal (mammalian)
Horse, fat	0.05			
Horse, meat	0.05			0.05 (*) meat (from mammals other than marine mammals)
Horse, meat byproducts	0.05			0.05 (*) edible offal (mammalian)
Milk	0.01			0.01 (*)
Sheep, fat	0.05			
Sheep, meat	0.05			0.05 (*) meat (from mammals other than marine mammals)
Sheep, meat byproducts	0.05			0.05 (*) edible offal (mammalian)
MRLs with NO U.S. Equivalent				
Cardamom				3
Coriander, seed				0.1
Cumin seed				5
Eggs				0.02 (*)
Fennel, seed				0.1
Mango				0.2
Mangostan				10
Peppers, chili				3
Poultry meat				0.05 (*)
Poultry, edible offal of				0.05 (*)
Spices, fruits, and berries				0.07
Spices, roots and rhizomes				0.05
Teas (tea and herb teas)				0.5
Tomato				10
Completed by: M. Negussie, 04/09/2015 and S. Levy, 10/19/2016				

[1] Mexico adopts U.S. tolerances and/or Codex MRLs for its export purposes.

[2] * = absent at the limit of quantitation; Po = postharvest treatment, such as treatment of stored grains. PoP = processed postharvest treated commodity, such as processing of treated stored wheat. (fat) = to be measured on the fat portion of the sample. MRLs indicated as proposed have not been finalized by the CCPR and the CAC.