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

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

Date: July 1, 2010

Subject: **Phosmet**. Human Health Risk Assessment to Support Amended Use Pattern to Increase Application Rate and Reduce PHI for Almonds and Pistachios.

PC Code: 059201
Decision No.: 396687 & 369721
Petition No.: 8F7383
Risk Assessment Type: Single Chemical Aggregate
TXR No.: NA
MRID No.: NA

DP Barcode: D355157 & D362528
Registration No.: 10163-169
Regulatory Action: Amended Use
Case No.: NA

CAS No.: 732-11-6
40 CFR: 180.261

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Attached please find the most recent HED human health risk assessment for phosmet to support the requested amended use on almonds and pistachios.

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1.0 Executive Summary

Phosmet, *N*-(mercaptomethyl) phthalimide *S*-(O,O-dimethyl phosphorodithioate) is an organophosphate insecticide registered for use on a variety of fruits, vegetables, and field crops, and for direct application to cattle and swine. Gowan Company has submitted a tolerance petition, PP#8F7383, which includes a request to amend the currently registered use patterns for phosmet on almonds and pistachios and proposes revised tolerances to support the amended use patterns. The end-use product relevant to this request is Imidan® 70-W Agricultural Insecticide (EPA Reg. No. 10163-169), a WP formulation containing 70% active ingredient (ai). For almonds and pistachios, the petitioner proposes to increase the maximum seasonal rate to 11.2 lb ai/A and to shorten the preharvest interval (PHI) to 5 days. The proposed maximum rate per application is 3.7 lbs ai/A for both crops.

Phosmet is an organophosphate insecticide, and like all members of this class, the mode of toxic action is the inhibition of cholinesterase. The predominant effects seen in various toxicity studies with phosmet are those associated with cholinesterase inhibition (red blood cell (RBC) and brain) that occurs following all routes and durations of exposure. Phosmet produces the associated clinical signs, including tremors, shaking, unsteady gait, subdued mood, decreased activity, salivation, muscle weakness, convulsions in rats and rabbits, and decreased cholinesterase activity in rats, mice, and dogs following acute, subchronic, and chronic exposures. In the acute and subchronic neurotoxicity studies, cholinesterase activity is significantly inhibited in the absence of clinical signs of cholinesterase inhibition.

Phosmet is acutely toxic via the oral and inhalation routes of exposure, but is not acutely toxic via the dermal route, is non-irritating to the skin, and is not an eye irritant in the rabbit. A dermal absorption factor of 10% was observed in the rat dermal absorption study. Additionally, a correction factor of 4.5 was used to account for the increased permeability of rat skin relative to human skin, based on *in vitro* dermal absorption data. Phosmet does not cause neurological changes indicative of delayed neurotoxicity in the hen, and there is no evidence of neuropathology in the acute, subchronic, and chronic studies in rats, in the chronic dog study, or in the mouse long-term study. Decreased motor activity was observed in both sexes at the time of peak effect in the acute neurotoxicity study in rats. No treatment-related effects are observed in the functional observational battery (FOB) parameters in the acute and subchronic neurotoxicity studies in rats. Phosmet does not produce developmental toxicity in the rat, although skeletal variations were observed in the rabbit. Reproductive toxicity was observed in the rat (decreased fertility in both generations/both litters). There is no indication of an increased sensitivity of offspring in rats or rabbits following prenatal and/or postnatal exposure to phosmet in the developmental and reproductive studies; however, in both the acute oral and repeat oral direct-dosing comparative cholinesterase studies, an increased sensitivity was observed in the postnatal day 11 (PND 11) rat pups compared to the young adult rats. Based on a weight-of evidence evaluation of the mutagenicity and carcinogenicity data for phosmet, there is suggestive evidence of carcinogenicity but not sufficient to assess human carcinogenic potential.

The residue chemistry database for phosmet is considered complete to support the requested amended uses. The nature of the residue in plants and animals is adequately understood. Adequate field trial data were submitted which were generated using a validated analytical method and are supported by sufficient storage stability data. The crop field trial data reflect the proposed revised use patterns for almonds and pistachios and support the new and revised tolerances noted below. For tolerance enforcement, the Pesticide Analytical Manual (PAM), Vol. II lists a gas chromatography method with flame photometric detection (GC/FPD) and a GC method with flame ionization detection (GC/FID) as Methods II and III, respectively. The reassessed animal tolerances cited in the 2001 RED are adequate to support the amended use patterns for almonds and pistachios. A Codex MRL is established for residues of parent only in tree nuts at 0.2 ppm. There are no Canadian or Mexican MRLs for phosmet on pistachios and almonds. It is not possible to harmonize with Codex at this time as the Codex residue definition does not include the phosmet oxon and the Codex level is insufficient to address residues likely from the amended uses specified in this action.

Acute probabilistic and chronic aggregate dietary exposure and risk assessments for food and drinking water were conducted to support the requested amended use. Acute dietary risk estimates for food alone and food and drinking water at the 99.9th percentile of exposure are below HED's level of concern. The exposure for food alone utilized 26% of the acute Population Adjusted Dose (aPAD) at the 99.9th percentile of exposure for females 13-49 years old, the subgroup with the highest risk. The exposure for food plus drinking water at the 99.9th percentile of exposure utilized 72% of the aPAD for all infants, the most highly exposed population subgroup. Chronic dietary risk estimates for food alone and food and drinking water that are below the HED's level of concern for chronic dietary exposure. For food alone, the highest exposure and risk estimates were for children 1-2 years old, with a chronic Population Adjusted Dose (cPAD) of 3.2%. The exposure for food plus drinking water utilized 18% of the cPAD, and infants were the most highly exposed population subgroup.

Since there are no registered residential uses for phosmet, aggregate exposure estimates include food and drinking water only. As noted above, aggregate risks are not of concern for the existing and amended uses of phosmet.

An occupational handler exposure assessment was conducted for phosmet use on pistachios and almonds. The short- and intermediate-term dermal and inhalation handler exposure assessment was completed assuming the maximum label application rate per application of 3.7 lb ai/ acre for both crops. The personal protective equipment (PPE) on the proposed label is double layer clothing and gloves for mixers/loaders; pilot aerial applicators must use the engineering control of fully enclosed cab aircraft; airblast applicators must use engineering control of fully enclosed cab, and if not must use double-layer clothing, chemical-resistant glove and PF10 respirator; and human flagging is prohibited according to the proposed label.

Occupational handler mixer/loader scenarios were assessed with engineering control of water soluble packets (the specified formulation) and resulted in estimated MOEs greater than 100 and, therefore, do not exceed HED's level of concern, except for the mixer/loader scenario in support of aerial application. This scenario has an MOE of **71**. Water soluble packets are the specific formulation on the proposed label of Imidan® 70-W.

Aerial applicator risks do not exceed HED's level of concern (MOE > 100) with engineering control of enclosed cab. Airblast applicator risks do not exceed HED's level of concern (MOEs > 100) with engineering control of enclosed cab; airblast applicators in an open cab using maximum dermal (double layer plus chemical-resistant gloves) and maximum inhalation PPE have an MOE of **85**.

An occupational postapplication exposure assessment was conducted for the amended use as well. Short- and intermediate- term postapplication dermal postapplication exposure assessments were conducted assuming the maximum application rate of 3.7 lbs ai/A for almonds and pistachios; chemical-specific dislodgeable foliar residue data were used. The restricted-entry interval (REI) is 3 days for phosmet and the proposed label requires that pruning cannot occur until 7 days after application. The proposed pre-harvest interval (PHI) is 5 days for both crops and the proposed label requires that the tree nuts must be harvested mechanically. Dermal MOEs were 150 for low exposure activities and **31** for the high exposure activity of hand thinning at the REI of 3 days; the dermal MOE was **40** for the high exposure activity of hand pruning at 7 days after application. The MOEs indicate there are risks of concern (MOEs< LOC of 100) for the high exposure activities of hand thinning and pruning until 21 days after application. The mechanical harvesting exposure activity was assessed, as mechanical harvesting is a requirement stated on the proposed label, and the MOE was estimated to be 880 at the PHI of 5 days for both almonds and pistachios.

This assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide. These studies, which comprise the Pesticide Handlers Exposure Database (PHED), have been determined to require a review of their ethical conduct, and have received that review. The studies in PHED were considered appropriate (or ethically conducted) for use in risk assessments.

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.eh.doe.gov/oepa/guidance/justice/eo12898.pdf.

Regulatory Recommendations and Data Needs

Residue Chemistry Recommendations

Provided the registrant submits a revised Section F reflecting the tolerance levels below, the submitted data indicates that the following tolerances for residues of phosmet under 40 CFR 180.261(a) would be required to support the requested label amendment:

Almond, hulls..... 65 ppm
Almond ..... 0.35 ppm
Pistachio..... 0.35 ppm

Note to RD: Should the tolerance for pistachio be established under 180.261(a), the existing tolerance for pistachios with a regional registration under 180.261(c) can be removed. Concurrent with establishing the tolerances above on almonds and pistachio, the tolerance under 180.261(a) for "nut" should be revised to reflect current commodity definitions and should exclude almonds and pistachio. A tolerance for nut, tree, group 14 (excluding almond and pistachio) should be established at 0.1 ppm.

Toxicology Data Requirements

The gestational component of the comparative cholinesterase assay required under the 2006 organophosphate DCI remains outstanding. Additionally, an immunotoxicity study is outstanding based on revised Part 158 data requirements.

Occupational Regulatory Recommendations

There are risks of concern for mixer/loaders in support of aerial application/ chemigation. Since these risk estimates reflect engineering controls, options for RD to mitigate the risk of mixing/loading in support of aerial application/chemigation identified by HED are to (1) reduce the application rate on almonds and pistachios, or (2) prohibit aerial application/ chemigation.

Based on occupational handler risks of concern for airblast applicators with the proposed label PPE of double layer clothing and respirator, options for RD to mitigate the risk of concern for airblast applicator scenarios are (1) requiring the use of enclosed cab (engineering control) for airblast applications; or (2) reducing the application rate.

The proposed REI is 3 days. Additionally, the label contains a proposed restriction against hand-pruning for 7 days. Restrictions on the current label include a restriction against hand-pruning for 7 days. For occupational post-application scenarios of hand pruning and hand thinning almonds and pistachios, MOEs are less than 100 at the proposed REI of 3 days for hand thinning and day 7 for hand pruning. MOEs are greater than 100 for pruning at 21 days after application and for thinning at 21 days after application. Potential options for RD to mitigate the risk concerns identified by HED are (1) extending the REI identified on the registered label for these crops; (2) reducing the application rate on almonds and pistachios relative to the timing of application and worker activity; or (3) prohibiting application until after hand thinning and pruning activities have been completed for these crops, and/or prohibiting any hand thinning or pruning for tree nuts after an application of phosmet. RD may determine which option is the most feasible based on timing of applications, use information, and worker activity.

2.0 Ingredient Profile

2.1 Summary of Proposed Uses

D355156, D. Davis, 5/18/10, Residue Chemistry Chapter

Phosmet, *N*-(mercaptomethyl) phthalimide *S*-(O,O-dimethyl phosphorodithioate) is an organophosphate insecticide registered for use on a variety of fruits, vegetables, and field crops, and for direct application to cattle and swine. Phosmet is sold in the U.S. by Gowan Company, the basic producer, under the trade name Imidan®. End-use products containing phosmet as the active ingredients are formulated as wettable powder (WP) or dust (D). Phosmet may be applied to crops using aerial and ground equipment via foliar, dormant, and delayed dormant treatments. Schering-Plough Animal Health Corporation markets the 1 lb/gal EC formulation Del_Phos® for dermal treatment of livestock via spray and back rubber application.

The phosmet tolerances established under 40 CFR §180.261 are expressed in terms of phosmet and its oxygen analog. The established tolerances for plant commodities under 40 CFR §180.261(a) range from 0.1 ppm (nuts, potatoes, and cottonseed) to 40 ppm (alfalfa), and the established tolerances for animal commodities are 0.2 ppm (fat, meat, and meat byproducts of cattle, goat, hog, horse, and sheep). No tolerances are established for milk or poultry commodities. Tolerances with regional registration are established under 40 CFR §180.261(c) for crabapple at 20 ppm and pistachio at 0.1 ppm.

Gowan Company has submitted a tolerance petition, PP#8F7383, which includes a request to amend the currently registered use patterns for phosmet on almonds and pistachios. The end-use product relevant to this request is Imidan® 70-W Agricultural Insecticide (EPA Reg. No. 10163-169), a WP formulation containing 70% a.i. For both almonds and pistachios, the petitioner proposes to increase the maximum seasonal rate to 11.2 lb ai/A and to shorten the preharvest interval (PHI) to 5 days. The maximum rate per application for both crops is 3.7 lbs ai/A. A summary of the use directions for these crops is shown in Table 2.1.

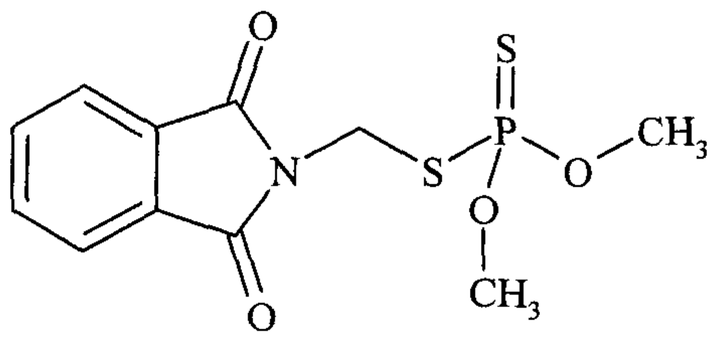
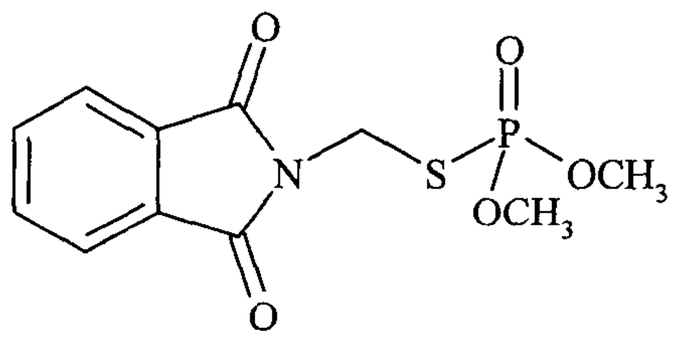
Table 2.1. Summary of Directions for Use of Phosmet on Almonds and Pistachios

Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Almond						
Broadcast foliar Ground or aerial	70% WP [10163-169]	3.0-3.7	Not specified (NS)	11.2	5	
Dormant Ground or aerial	70% WP [10163-169]	3.0-3.7	NS	11.2	5	Tank mix use with dormant spray oil.
Pistachio						
Broadcast foliar Ground or aerial	70% WP [10163-169]	3.0-3.7	NS	11.2	5	Do not allow livestock to graze or feed on cover crops.

Table 2.1. Summary of Directions for Use of Phosmet on Almonds and Pistachios						
Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Dormant Ground or aerial	70% WP [10163-169]	2.1-3.0	NS	11.2	5	Tank mix use with dormant spray oil. Do not allow livestock to graze or feed on cover crops.

2.2 Structure and Nomenclature

Table 2.2, below contains a summary of the nomenclature for phosmet and its oxon metabolite.

Table 2.2. Phosmet Nomenclature	
Compound	
Common name	Phosmet
IUPAC name	O,O-dimethyl S-phthalimidomethyl phosphorodithioate or N-(dimethoxyphosphinothioylthiomethyl)phthalimide
CAS name	S-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl]O,O-dimethylphosphorodithioate
CAS registry number	732-11-6
End-use product (EP)	Imidan® 70-W (EPA Reg. No. 10163-169)
Compound	
Common name	Phosmet oxon
Chemical name	O,O-Dimethyl-s-(phthalimidomethyl)phosphorothioate

2.3 Physical and Chemical Properties

Table 2.3, below contains a summary of the physicochemical properties of phosmet.

Table 2.3. Physicochemical Properties of Phosmet

Parameter	Value	Reference
Melting point/range	66-69 °C	RCB# 2628, G. Makhijani, 9/29/87
pH	3.74 (1% solution)	
Density	1.439 g/mL (PAI)	
Water solubility	(20°C) 20 ± 2 mg/L	
Solvent solubility	(g/100 mL at 25° C) Acetone >100 Chloroform >100 Xylene >100 Ethanol <1.0 Kerosene <1.0	
Vapor pressure	4×10^{-7} mbar at 25 °C (PAI)	Phosmet Registration Standard Update, R. Schmitt, 3/8/90
Dissociation constant, pK_a	Not required because the TGAIs are not acids or bases	
Octanol/water partition coefficient, $Log(K_{OW})$	9×10^{2} at 25 °C (PAI)	Phosmet Registration Standard Update, R. Schmitt, 3/8/90
UV/visible absorption spectrum	Not Available.	

3.0 Hazard Characterization

Phosmet is an organophosphate insecticide, and like all members of this class, the mode of toxic action is the inhibition of cholinesterase. The predominant effects seen in various toxicity studies on phosmet are those associated with cholinesterase inhibition (red blood cell (RBC), and brain) that occurs following all routes and durations of exposure. Phosmet produces the associated clinical signs, including tremors, shaking, unsteady gait, subdued mood, decreased activity, salivation, muscle weakness, convulsions in rats and rabbits (2-generation reproduction study in rats and developmental toxicity studies in rats and rabbits), and decreased cholinesterase activity in rats, mice, and dogs following acute, subchronic, and chronic exposures. In the acute and subchronic neurotoxicity studies and the acute and repeat dose comparative cholinesterase assays, cholinesterase activity is significantly inhibited in the absence of clinical signs of cholinesterase inhibition.

Phosmet is acutely toxic via the oral and inhalation routes of exposure, but is not acutely toxic via the dermal route, is non-irritating to the skin, and is not an eye irritant in the rabbit. An acceptable dermal absorption study conducted in rats indicates a dermal absorption factor of 10% is appropriate for phosmet risk assessment. An acceptable *in vitro* dermal penetration study provides a comparison of permeability between rat and

human skin (*in vitro* correction factor of 4.5). Phosmet does not cause neurological changes indicative of delayed neurotoxicity in the hen, and there is no evidence of neuropathology in the acute, subchronic, and chronic studies in rats, in the chronic dog study, or in the mouse long-term study. Decreased motor activity was observed in both sexes at the time of peak effect in the acute neurotoxicity study in rats. No treatment-related effects are observed in the functional observational battery (FOB) parameters in the acute and subchronic neurotoxicity studies in rats. Phosmet does not produce developmental toxicity in the rat, although skeletal variations were observed in the rabbit. Reproductive toxicity was observed in the rat (decreased fertility in both generations/both litters). There is no indication of an increased sensitivity of offspring in rats or rabbits following prenatal and/or postnatal exposure to phosmet in the developmental and reproductive studies; however, in both the acute oral and repeat oral direct-dosing comparative cholinesterase studies, an increased sensitivity was observed in the postnatal day 11 (PND 11) rat pups compared to the young adult rats. In the mouse carcinogenicity study, phosmet causes increases in liver carcinomas/adenomas in males and increased mammary gland tumors in females. Phosmet is not carcinogenic in rats. Phosmet is considered to cause direct effects on DNA *in vitro*, inducing mutations in bacteria and mammalian cells in the absence of exogenous metabolic activation. In the *in vivo* systems, there is no evidence of a mutagenic effect. Overall, the data indicate that phosmet has intrinsic mutagenic potential that is not expressed in whole animals. Based on a weight-of evidence evaluation of the mutagenicity and carcinogenicity data for phosmet, there is suggestive evidence of carcinogenicity but not sufficient to assess human carcinogenic potential. Assessment of risk using the chronic population adjusted dose is considered protective for any potential carcinogenic effects.

3.1 Hazard and Dose-Response Characterization

3.1.1 Database Summary

The toxicology database for phosmet is substantially complete and of acceptable quality to assess the potential hazard to humans, including special sensitivity of infants and children. The database includes prenatal developmental toxicity studies in rats and rabbits, a two-generation reproduction study in rats, an acute delayed neurotoxicity study in hens, a 21-day-day dermal toxicity study in rats, a dermal absorption study in rats, an *in vitro* comparative dermal penetration study in rat and human skin, an acute neurotoxicity study in rats, a subchronic neurotoxicity study in rats, and an acute and repeat dose comparative cholinesterase studies in adult and immature rats. In addition to these studies, the registrant has submitted an extensive database of guideline toxicology studies, as required in 40 CFR Part 158.340 (acute, subchronic, chronic, carcinogenicity, mutagenicity, and metabolism studies).

The gestational component of the comparative cholinesterase assay required under the 2006 organophosphate DCI remains outstanding. Additionally, an immunotoxicity study is outstanding based on revised Part 158 data requirements (see Attachment 2 for DCI justification). Results of the required studies will provide additional information on specific aspects of the hazard of phosmet.

3.1.2 Mode of Action, Metabolism, Toxicokinetic Data

Phosmet belongs to a class of insecticides (organophosphorous compounds) that act as cholinesterase inhibitors through phosphorylation of the active site of the acetylcholinesterase. Acetylcholinesterase is an enzyme found in cholinergic neurons whose function is to break down acetylcholine and thus terminate acetylcholine's ability to properly bind at the receptor sites. Inhibition of this enzyme leads to an accumulation of free, unbound acetylcholine at nerve endings. Measurement of cholinesterase inhibition to properly assess cholinergic pathways of the peripheral nervous system is typically not submitted to EPA as part of pesticide registration. As a surrogate, cholinesterase activity in circulating blood is used as an indicator of possible neuronal cholinesterase activity. Cholinesterase activity in the brain is a reasonable measure of effects on the central nervous system, and these data are typically provided to EPA in animal studies.

Phosmet requires metabolic activation to the oxon to cause cholinesterase inhibition. The oxon is the active cholinesterase inhibiting metabolite of most organophosphate compounds that require metabolic activation. The phosmet oxon is included in the tolerance expression, but oxon residues, when detected, are generally an order of magnitude lower than parent residues. There are no toxicological data available on this phosmet metabolite.

Phosmet is rapidly absorbed from the gastrointestinal tract following oral administration, distributed, metabolized, and eliminated in the urine and feces, with most of the radioactivity being eliminated within 24 hours of dosing. Very low levels of radioactivity (less than 1% of the administered dose) were found in tissues, with the liver and whole blood showing the highest and fat and bone showing the lowest levels. Phosmet does not bioaccumulate. Metabolites identified in the urine consist of phthalamic acid conjugates. Although unidentified radioactivity was found in the urine and feces, there was no attempt to determine whether phosmet *per se* was present.

3.2 FQPA Considerations

3.2.1 Adequacy of the Toxicity Database

The toxicology database for phosmet is adequate to assess potential risk to infants and children. The specific studies in the database that address potential differences between the young and adult are the prenatal developmental toxicity studies in rats and rabbits, a two-generation reproduction study in rats, an acute neurotoxicity study in rats, a subchronic neurotoxicity study in rats, and an acute and a 7-day repeat exposure comparative cholinesterase studies in adult and immature (postnatal day/PND 11) rats.

The requirement for a developmental neurotoxicity study was waived based on the lack of evidence of any sensitivity in the developmental and reproductive studies and lack of any neuropathology in any study on phosmet, including the neurotoxicity studies; furthermore, comparative cholinesterase studies measure the most sensitive endpoint

(ChEI) for organophosphate pesticides. There is an acute oral comparative cholinesterase assay in PND 11 pups and adult rats and a 7-day repeat oral exposure comparative cholinesterase assay in PND 11 pups and adult rats that were submitted in response to the Data Call-In for comparative cholinesterase assays on all organophosphate pesticides (2006). However, the gestational exposure component in the comparative cholinesterase assay has not been submitted to date.

Although increased sensitivity of the PND 11 pups was observed in the comparative cholinesterase assays following acute and repeat oral exposure, both the acute and chronic dietary risk assessments (dose and endpoint), as well as the non-occupational, short- and intermediate-term dermal and inhalation exposure scenarios for infants and children, are based on the PND 11 pup cholinesterase response in these assays, and an additional safety factor for sensitivity of the young is not required for these risk assessments. Due to the lack of the comparative cholinesterase gestational exposure assay, an additional 10X FQPA SF/UF_{DB} is required for females 13-49 years old for the acute and chronic dietary risk assessments, as well as the non-occupational, short- and intermediate-term dermal and inhalation exposure scenarios, which are based on the adult cholinesterase response.

3.2.2 Evidence of Neurotoxicity

Phosmet does not cause neurological changes indicative of delayed neurotoxicity in the hen. Acute, subchronic, and chronic oral exposures to adult rats, mice, and dogs resulted in cholinesterase inhibition in one or more compartments (plasma, RBC, brain), and no neuropathology. No treatment-related effects are observed in the functional observational battery (FOB) parameters or on motor activity in the acute and subchronic neurotoxicity studies in rats, and neuropathology is not observed in either study. The phosmet database indicates that the RBC compartment is the most sensitive compartment for cholinesterase inhibition in the adult rat. The acute and repeat dose comparative cholinesterase assays show that the pup RBC and brain cholinesterase inhibition are similar in magnitude. No clinical signs were observed in the neurotoxicity and comparative cholinesterase assays that were indicative of neurotoxicity. The comparative cholinesterase assays provided evidence of sensitivity in the young animal based on cholinesterase inhibition in all compartments. Executive summaries of the acute and repeat comparative cholinesterase assays and the acute and subchronic neurotoxicity studies are in Appendix A.

3.2.3 Pre- and/or Postnatal Toxicity

3.2.3.1 Developmental Toxicity Studies

Adequate data are available for phosmet for evaluation of developmental toxicity in rats and rabbits. In rabbits, developmental effects (increased incidence of skeletal variations) were noted at 15 mg/kg/day (highest dose tested) where maternal toxicity was also observed (unsteady gait, shaking, salivation, irregular breathing, decreased body weight). No developmental toxicity was observed in rats at the highest dose tested (15 mg/kg/day)

where maternal toxicity was observed (tremors/shaking, salivation, piloerection, subdued mood, and decreased body-weight gain and food consumption). Executive summaries for both studies are in Appendix A.

3.2.3.2 Reproductive Toxicity Study

Phosmet exposure resulted in reduced fertility and lactation indices and decreased number of live pups/litter and decreased pup body weight at dose levels that resulted in significant RBC cholinesterase inhibition. At the highest dose level, tremors, convulsions, hypothermia, decreased activity, and muscle weakness were observed in a few of the dams in both generations. Offspring NOAEL was higher than the parental NOAEL, although cholinesterase activity was not monitored in the offspring. There was no evidence of sensitivity based on the parameters measured. The executive summary for this study is in Appendix A.

3.3 Determination of Susceptibility

There is concern for pre- and/or postnatal toxicity resulting from exposure to phosmet. Sensitivity was observed in the acute and repeat dose comparative cholinesterase assays, and cholinesterase inhibition is the endpoint of concern. There is a lack of a gestational exposure component of the comparative cholinesterase assay.

Since the acute dietary risk assessment (dose and endpoint) for infants and children is based on the PND 11 pup cholinesterase response in the acute comparative cholinesterase assay, an additional safety factor for sensitivity of the young is not required for the acute dietary risk assessment for infants and children. Since the chronic dietary risk assessment and the non-occupational dermal and inhalation assessments (dose and endpoint) for infants and children are based on the PND 11 pup cholinesterase response in the 7-day repeat dose comparative cholinesterase assay, an additional safety factor for sensitivity of the young is not required for the these risk assessments for infants and children.

3.4 Hazard Identification and Toxicity Endpoint Selection

The acute and chronic dietary assessments have separate points of departure (PoDs) for each of three subpopulations (females 13-49 years old, infants and children, and general population excluding infants and children and females 13-40 years old). Different PoDs were selected for each population due to the biological differences in the pattern of cholinesterase inhibition seen throughout the different life stages.

3.4.1 Acute Reference Dose (aRfD) – Females 13-49 years old

Study Selected: acute oral comparative cholinesterase assay – rat
MRID No.: 47087401
Executive Summary: See Appendix A
Dose and Endpoint for Risk Assessment: $BMDL_{10}$ = 3.56 mg/kg/day, based on RBC cholinesterase inhibition in adult rats (combined sexes)
Uncertainty Factor(s): 1000X (10X interspecies; 10X intraspecies; 10X FQPA database UF)
Comments about Study/Endpoint/Uncertainty Factors: The effects observed occurred after a single dose. The route and duration of exposure are appropriate for this exposure scenario. An additional FQPA uncertainty factor is required for the lack of the gestational exposure component in the CCA study. A benchmark dose (BMD) analysis of the comparative cholinesterase study was performed on RBC and brain cholinesterase data from adult animals. The estimated dose at which 10% cholinesterase inhibition is observed (BMD_{10}) and the lower 95% confidence intervals ($BMDL_{10}$) were estimated by fitting the cholinesterase activity data to an exponential dose response model using generalized nonlinear least squares. The BMD_{10} was selected because it is generally at or near the limit of sensitivity for discerning a statistically significant decrease in cholinesterase activity across the blood and brain compartments and is a response level close to background cholinesterase activity. The database for phosmet shows the RBC compartment to be the more sensitive compartment in adult animals with respect to cholinesterase inhibition.

3.4.2 Acute Reference Dose (aRfD) – Infants and Children

Study Selected: acute oral comparative cholinesterase assay – rat
MRID No.: 47087401
Executive Summary: See Appendix A
Dose and Endpoint for Risk Assessment: $BMDL_{10}$ = 1.2 mg/kg/day, based on brain cholinesterase inhibition in PND 11 female pups.
Uncertainty Factor(s): 100X (10X interspecies; 10X intraspecies)
Comments about Study/Endpoint/Uncertainty Factors: The effects observed occurred after a single dose. The route and duration of exposure are appropriate for this exposure scenario. An additional safety factor for sensitivity of the young is not required because the response in the young animal is the basis of the dose and endpoint. Additionally, retention of an FQPA database UF for this assessment is not required as gestational exposure is not relevant for this population. A benchmark dose (BMD) analysis of the comparative cholinesterase study was performed on RBC and brain cholinesterase data from juvenile animals. The estimated dose at which 10% cholinesterase inhibition is observed (BMD_{10}) and the lower 95% confidence intervals ($BMDL_{10}$) were estimated by fitting the cholinesterase activity data to an exponential dose response model using generalized nonlinear least squares. The BMD_{10} was selected because it is generally at or near the limit of sensitivity for discerning a statistically significant decrease in cholinesterase activity across the blood and brain compartments and is a response level close to background cholinesterase activity. The selected acute comparative

cholinesterase study shows that the pup RBC and brain cholinesterase inhibition are similar in magnitude. In the pups, the detoxification enzymes are not yet developed as in adults and more OP reaches the brain, resulting in more cholinesterase inhibition in the pup brain than in the adult. The $BMDL_{10}$ for pup RBC cholinesterase inhibition (1.4 mg/kg/day) is slightly greater than the pup brain $BMDL_{10}$ (1.2 mg/kg/day).

3.4.3 Acute Reference Dose (aRfD) – General Population, excluding infants and children and females 13-49 years old

Study Selected: acute oral comparative cholinesterase assay – rat
MRID No.: 47087401
Executive Summary: See Appendix A
Dose and Endpoint for Risk Assessment: $BMDL_{10}$ = 3.56 mg/kg/day, based on RBC cholinesterase inhibition in adult rats (combined sexes)
Uncertainty Factor(s): 100X (10X interspecies; 10X intraspecies)
Comments about Study/Endpoint/Uncertainty Factors: The effects observed occurred after a single dose. The route and duration of exposure are appropriate for this exposure scenario. An additional FQPA uncertainty factor is not required for the lack of the gestational exposure component in the CCA study as gestational exposure is not relevant for this population. A benchmark dose (BMD) analysis of the comparative cholinesterase study was performed on RBC and brain cholinesterase data from adult animals. The estimated dose at which 10% cholinesterase inhibition is observed (BMD_{10}) and the lower 95% confidence intervals ($BMDL_{10}$) were estimated by fitting the cholinesterase activity data to an exponential dose response model using generalized nonlinear least squares. The BMD_{10} was selected because it is generally at or near the limit of sensitivity for discerning a statistically significant decrease in cholinesterase activity across the blood and brain compartments and is a response level close to background cholinesterase activity. The database for phosmet shows the RBC compartment to be the more sensitive compartment in adult animals with respect to cholinesterase inhibition.

3.4.4 Chronic Reference Dose (cRfD) – Females 13-49 years old

Study Selected: 7-day repeat dose comparative cholinesterase assay – rat
MRID No.: 47695401
Executive Summary: See Appendix A
Dose and Endpoint for Risk Assessment: $BMDL_{10}$ = 0.6 mg/kg/day, based on adult RBC cholinesterase inhibition (combined sexes).
Uncertainty Factor(s): 1000X (10X interspecies; 10X intraspecies; 10X UF_{DB}/FQPA SF)
Comments about Study/Endpoint/Uncertainty Factors: The endpoint, RBC cholinesterase inhibition following repeat exposure, is appropriate for this risk assessment. RBC is the most sensitive compartment for phosmet in the adult animal. The 7-day repeat dose study is appropriate for a chronic exposure since a comparison of the BMD_{10}/ $BMDL_{10}$'s across all studies/durations (subchronic neurotoxicity studies (3- and 13-weeks), chronic toxicity study (6 months), and repeat 7-day CCA studies) showed that the BMD_{10} and $BMDL_{10}$ for RBC were similar across studies and did not increase with increasing duration. This was also true for the BMD_{10} and $BMDL_{10}$ for brain. An

overall safety factor of 1000 should be applied for females 13-49 years old (100X for inter- and intra-species variability, and an FQPA database UF of 10X) for a lack of the gestational exposure component in the comparative cholinesterase assay. This additional 10-fold FQPA uncertainty factor is appropriate for this population subgroup only.

3.4.5 Chronic Reference Dose (cRfD) – Infants and Children

Study Selected: 7-day repeat dose comparative cholinesterase assay – rat
MRID No.: 47695401
Executive Summary: See Appendix A
Dose and Endpoint for Risk Assessment: $BMDL_{10}$ = 0.16 mg/kg/day, based on pup RBC cholinesterase inhibition (combined sexes).
Uncertainty Factor(s): 100X (10 interspecies; 10X intraspecies)
Comments about Study/Endpoint/Uncertainty Factors: The endpoint, RBC cholinesterase inhibition following repeat exposure, is appropriate for this risk assessment. The 7-day repeat dose study is appropriate for a chronic exposure since a comparison of the BMD_{10}/ $BMDL_{10}$'s across all studies/durations (subchronic neurotoxicity studies (3- and 13-weeks), chronic toxicity study (6 months), and repeat 7-day CCA studies) showed that the BMD_{10} and $BMDL_{10}$ for RBC were similar and did not decrease with increasing duration. This was also true for the BMD_{10} and $BMDL_{10}$ for brain. An additional FQPA uncertainty factor is not required as gestational exposure is not relevant for this population.

3.4.6 Chronic Reference Dose (cRfD) – General Population excluding infants and children and females 13-49 years old

Study Selected: 7-day repeat dose comparative cholinesterase assay – rat
MRID No.: 47695401
Executive Summary: See Appendix A
Dose and Endpoint for Risk Assessment: $BMDL_{10}$ = 0.6 mg/kg/day, based on adult RBC cholinesterase inhibition (combined sexes).
Uncertainty Factor(s): 100X (10 interspecies; 10X intraspecies)
Comments about Study/Endpoint/Uncertainty Factors: The endpoint, RBC cholinesterase inhibition following repeat exposure, is appropriate for this risk assessment. RBC is the most sensitive compartment for phosmet in the adult animal. The 7-day repeat dose study is appropriate for a chronic exposure since a comparison of the BMD_{10}/ $BMDL_{10}$'s across all studies/durations (subchronic neurotoxicity studies (3- and 13-weeks), chronic toxicity study (6 months), and repeat 7-day CCA studies) showed that the BMD_{10} and $BMDL_{10}$ for RBC were similar and did not decrease with increasing duration. This was also true for the BMD_{10} and $BMDL_{10}$ for brain. An additional FQPA uncertainty factor is not required as gestational exposure is not relevant for this population.

3.4.7 Dermal Absorption

There are dermal absorption data on phosmet. A dermal absorption factor of 10% was observed in the rat dermal absorption study. Additionally, a correction factor of 4.5 is used to account for the increased permeability of rat skin relative to human skin. The executive summaries of the dermal absorption study and the *in vitro* rat and human skin permeability study may be found in Appendix A.

3.4.8 Occupational Dermal Exposure (Short- and Intermediate-Term)

Study Selected: 7-day repeat dose comparative cholinesterase assay – rat
MRID No.: 47695401
Executive Summary: See Appendix A
Dose and Endpoint for Risk Assessment: $BMDL_{10}$ = 0.6 mg/kg/day, based on adult RBC cholinesterase inhibition (combined sexes).
Uncertainty Factor(s): 100X (10 interspecies; 10X intraspecies)
Comments about Study/Endpoint/Uncertainty Factors: The endpoint, RBC cholinesterase inhibition following repeat exposure, is appropriate for this risk assessment. RBC is the most sensitive compartment for phosmet in the adult animal. The 7-day repeat dose study is appropriate for both durations of exposure since a comparison of the BMD10/ $BMDL_{10}$'s across all studies/durations (subchronic neurotoxicity studies (3- and 13-weeks), chronic toxicity study (6 months), and repeat 7-day CCA studies) showed that the BMD_{10} and $BMDL_{10}$ for RBC and brain cholinesterase data, were similar (within a 2-fold range) and did not decrease with increasing duration. Since the dermal exposure scenario is based on an oral study, both a 10% dermal absorption factor and a 4.5 *in vitro* dermal correction factor are applicable.

3.4.9 Occupational Inhalation Exposure (Short- and Intermediate-Term)

Study Selected: 7-day repeat dose comparative cholinesterase assay – rat
MRID No.: 47695401
Executive Summary: See Appendix A
Dose and Endpoint for Risk Assessment: $BMDL_{10}$ = 0.6 mg/kg/day, based on adult RBC cholinesterase inhibition (combined sexes) at the $BMDL_{10}$ of 1.19 mg/kg/day.
Uncertainty Factor(s): 100X (10 interspecies; 10X intraspecies)
Comments about Study/Endpoint/Uncertainty Factors: The endpoint, RBC cholinesterase inhibition following repeat exposure, is appropriate for these risk assessments. RBC is the most sensitive compartment for phosmet in the adult animal. The 7-day repeat dose study is appropriate for both durations of exposure since a comparison of the BMD10/ $BMDL_{10}$'s across all studies/durations (subchronic neurotoxicity studies (3- and 13-weeks), chronic toxicity study (6 months), and repeat 7-day CCA studies) showed that the BMD_{10} and $BMDL_{10}$ for RBC and brain cholinesterase data, were similar (within a 2-fold range) and did not decrease with increasing duration. Since the inhalation exposure scenario is based on an oral study, inhalation toxicity is assumed to be equivalent to oral toxicity.

3.5 Margins of Exposure

The target margins of Exposure (MOEs) for occupational risk assessments are 100 (10X interspecies; 10X intraspecies).

3.6 Classification of Carcinogenic Potential

Phosmet is classified as suggestive evidence of carcinogenicity but not sufficient to assess human carcinogenic potential. Assessment of risk using the chronic population adjusted dose is considered protective for any potential carcinogenic effects.

3.7 Summary of Toxicological Doses and Endpoints

Table 3.7.1 Summary of Toxicological Doses and Endpoints for Phosmet for Use in Dietary Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (females 13-49 years old)	$BMDL_{10}$ = 3.56 mg /kg/day	UF_A= 10x UF_H=10x UF_{FQPA}=10x	Acute RfD= 0.0356 aPAD = 0.00356 mg/kg/day	**Acute oral comparative CCA study – rat** **MRID 47087401** BMD_{10} = 7.092 mg/kg/day, based on RBC cholinesterase inhibition in adult rats (combined sexes)
Acute Dietary (infants and children)	$BMDL_{10}$ = 1.2 mg /kg/day	UF_A= 10x UF_H=10x	Acute RfD= 0.012 aPAD = 0.012 mg/kg/day	**Acute oral comparative CCA study – rat** **MRID 47087401** BMD_{10} = 1.9 mg/kg/day, based on female **PND 11 pup** brain cholinesterase inhibition
Acute Dietary (general pop, **excluding** infants and children and females 13-49 years old)	$BMDL_{10}$ = 3.56 mg /kg/day	UF_A= 10x UF_H=10x	Acute RfD= 0.0356 aPAD = 0.0356 mg/kg/day	**Acute oral comparative CCA study – rat** **MRID 47087401** BMD_{10} = 7.092 mg/kg/day, based on RBC cholinesterase inhibition in adult rats (combined sexes)
Chronic Dietary (females 13-49 years old)	$BMDL_{10}$ = 0.6 mg /kg/day	UF_A= 10x UF_H=10x UF_{FQPA}=10x	Acute RfD= 0.006 aPAD = 0.0006 mg/kg/day	**7-day repeat oral comparative CCA study – rat** **MRID 47695401** BMD_{10} = 1.19 mg/kg/day, based on RBC cholinesterase inhibition in adult rats (combined sexes)
Chronic Dietary (infants and children)	$BMDL_{10}$ = 0.16 mg /kg/day	UF_A= 10x UF_H=10x	Acute RfD= 0.0016 aPAD = 0.0016 mg/kg/day	**7-day repeat oral comparative CCA study – rat** **MRID 47695401** BMD_{10} = 0.36 mg/kg/day, based on RBC cholinesterase inhibition in pups (combined sexes)
Chronic Dietary (general pop, **excluding** infants and children and females 13-49 years old)	$BMDL_{10}$ = 0.6 mg /kg/day	UF_A= 10x UF_H=10x	Acute RfD= 0.006 aPAD = 0.006 mg/kg/day	**7-day repeat oral comparative CCA study – rat** **MRID 47695401** BMD_{10} = 1.19 mg/kg/day, based on RBC cholinesterase inhibition in adult rats (combined sexes)

Table 3.7.1 Summary of Toxicological Doses and Endpoints for Phosmet for Use in Dietary Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Cancer (oral, dermal, inhalation)	Classification: suggestive evidence of carcinogenicity but not sufficient to assess human carcinogenic potential			

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_{FQPA} = lack of gestational component in comparative cholinesterase assay; PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Table 3.7.2. Summary of Toxicological Doses and Endpoints for Phosmet for Use in Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal (short- and intermediate-term)	$BMDL_{10}$ = 0.6 mg /kg/day 10% dermal absorption 4.5 *in vitro* correction factor	UF_A= 10x UF_H=10x	Occupational LOC for MOE = 100	**7-day repeat oral comparative CCA study – rat** **MRID 47695401** BMD_{10} = 1.19 mg/kg/day, based on RBC cholinesterase inhibition in adult rats (combined sexes)
Dermal Long-Term	*Not required based on use pattern.*			
Inhalation (short- and intermediate-term)	$BMDL_{10}$ = 0.6 mg /kg/day inhalation hazard assumed to be equivalent to oral hazard	UF_A= 10x UF_H=10x	Occupational LOC for MOE = 100	**7-day repeat oral comparative CCA study – rat** **MRID 47695401** BMD_{10} = 1.19 mg/kg/day, based on RBC cholinesterase inhibition in adult rats (combined sexes)
Inhalation Long-Term (>6 months)	*Not required based on use pattern.*			
Cancer (oral, dermal, inhalation)	Classification: suggestive evidence of carcinogenicity but not sufficient to assess human carcinogenic potential			

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). PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

3.8 Endocrine Disruption

As required under FFDCA section 408(p), EPA has developed the Endocrine Disruptor Screening Program (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, and 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.

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. This list of chemicals was selected based on the potential for human exposure through pathways such as food and water, residential activity, and certain post-application agricultural scenarios. This list should not be construed as a list of known or likely endocrine disruptors.

Phosmet is among the group of 58 pesticide active ingredients on the initial list to be screened under the EDSP. The Agency will review the EDSP Tier 1 data and any "other scientifically relevant information" submitted in response to test orders. Based on this review the Agency will determine the need for additional testing. For further information on the status of the EDSP, the policies and procedures, the list of 67 chemicals, the test guidelines and the Tier 1 screening battery, please visit our website: http://www.epa.gov/endo/.

4.0 Dietary Exposure/Risk Characterization

4.1 Metabolism and Environmental Degradation

D250029, 11/23/98, C. Swartz, Revised Residue Chemistry Chapter of the HED RED for Phosmet

The nature of phosmet residues in plants and animals is adequately understood based on cherry, potato, and corn metabolism studies. The HED Metabolism Committee (M. Metzger, 8/11/95) has concluded that the residues of concern in plants and livestock commodities include phosmet and its oxygen analog.

4.2 Environmental Degradation

D355159, 2/9/09, R. Baris, Drinking Water Memorandum

Phosmet is soluble in water and is not expected to volatilize significantly based on its low vapor pressure. There are no data on the bioaccumulation potential of phosmet in fish;

however, the octanol/water partition coefficient suggests low potential for bioaccumulation. Phosmet is subject to rapid hydrolysis under alkaline and neutral conditions and to a lesser degree under acidic conditions. Microbial-mediated degradation may also be a route of dissipation. Phosmet degrades under aerobic conditions in soil, and under anaerobic conditions. Phosmet is slightly to moderately mobile in soils. Phosmet oxon (O, O-dimethyl-S-phthalimido-methylphosphorothioate), the only known degradate of toxicological concern, was identified in minor amounts (≤ 0.5%) in the environmental fate studies.

4.3 Analytical Methodology

4.3.1 Data Collection Methodology

D355156, D. Davis, 5/18/10, Residue Chemistry Chapter

Residue field trial samples submitted in support of this amended use action were analyzed for residues of phosmet and its oxon metabolite (phosmet oxon) using a gas chromatographic method with flame photometric detection in the phosphorous mode (GC/FPD; Morse Laboratories Analytical Method #Meth-117, Revision #3), entitled, "Determination of Selected Organophosphate Pesticides in Fruits and Vegetables", with modifications. A complete description of the method was included in the study report. Method verification and concurrent method recoveries were within the acceptable range of 70-120% for almond nutmeat fortified at 0.01-0.5 ppm with phosmet or phosmet oxon, for almond hulls fortified at 0.01-50 ppm with phosmet, and for almond hulls fortified at 0.01-0.5 ppm with phosmet oxon. Based on the lowest level of method validation (LLMV), the limit of quantitation (LOQ) was 0.01 ppm.

4.3.2 Enforcement Methodology

D250029, 11/23/98, C. Swartz, Revised Residue Chemistry Chapter of the HED RED for Phosmet

The Pesticide Analytical Manual (PAM), Vol. II lists a gas chromatography method with flame photometric detection (GC/FPD) and a GC method with flame ionization detection (GC/FID) as Methods II and III, respectively, for tolerance enforcement. These methods are adequate to enforce the new and revised tolerances proposed herein.

4.4 Drinking Water Residue Profile

The drinking water residues used in the dietary risk assessment were provided by the Environmental Fate and Effects Division in the following memorandum: "Revised Tier II Drinking Water Exposure Assessment for the Section 3 New Use Registration of Phosmet on Almonds and Pistachios and Re-evaluation of All Labeled Uses" (D374889, 5/25/2010) and incorporated directly into this dietary assessment. The revised Tier II drinking water assessment was conducted using new hydrolysis data, as well as incorporating revised labels that include label mitigation recommendations from the 2001 Interim Reregistration Eligibility Decision, and the proposed amendments for almonds and pistachio. Water residues were incorporated in the DEEM-FCID into the food categories "water, direct, all sources" and "water, indirect, all sources."

The drinking water assessment used modeling to provide estimates of surface water and groundwater concentrations of phosmet residues. The coupled models PRZM and EXAMS were used to assess exposure in surface water due to runoff and drift from the proposed and existing phosmet uses. Exposure in groundwater due to leaching was assessed with the screening model SCI-GROW. The model and its description are available at the EPA internet site: http://www.epa.gov/oppefed1/models/water/.

Phosmet oxon is the only environmental degradate of phosmet that has been identified as having toxicological concern. Phosmet oxon was only detected in minor amounts (≤0.5%) in the environmental fate studies and its formation and decline in the environment is not characterized well enough to estimate environmental concentrations. Information on drinking water treatment effects suggests that oxidative chlorination will result in the formation of phosmet oxon in drinking water facilities; however, qualitative data show that phosmet oxon does not appear to persist through distribution as it was not detected in finished water four hours post-treatment (Kamel *et al*, 2009). Additional quantitative information on the formation and stability of phosmet oxon resulting from drinking water treatment would be needed to estimate potential exposure in drinking water.

An extensive list of EDWCs were provided for phosmet; the bolded values shown in Table 4 represent the EDWCs utilized in this dietary assessment. The acute probabilistic analyses were performed incorporating the entire distribution of drinking water residues from the PRZM-EXAMS model. This distribution was based on the Georgia walnut (tree nuts) use pattern, since this crop yielded the highest EDWC value. For the chronic assessment, analyses were performed using the EDWC based on the North Carolina apple (fruit tree) use pattern, since this use produced the highest value for the chronic exposure duration.

Table 4. Tier II Estimated Drinking Water Concentrations (EDWCs) Resulting From Selected Use Patterns for Phosmet

Drinking water source (model)	**Use**	**1-in-10 year acute (ppb)**	**1-in-10 year chronic (ppb)**	**30- year average (ppb)**
Surface water (PRZM/EXAMS)	Alfalfa	49	1.3	0.4
	Almonds & Pistachios (proposed)	56	0.7	0.3
	Citrus	122	2.1	0.3
	Fruit Tree	176	3.7	0.6
	Forestry	22	0.3	0.1
	Tree Nuts	205	3.3	0.5
Groundwater (SCIGROW)	Alfalfa	0.38	<0.38	<0.38
	Almonds & Pistachios (proposed)	0.47	<0.47	<0.47
	Citrus	0.18	<0.18	<0.18

Table 4. Tier II Estimated Drinking Water Concentrations (EDWCs) Resulting From Selected Use Patterns for Phosmet				
Drinking water source (model)	**Use**	**1-in-10 year acute (ppb)**	**1-in-10 year chronic (ppb)**	**30- year average (ppb)**
	Fruit Tree	0.63	<0.63	<0.63
	Forestry	0.13	<0.13	<0.13
	Tree Nuts	0.50	<0.50	<0.50

4.5 Food Residue Profile

D355156, D. Davis, 5/18/10, Residue Chemistry Chapter

An adequate number of field trials with appropriate geographic representation have been provided to allow HED to establish new and revised tolerances to support increased application rates and PHIs for almonds and pistachios. Sufficient storage stability data are available to support the field trial data and the data were generated using an appropriate data collection method. Almond field trial data will be translated to pistachios.

Five almond trials were conducted in the United States in Zone 10 (CA) during the 2006 growing season. At each test location, three foliar broadcast applications were made of the 70% WP formulation of phosmet, at rates of ~3.73 lb ai/A per application, with 29- to 59-day retreatment intervals, for a total of ~11.2 lb ai/A (1x the maximum proposed seasonal rate). Applications were made using a pH-adjusting RNA Bu-pH-er as an adjuvant. The first applications were made when the trees were at 10% fruit maturity, the second applications at 1% hull split, and the third applications 5 days prior to harvest. Samples of almond hulls and nutmeat were analyzed for residues of phosmet and its oxon metabolite (phosmet oxon) using gas chromatography with flame photometric detection in the phosphorous mode (GC/FPD).

The results of the field trials (see Table 4.5, below) indicate that the maximum combined residues of phosmet and phosmet oxon were <0.235 ppm in/on almond nutmeat and 42.4 ppm in/on almond hulls harvested five days following the last of three foliar broadcast applications of the 70% WP formulation of phosmet at a total rate of ~11.2 lb ai/A, with 29- to 59-day retreatment intervals. The maximum individual residues of phosmet were 0.225 ppm in/on almond nutmeat and 42.1 ppm in/on almond hulls, and maximum individual residues of phosmet oxon were <0.01 ppm in/on almond nutmeat and 0.397 ppm in/on almond hulls.

Table 4.5. Summary of Residue Data from Almond Field Trials with Phosmet.

Commodity	Total Applic. Rate (lb ai/A)	PHI (days)	Analyte	Residue Levels (ppm)[1] n	Min.	Max.	HAFT[2]	Median (STMdR)	Mean (STMR)	Std. Dev.
Almond (proposed use = 11.2 lb ai/A total application rate, 5-day PHI)										
Almond, nutmeat	11.18-11.24	5	Phosmet	10	0.0168	0.225	0.212	0.0246	0.0632	0.0796
			Phosmet oxon	10	<0.010	<0.010	0.010	0.010	0.010	--
			Combined residues	10	<0.0268	<0.235	0.222	0.0346	0.0732	0.0796
Almond, hulls	11.18-11.24	5	Phosmet	10	7.71	42.1	39.7	17.3	18.9	12.0
			Phosmet oxon	10	0.103	0.397	0.392	0.218	0.243	0.118
			Combined residues	10	7.86	42.4	40.1	17.7	19.2	12.1

[1] When calculating the median, mean, and standard deviation, the LOQ (0.01 ppm for each analyte in each matrix) was used for values reported <LOQ.
[2] HAFT = Highest Average Field Trial.

There are no processed commodities associated with almonds or pistachios. The only feed item associated with the uses on almonds and pistachios is almond hulls, which is a feed item for dairy cattle only. The inclusion of almond hulls in the dietary burden calculation for dairy cattle will not result in an increase in anticipated residues in livestock; therefore, HED concludes that the reassessed tolerances for meat, meat byproducts, and fat of cattle, goats, horses, and sheep are adequate to support the proposed uses addressed herein.

4.6 Tolerances and International Residue Limits

Phosmet tolerances are established under 40 CFR §180.261(a) and (c) and are expressed in terms of phosmet and its oxygen analog.

Tolerances are currently established under 40 CFR §180.261(a) on almond hulls at 10 ppm and nut at 0.1 ppm (N). A tolerance with regional registration is established under 40 CFR §180.261(c) on pistachio at 0.1 ppm. The 10/2001 IRED for phosmet indicated that sufficient data were available to assess the tolerances of almond hulls, pistachio, and nut crops and made the following recommendations: (i) remove the "N" designation, which means negligible residues, from all entries; (ii) revise the commodity definition from "nuts" to "nut, tree, group"; and (iii) revoke the 0.1 ppm tolerance for pistachios under §180.261(c) once the nut, tree, group tolerance is established under §180.261(a). These recommendations have not yet been implemented.

The Agency's *Guidance for Setting Pesticide Tolerances Based on Field Trial Data* was used to determine appropriate tolerance levels for almond hulls and almonds. Almond data was translated to pistachios to determine an appropriate tolerance level for pistachio nutmeat. The recommended tolerances and commodity definitions are shown in Table 4.6.

Codex has established maximum residue limits for phosmet residues in/on tree nuts at 0.2 ppm. The Codex MRLs for phosmet are expressed in terms of phosmet only. The U.S. tolerance definition and the recommended tolerance levels for almond and pistachio are not in harmony with Codex. It is not possible to harmonize with Codex at this time as the Codex MRL expression does not include the phosmet oxon and the level is insufficient to address residues likely from the amended uses specified in this action. There are no Canadian or Mexican MRLs for phosmet for the crop commodities that are the subject of this risk assessment.

Table 4.6. Tolerance Summary for Phosmet

Commodity	Current §180.261 Tolerance (ppm)	Proposed §180.261 Tolerance (ppm)	Recommended §180.261 Tolerance (ppm)	Comments; *Correct Commodity Definition*
Tolerances under 40 CFR 180.261(a)				
Almond, hulls	10	50	65	
Almond	0.1 (N)	0.3	0.35	A separate almond tolerance has not been established. The existing use for almonds is covered under a tolerance for "nut". *Almond*
Pistachios	0.1	0.3	0.35	A tolerance with regional registration is currently established under 180.261(c). This tolerance should be removed concurrently with establishing a revised tolerance for pistachio under 180.261(a). *Pistachio*
Nut	0.1(N)	None	0.1	The RED recommended revision of the established "nut" tolerance to remove the "N" and to revise the commodity definition. This petition establishing new almond and pistachio tolerances means that the "nut" tolerance should be further modified as shown below. *Nut, tree, group 14 (excluding almond and pistachio)*

4.7 Dietary Exposure and Risk

D362527, T. Goodlow, 7/1/10, Dietary Risk Assessment

Acute probabilistic and chronic aggregate dietary exposure and risk assessments for food and drinking water were conducted using the Dietary Exposure Evaluation Model DEEM-FCID™, Version 2.03 which uses food consumption data from the U.S. Department of Agriculture's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. These analyses were performed in order to determine the exposure and risk estimates that result from the Section 3 request to amend the currently registered use patterns for phosmet on almonds and pistachios. The dietary analyses also incorporated updated toxicological information, percent crop treated (%CT), drinking water estimates, and USDA's Pesticide Data Program (PDP) information. HED

generated anticipated residues (ARs) for phosmet based on PDP monitoring data, field trial data, and usage information.

4.7.1. Acute Dietary Exposure/Risk

A refined acute probabilistic dietary exposure assessment was performed for phosmet, since acute exposure estimates using tolerance level residues presented risks of concern. The refined assessment incorporated percent crop treated estimates, PDP data, empirical and default processing factors (PFs), and field trial residues. The full distribution of drinking water residues, as provided by the Environmental Fate and Effects Division (EFED), was also incorporated. Acute dietary risk estimates for food alone and food and drinking water at the 99.9th percentile of exposure are below HED's level of concern. The exposure for food alone utilized 26% of the acute Population Adjusted Dose (aPAD) at the 99.9th percentile of exposure for females 13-49 years old, the most highly exposed population subgroup. The exposure for food plus drinking water at the 99.9th percentile of exposure utilized 72% of the aPAD for all infants, the most highly exposed population subgroup. Acute dietary results for all populations are shown in Tables 4.7.4.1 and 4.7.4.2.

4.7.2 Chronic Non-Cancer Dietary Exposure/Risk

A refined chronic dietary exposure assessment was also performed for phosmet, since chronic exposure estimates using tolerance level residues also presented risks of concern. The refined analysis included PDP data, %CT information, field trial data, and empirical and default PFs. Estimated Drinking Water Concentration (EDWC) values were also included in the chronic assessment. The analyses resulted in dietary risk estimates for food alone and food and drinking water that are below the HED's level of concern for chronic dietary exposure. For food alone, the highest exposure and risk estimates were for children 1-2 years old, with a risk of 3.2% of the cPAD. The exposure for food plus drinking water utilized 18% of the cPAD, and infants were the most highly exposed population subgroup. Chronic dietary results for all populations are shown in Tables 4.7.4.1 and 4.7.4.2.

4.7.3 Cancer Dietary Risk

Phosmet is classified as having "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential." Therefore, cancer risk was not separately quantified. Risk assessment utilizing the cPAD is protective of chronic effects.

4.7.4 Acute and Chronic Dietary Exposure and Risk Summary

Table 4.7.4.1 Acute and Chronic Dietary (Food Only) Exposure and Risk Estimates for Phosmet

Population Subgroup	PAD (mg/kg/day)	DEEM-FCID	
		Exposure (mg/kg/day)	% PAD
Acute Dietary Estimates (99.9th Percentile of Exposure)			
General U.S. Population	0.0356	0.001174	3.3
All Infants (< 1 year old)	0.012	0.001414	12
Children 1-2 years old	0.012	0.003036	25
Children 3-5 years old	0.012	0.002499	21
Children 6-12 years old	0.012	0.001497	12
Youth 13-19 years old	0.0356	0.000741	2.1
Adults 20-49 years old	0.0356	0.000837	2.4
Adults 50+ years old	0.0356	0.001038	2.9
Females 13-49 years old	0.00356	0.000927	26
Chronic Dietary Estimates			
General U.S. Population	0.006	0.000012	<1
All Infants (< 1 year old)	0.0016	0.000028	1.7
Children 1-2 years old	0.0016	0.000051	3.2
Children 3-5 years old	0.0016	0.000037	2.3
Children 6-12 years old	0.0016	0.000018	1.1
Youth 13-19 years old	0.006	0.000007	<1
Adults 20-49 years old	0.006	0.000007	<1
Adults 50+ years old	0.006	0.000009	<1
Females 13-49 years old	0.0006	0.000008	1.3
Cancer Dietary Estimates			
Phosmet is classified as having "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential." Therefore, a cancer dietary assessment was not performed.			

Table 4.7.4.2 Acute and Chronic Dietary (Food and Water) Exposure and Risk Estimates for Phosmet

Population Subgroup	PAD (mg/kg/day)	DEEM-FCID	
		Exposure (mg/kg/day)	% PAD
Acute Dietary Estimates (99.9th Percentile of Exposure)			
General U.S. Population	0.0356	0.002824	7.9
All Infants (< 1 year old)	0.012	0.008631	72
Children 1-2 years old	0.012	0.005117	43
Children 3-5 years old	0.012	0.004387	37
Children 6-12 years old	0.012	0.002876	24
Youth 13-19 years old	0.0356	0.002010	5.6
Adults 20-49 years old	0.0356	0.002434	6.8
Adults 50+ years old	0.0356	0.002491	7.0
Females 13-49 years old	0.00356	0.002491	70
Chronic Dietary Estimates			
General U.S. Population	0.006	0.000090	1.5
All Infants (< 1 year old)	0.0016	0.000283	18
Children 1-2 years old	0.0016	0.000167	10
Children 3-5 years old	0.0016	0.000145	9.1
Children 6-12 years old	0.0016	0.000093	5.8
Youth 13-19 years old	0.006	0.000064	1.1
Adults 20-49 years old	0.006	0.000080	1.3
Adults 50+ years old	0.006	0.000086	1.4
Females 13-49 years old	0.0006	0.000080	13
Cancer Dietary Estimates			
Phosmet is classified as having "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential." Therefore, a cancer dietary assessment was not performed.			

5.0 Residential Exposure/ Risk Pathway

There are no residential handler uses proposed for this use of phosmet. This product is limited for use only in occupational settings; therefore a residential assessment was not requested nor performed.

5.1 Spray Drift Exposure

Spray drift is always a potential source of exposure to residents nearby to spraying operations from occupational handlers. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the airblast and groundboom application method additionally employed for phosmet. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

5.2 Residential Postapplication Inhalation Exposure

Based on the Agency's current practices, a quantitative postapplication inhalation exposure assessment was not performed for phosmet at this time. However, volatilization of pesticides may be a potential source of postapplication inhalation exposure to individuals nearby to pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009. The Agency received the SAP's final report on March 2, 2010 (http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html). The Agency is in the process of evaluating the SAP report and may, as appropriate, developing policies and procedures, to identifying the need for and, subsequently, the way to incorporate postapplication inhalation exposure into the Agency's risk assessments. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative postapplication inhalation exposure assessment for phosmet.

6.0 Aggregate Risk Assessments and Risk Characterization

There are no proposed uses which result in residential exposures; therefore, aggregate risk assessments for phosmet consider exposure from food and water only. Since the dietary exposure analysis included both food and drinking water estimates, the exposure and risk estimates presented in Sections 4.7.1 and 4.7.2 represent aggregate acute and aggregate chronic exposure and risk, respectively. There are no acute or chronic aggregate risks of concern for the existing and proposed uses of phosmet.

7.0 Cumulative Risk Characterization/Assessment

The Food Quality Protection Act (FQPA) requires the Agency to consider the cumulative risks of chemicals sharing a common mechanism of toxicity. Phosmet is a member of the organophosphate common mechanism group. The most recent cumulative risk assessment for the organophosphates was published on July 31, 2006 and is available at http://www.epa.gov/pesticides/cumulative/2006-op/op_cra_main.pdf. No cumulative risks of concern were identified in that assessment.

The previously registered use of phosmet on almonds and pistachios was considered as part of the 2006 organophosphate cumulative risk assessment. Quantifiable residues of phosmet were not seen in either the field trial residue or in monitoring data from the previously registered use pattern. Further, residues of phosmet were not detected in animals fed phosmet treated feed items. Therefore, the previously registered use of phosmet on almonds and pistachios did not contribute to the cumulative risk for the organophosphates.

This amended use on almonds and pistachios includes both an increase in the application rate and a shortening of the PHI. Residue data (field trials) have been provided which demonstrate that quantifiable residues are still not likely in almond and pistachio nutmeat despite the increased use rates and the decreasing PHI. Further, the only feed item associated with this amended use is almond hulls. The increased application rate and decreased PHI do result in higher residues in almond hulls. However, the Agency has reviewed the almond hull field trial data and available ruminant metabolism data, as well as the cattle feeding study. The Agency concludes that there is a reasonable expectation that residues of phosmet will not transfer to animal commodities as a result of feeding phosmet treated feed items including almond hulls treated at the higher application rate and shorter PHI requested in this amended use. Therefore, the Agency concludes that the amended uses on almonds and pistachios will not have an impact on the cumulative assessment, as these commodities are not expected to contribute to the organophosphate cumulative risk either directly or as animal feed items.

8.0 Occupational Exposure

This section presents a summary of the occupational exposure and risk estimates for phosmet. Please see DP Barcode D362951: Phosmet: Occupational Handler and Postapplication Exposure and Risk Calculations for Phosmet Amended Use on Almonds and Pistachios, A. LaMay, 7/1/10 for the complete phosmet exposure assessment.

8.1 Occupational Handler Risk

Exposure Scenarios

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. Pesticide handler exposure to Imidan® 70-W is likely to occur during its use in a variety of occupational environments. The anticipated use

patterns and current labeling indicate several occupational exposure scenarios based on types of equipment and techniques that can potentially be used for product applications. The product is packaged as water soluble packets and can be applied to tree nuts using airblast or aerial application at a maximum application rate of 3.7 lbs ai/A per application. The PPE on the proposed label is double layer clothing and gloves for mixers/loaders. Pilot aerial applicators must be using engineering control of fully enclosed cab aircraft. Airblast applicators must use engineering control of fully enclosed cab, and if not must use double-layer clothing, chemical-resistant glove and PF10 respirator. Human flagging is prohibited according to the proposed label. Short- and intermediate-term exposure are assessed for occupational handlers of phosmet based on use data and label instructions; HED believes that occupational exposures may occur over a single day or up to weeks at a time for many use-patterns and that intermittent exposure over several weeks may also occur. Some applicators may apply the product over a period of weeks, because they are commercial applicators who are completing multiple applications for multiple clients. Long-term handler exposures are not expected for phosmet. The quantitative short- and intermediate-term exposure/risk assessment developed for occupational handlers of phosmet is based on the following scenarios. A handler would mix/load or apply phosmet to almonds and pistachios by:

- mixing/loading water soluble packets for aerial application/ chemigation
- mixing/loading water soluble packets for airblast application
- applying spray by an enclosed cab fixed-wing aircraft
- applying spray by airblast (open cab and closed cab)

Risk estimates were calculated using the Margin of Exposure (MOE) which is a ratio of the toxicological PoD to the daily dose. Daily dose values are calculated by first calculating exposures by considering application parameters (i.e., application rate and area treated) along with unit exposures. Exposures are then normalized by body weight to calculate dose levels. Dermal and inhalation short- and intermediate-term exposure is compared to the dermal and inhalation PoD. A combined dermal and inhalation MOE was also calculated for each exposure duration for phosmet since common toxicity endpoints were identified for both the dermal and inhalation routes of exposure.

The following assumptions and factors were used in order to complete the exposure and risk assessment for occupational handlers/applicators:

- All worker scenarios were assumed to be short- and intermediate-term in exposure durations (i.e., 1-30 days and 1-6 months).
- The exposure assessment assumes an 8 hour work day.
- The maximum application rate of 3.7 lbs ai/A has been assessed for the both exposure durations.
- A body weight of 70 kg was assumed because the relevant toxicological PoDs were not gender specific.
- The daily areas treated were defined for each handler scenario (in appropriate units) by determining the amount that can be reasonably treated in a single day. When possible, the assumptions for daily areas treated are taken from the Health Effects Division Science Advisory Committee on Exposure ExpoSAC #9:

"Standard Values for Daily Acres Treated in Agriculture", which was revised on July 5, 2000. Area treated in each scenario: 40 acres for airblast; 350 acres for aerial application.

- Occupational handler exposure estimates were based on surrogate data from the Pesticide Handlers Exposure Database (PHED, V.1.1, 1998).
- HED has developed standard unit exposures for many occupational scenarios to ensure consistency in exposure assessments. These standard values were used to calculate handler exposures for the associated scenarios. For those scenarios where standard values have not been developed, surrogate values based on similar scenarios were used.
- Aerial application in this assessment is assumed to be by closed cab fixed-wing aircraft only (per ExpoSAC Policy #6).
- Handlers were assessed assuming the proposed label PPE used:
  - Mixer/loaders are assumed to be handling water soluble packets (engineering control) as well as double layer clothing and gloves.
  - Pilot aerial applicators must be using engineering control of fully enclosed cab aircraft.
  - Airblast applicators must use engineering control of fully enclosed cab, and if not must use double-layer clothing, chemical-resistant glove and PF10 respirator.
  - Human flagging is prohibited according to the proposed label.

Risk Characterization:

Occupational handler short- and intermediate-term mixer/loader scenarios were assessed with engineering control of water soluble packets (the specified formulation) and resulted in estimated MOEs greater than 100 and, therefore, do not exceed HED's level of concern, except for the mixer/loader scenario in support of aerial application. This scenario has an MOE of 71, which indicates the risk exceeds HED's level of concern.

Aerial applicator risks do not exceed HED's level of concern (MOE > 100) with engineering control of enclosed cab. Airblast applicator risks do not exceed HED's level of concern (MOEs > 100) with engineering control of enclosed cab; airblast applicators in an open cab using maximum dermal (double layer plus chemical-resistant gloves) and maximum inhalation PPE have an MOE of **85,** which indicates the risk exceeds the level of concern.

Table 8.1e Short and Intermediate Term Exposures and Risks for Occupational Handlers of Phosmet, use on Almonds and Pistachios

Exposure Scenario and PPE	Dermal Unit Exposure (mg/lb a.i.)	Inhalation Unit Exposure (µg/lb a.i.)	Application Rate[3] (lb a.i./ acre)	Area Treated Daily[4] (acres)	Dermal Dose[5] (mg/kg/ day)	Inhalation Daily Dose[6] (mg/kg/ day)	Dermal MOE[7]	Inhalation MOE[8]	Total MOE[9]
Applicator Scenario- Maximum Dermal PPE (double layer clothing plus gloves) and Maximum Inhalation PPE (respirator with PF10)									
Airblast Application, Open Cab, Maximum PPE	0.13	0.45	3.7	40	0.0275	0.00095	**98**	630	**85**
Mixer/Loader Scenarios- Engineering Control of Water Soluble Packets for both Dermal and Inhalation Exposure									
Mixing/loading in support of aerial application/ chemigation; Water Soluble Packets	0.0098	0.24	3.7	350	0.018	0.004	150	140	**71**
Mixing/loading in support of airblast application; Water Soluble Packets				40	0.0021	0.00051	1,300	1,200	620
Applicator Scenarios- Engineering Control of Enclosed Cab for both Dermal and Inhalation Exposure									
Aerial Application, Enclosed Cab Engineering control	0.0055	0.068	3.7	350	0.01	0.0013	270	480	170
Airblast Application, Enclosed Cab Engineering Control	0.019	0.09		40	0.004	0.00019	670	3,200	550

+ Bolded MOEs exceed HED's level of concern (i.e., MOEs<100)

[1]Maximum dermal PPE unit exposures represent double layer clothing, with chemical-resistant gloves. Engineering Control dermal unit exposures represent enclosed cab for applicator scenarios, and the use of water soluble packets for mixer/loader scenarios. Values are reported in the PHED Surrogate Exposure Guide dated August 1998.

[2]Maximum PPE inhalation unit exposures represent use of a respirator (air purifying respirators with appropriate cartridges worn i.e., a protection factor of 10). Engineering Control inhalation unit exposures represent enclosed cab for applicators scenarios, and the use of water soluble packets for mixer/loader scenarios. Values are reported in the PHED Surrogate Exposure Guide dated August 1998.

[3]Application rates are based on maximum values found on the label.

[4]Area treated daily values are from the EPA HED estimates of acreage treated in a single day for each exposure scenario of concern.

[5]Daily Dermal Dose = (Dermal Unit Exposure (mg ai /lb ai) * Application Rate (lb ai /A) * Area Treated (A /day))/ Body Weight (70 kg) * Dermal Absorption Factor of 10% (0.1)

[6] Daily Inhalation Dose = (Inhalation Unit Exposure (µg ai / lb ai) * Conversion Factor (1 mg /1000 µg) * Application Rate (lb ai /A) * Area Treated (A /day)) / Body Weight (70 kg)

[7] Dermal MOE = PoD ($BMDL_{10}$ of 0.6 mg/kg/day) * 4.5X *in vitro* dermal correction factor / Daily dermal dose (mg/kg/day)

[8] Inhalation MOE = PoD ($BMDL_{10}$ of 0.6 mg/kg/day) / Daily inhalation dose (mg/kg/day)

[9]Total MOE = 1/ (1/Dermal MOE + 1/Inhalation MOE)

8.2 Occupational Postapplication Risk

HED uses the term postapplication to describe exposures that occur when individuals enter areas previously treated with a pesticide to perform job functions. An occupational postapplication exposure assessment was conducted for phosmet use on almonds and pistachios. The calculations for postapplication exposure focus on dermal exposures. Applications of phosmet to almonds and pistachios can occur up to three times per year,

as is the maximum number of applications per year on the proposed label. The Agency uses a concept known as the transfer coefficient to numerically represent the postapplication exposures one would receive (i.e., generally presented as cm^2/hour). These transfer coefficients are listed in Policy 3.1 Science Advisory Council for *Exposure Policy Regarding Agricultural Transfer Coefficients*.

For phosmet, the Agency has completed short- and intermediate-term postapplication assessments because of the toxicity profile of phosmet and concerns over extended periods of exposure for a segment of the user population. The Agency believes that there is potential for phosmet exposures over a single day or up to several weeks at a time for postapplication workers, even though many crops are likely treated only a couple of times per season.

Calculation Methods

Post application exposures are calculated by considering transferable residue levels in areas where people work and the kinds of jobs or tasks that are required to produce agricultural commodities. These factors are represented by dislodgeable foliar residue (DFR) concentrations and by transfer coefficients. Exposures are calculated by multiplying these factors by a time component (i.e., an 8 hour work day assumed for seasonal reentry work). Exposures are then normalized by body weight and adjusted for dermal absorption to calculate absorbed doses. Risk estimates were then calculated using the MOE, which is a ratio of the toxicological PoD to the daily dose. Postapplication risks diminish over time because phosmet residues dissipate in the environment.

The postapplication risk assessment for phosmet has been developed using chemical-specific dislodgeable foliar residue data on pears (MRID 404253-01). The Agency has extrapolated phosmet-specific dissipation data in the risk assessment for the pistachios and almonds. The data have been determined to be of sufficient quality to be used for exposure and risk assessment purposes. This extrapolation was completed because of similarities in the application method, the crop canopy, and application rates (i.e., between the study and current labels). These data were extrapolated to application rates of 3.7 lb ai/acre for both almonds and pistachios.

Exposure Data and Assumptions

Key assumptions used in the postapplication risk assessment calculations are detailed as follows:

- Short- and intermediate-term exposures were assessed for all available postapplication scenarios.
- The average occupational workday is assumed to be 8 hours.
- The adverse effects for the short- and intermediate-term dermal PoD's are based on studies where the effects were observed in both sexes; therefore, the body weight of 70 kg was used to estimate exposure.
- HED has developed standard transfer coefficient values for occupational postapplication scenarios to ensure consistency in exposure assessments. These standard values were used to calculate postapplication exposures.

- Anticipated postapplication activities and their respective dermal transfer coefficients (TCs) information is based on the Science Advisory Council for Exposure Policy Number 3.1.
- Calculations of postapplication exposures are completed using proposed maximum application rates of the product.
- When the Agency extrapolated the available DFR data to other crops, the data are adjusted for differences in application rate using a simple proportional approach. This approach seems to be the most appropriate given the data which are available. This approach is commonly used by the Agency to conduct postapplication risk assessments.
- Discussion around the risk estimates for both short- and intermediate-term risks are based upon the REIs for phosmet (Toxicity Category II). The proposed REIs for these uses are 3 days.
- The use of personal protective equipment or other types of equipment to reduce exposures for postapplication workers is not considered a viable alternative for the regulatory process except in specialized situations (e.g., a rice scout will wear rubber boots in flooded paddies). This is described in some detail in the Agency's Worker Protection Standard (40 CFR 170).

Risk Summary

The proposed label requires that the tree nuts must be harvested mechanically and that pruning cannot occur until 7 days after application. The proposed pre-harvest interval (PHI) is 5 days for both crops and the restricted-entry interval (REI) is 3 days for phosmet.

The LoC for short- and intermediate-term postapplication exposures is an MOE of less than the LoC of 100. The low exposure and high exposure activities could potentially occur at the REI of 3 days; the short- and intermediate-term exposures for low exposure activities at 3 days after application for both crops are above the LoC with an MOE of 150. The short- and intermediate-term MOE is **31** for the high exposure activity of hand thinning tree nuts at 3 days after application for both crops, which is below the LoC. The short- and intermediate-term MOE is **40** for the high exposure activity of hand pruning tree nuts at 7 days after application for both crops, which is below the LoC. The MOEs indicate the risks exceed the LoC for all high exposure activities until 21 days after application. The mechanical harvesting activity could potentially occur at the PHI of 5 days; the short- and intermediate-term MOE is 880 for mechanical harvesting activity at the PHI of 5 days after application for both crops, which is above the LoC.

Occupational postapplication risk estimates are presented in Table 8.2.

Table 8.2. Phosmet Occupational Post-application Short- & Intermediate-Term Risk Estimates

Crop Group Crop (DFR data source) Maximum Application Rate	MOE at REI; Post-application Activity Exposure Scenario		MOE at PHI; Harvesting Scenario
	Low Exposure Activities	High Exposure Activities	Harvesting
	MOE on REI of Day 3 for Low Exposure Activities and Hand Thinning MOE on Day 7 for Hand Pruning (Days when MOE > 100)		MOE on PHI [Day 5]
Tree, "Nut", *Almonds and Pistachios* *(Pear DFR data)* Application Rate: 3.72 lbs ai/A	Day 3: 150	Day 3: Thinning: **31**(21)[1] Day 7: Pruning: **40**(21)[1]	880[2]

+ Bolded MOEs exceed HED's level of concern (i.e., MOEs<100)

1- The proposed label only allows for mechanical harvesting of all tree nuts, therefore the high exposure activity of hand harvesting would not occur at the REI of 3 days after application. However, the high exposure post-application activity of hand thinning can occur at the REI of day 3 for these crops; the MOEs are of concern for these activities with an MOE of **31**. The high exposure post-application activity of hand pruning can occur at 7 days after application, with an MOE of **40**, the MOE is of concern for this activity. The MOEs did not exceed 100 until 21 days after application for these exposure activities.

2- Proposed label only allows for mechanical harvesting of all tree nuts (TC is 100 cm^2/hr). No hand harvesting would occur at the PHI. This is the harvesting scenario assessed for tree nuts at the PHI.

It should be noted that even though the Agency has completed this assessment, it is unlikely that many individuals will be exposed in this manner given the way that phosmet is likely used. Even with a relative few number of applications per growing season, postapplication exposure activities like harvesting and thinning can take place over a course of several weeks. HED does not expect postapplication workers to be exposed to maximum residues every day over the course of the short-term exposure duration (up to 30 days). Therefore, intermediate-term risk estimates are likely a conservative estimate of risk.

Occupational Postapplication Inhalation Exposure

Based on the Agency's current practices, a quantitative occupational postapplication inhalation exposure assessment was not performed for phosmet at this time. However, there are multiple potential sources of postapplication inhalation exposure to individuals performing postapplication activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009. The Agency received the SAP's final report on March 2, 2010 (http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html). The Agency is in the process of evaluating the SAP report as well as available postapplication inhalation

exposure data generated by the Agricultural Reentry Task Force and may, as appropriate, develop policies and procedures, to identify the need for and, subsequently, the way to incorporate occupational postapplication inhalation exposure into the Agency's risk assessments. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational postapplication inhalation exposure assessment for phosmet.

8.3 REI

The label-required restricted entry interval (REI) of 3 days is in compliance with the Worker Protection Standard.

9.0 Data Needs and Label Recommendations

9.1 Toxicology

- Immunotoxicy Study
- Gestational component of the CCA Study

9.2 Residue Chemistry

- The registrant should submit a revised Section F reflecting the tolerance levels and commodity definitions specified above and in Table 4.6.

9.3 Occupational and Residential Exposure

- None

10.0 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.eh.doe.gov/oepa/guidance/justice/eo12898.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 Continuing Survey of Food Intake by Individuals (CSFII) 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, season of the year, ethnic group, and region of the country. 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 postapplication 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.

11.0 Human Studies

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies, which comprise the Pesticide Handlers Exposure Database (PHED), Version 1.1, the PHED Task Force, 1998, have been determined to require a review of their ethical conduct, and have received that review.

References

Barcode: D262365
Title: HED Revised Human Health Risk Assessment for the Reregistration Eligibility Decision Document (RED).
Author: Christina Swartz
Date: 2/9/2000

Barcode: D250029
Title: Phosmet. Revised Product and Residue Chemistry Chapters of the HED RED.
Author: Christina Swartz
Date: 11/23/98

Barcode: D355156
Title: Phosmet. Petition for Amended Use Patterns on Almond and Pistachio. Summary of Analytical Chemistry and Residue Data.
Author: Donna Davis
Date: 5/18/10

Barcode:	D374889
Title:	Revised Tier II Drinking Water Exposure Assessment for the Section 3 New Use Registration of Phosmet on Almonds and Pistachios and Re-evaluation of All Labeled Uses
Author:	Reuben Baris
Date:	5/25/10

Barcode:	D362951
Title:	Phosmet: Occupational Handler and Postapplication Exposure and Risk Calculations for Phosmet Amended Use on Almonds and Pistachios
Author:	Alexandra LaMay
Date:	7/1/10

Attachments

Attachment 1. Toxicology Profile and Executive Summaries
Attachment 2. Immunotoxicity DCI Justification
Attachment 3. International Residue Limit Status Sheet

Attachment 1. Toxicology Assessment

Acute Toxicity Profile of Phosmet

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral – rat	00046189	LD_{50} = 113 mg/kg	II
81-2	Acute Dermal – rabbit	00046190	LD_{50} >5000 mg/kg	III
81-3	Acute Inhalation – rat	00063197	LC_{50} >0.152 mg/L	I
81-4	Primary Eye Irritation	00046192	moderate eye irritant	III
81-5	Primary Skin Irritation	00046191	not a skin irritant	IV
81-6	Dermal Sensitization	?		N/A
81-7	Delayed Neurotoxicity	44587601	unsteadiness, subdued behavior, recumbency, salivation; no ataxia; no decreases in brain or spinal cord NTE; brain ChE decreased 63%; no neuropathology.	N/A
81-8	Acute Neurotoxicity	44673301	NOAEL 4.5 mg/kg LOAEL 22.5 mg/kg, based on cholinesterase inhibition [plasma, RBC, brain] and decreased motor activity in both sexes.	N/A

Toxicology Profile of Phosmet		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.6200 acute neurotoxicity – rat	MRID 44673301 (1998) 0, 3.0, 4.5, or 22.5 mg/kg gavage	NOAEL = 4.5 mg/kg LOAEL = 22.5 mg/kg, based on cholinesterase inhibition [plasma, red blood cell, and brain] and decreased motor activity in both sexes. BMD analysis performed (sexes combined) Males-RBC: BMD_{10}=4.24; $BMDL_{10}$=2.667 Females-RBC: BMD_{10}=3.25; $BMDL_{10}$=2.089 Males- brain: BMD_{10}=8.718; $BMDL_{10}$=6.73 Females- brain: BMD_{10}=7.824; $BMDL_{10}$=6.043
acute comparative cholinesterase assay - rat (CCA)	MRID 47087401 (2007) 0, 2.5, 5, 10 mg/kg young adult and PND 11 pups gavage	Adult NOAEL = 5 mg/kg Adult LOAEL = 10 mg/kg, based on RBC, brain, plasma cholinesterase inhibition PND 11 NOAEL <2.5 mg/kg PND 11 LOAEL = 2.5 mg/kg, based on brain cholinesterase inhibition BMD analysis performed (sexes combined) adult-RBC: BMD_{10}=7.092; $BMDL_{10}$=3.56 pup-RBC: BMD_{10}=2.4; $BMDL_{10}$=1.4 adult- brain: BMD_{10}=6.826; $BMDL_{10}$=5.122 pup- brain: BMD_{10}=1.9; $BMDL_{10}$=1.2

Toxicology Profile of Phosmet		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
repeat dose comparative cholinesterase assay - rat	MRID 47695401 (2007) 0, 1.25, 2.5, or 5 mg/kg/day young adult and PND 11 pups 7 consecutive doses Gavage	Adult LOAEL for brain cholinesterase inhibition = 5 mg/kg/day; Adult NOAEL for brain cholinesterase inhibition = 2.5 mg/kg/day. Adult LOAEL for RBC cholinesterase inhibition = 1.25 mg/kg/day. Adult NOAEL for RBC cholinesterase inhibition < 1.25 mg/kg/day Adult LOAEL for plasma cholinesterase inhibition = 5 mg/kg/day. Adult NOAEL for plasma cholinesterase inhibition = 2.5 mg/kg/day. Pup LOAEL for brain cholinesterase inhibition = 1.25 mg/kg/day; Pup NOAEL for brain cholinesterase inhibition <1.25 mg/kg/day. Pup LOAEL for RBC cholinesterase inhibition = 1.25 mg/kg/day. Pup NOAEL for RBC cholinesterase inhibition < 1.25 mg/kg/day Pup LOAEL for plasma cholinesterase inhibition = 1.25 mg/kg/day (females), 2.5 mg/kg/day (males). Pup NOAEL for plasma cholinesterase inhibition <1.25 mg/kg/day (females), 1.25 mg/kg/day (males). BMD analysis performed (sexes combined) adult-RBC: BMD_{10}=1.194; $BMDL_{10}$=0.601 pup-RBC: BMD_{10}=0.360; $BMDL_{10}$=0.163 adult- brain: BMD_{10}=3.856; $BMDL_{10}$=2.840 pup- brain: BMD_{10}=0.822; $BMDL_{10}$=0.640
870.3100 90-day/4-week oral toxicity rat	MRID 00081426 ( ) 0, 20, 100, 500 ppm 0, mg/kg/day Acceptable/guideline	Systemic NOAEL = 100 ppm (10 mg/kg/day) Systemic LOAEL = 500 ppm (50 mg/kg/day), based on decreased body weight NOAEL (cholinesterase) = 20 ppm (2 mg/kg/day) LOAEL (cholinesterase) = 100 ppm (10 mg/kg/day) RBC compartment (@ week 3: ♂ 56%/♀ 61%;@ 11 weeks: ♂ 62%/♀ 54% @ 500 ppm: @ 500 ppm, males displayed 100% and 97% RBC inhibition at 3 and 11 weeks; females displayed 100% RBC inhibition at both time points.
870.3200 21-day dermal toxicity - rat	MRID 47262502 (2007) 0, 30, 40, 50, 60, 90, or 120 mg/kg bw/day, 6 hours/day for 5 days/week during a 3-week period unacceptable/non-guideline; together with MRID 44795801 satisfies guideline requirement for all parameters except cholinesterase activity.	NOAEL <30 mg/kg/day LOAEL = 30 mg/kg/day, based on female RBC cholinesterase inhibition
870.3200 21-day dermal toxicity rat	MRID 44795801 (1999) 0, 15, 22.5, 60 mg/kg/day	NOAEL = 15 mg/kg/day LOAEL = 22.5 mg/kg/day, based on decreased brain cholinesterase in females

Toxicology Profile of Phosmet		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.6200 Subchronic neurotoxicity - rat	MRID 44811801 (1999) 0, 25, 50, 150 ppm 0, 1.5/1.6, 2.7/3.1, 9.4/11 mg/kg/day Acceptable/guideline	NOAEL = not determined LOAEL = 22 ppm (1.5 males/1.6 females mg/kg/day), based on dose-related decreases in plasma, whole blood, RBC, and brain cholinesterase activity levels BMD analysis performed (sexes combined) 3-week assessment: RBC: BMD_{10}=1.949; $BMDL_{10}$=1.036 13-week assessment: RBC: BMD_{10}=0.927; $BMDL_{10}$=0.48 3-week assessment: brain: BMD_{10}=2.794; $BMDL_{10}$=2.22
870.3700a Prenatal developmental - rat	MRID 41962902 (1991) 0, 5, 10, 15 mg/kg/day GD 6-15 (gavage) Acceptable/guideline	Maternal NOAEL = 10 mg/kg/day Maternal LOAEL = 15 mg/kg/day, based on clinical signs (tremors/shaking in 4 dams on days 12-16), salivation, piloerection, subdued mood (2 dams on days 16-19), and decreased body weight gain/food consumption. Developmental toxicity NOAEL = 15 mg/kg/day, HDT
870.3700b Prenatal developmental rabbit	MRID 41962901 (1991) 0, 5, 10, 15 mg/kg/day GD 6-15 (gavage) Acceptable/guideline	Maternal NOAEL = 5 mg/kg/day Maternal LOAEL = 15 mg/kg/day, based on clinical signs (2 does on days 16 and 18 showed unsteady gait, shaking, salivation, irregular breathing), decreased body weight Developmental toxicity NOAEL = 5 mg/kg/day Developmental toxicity LOAEL = 15 mg/kg/day, based on an increased incidence of skeletal variations
870.3800 Reproduction and fertility effects - rat	MRID 41520001 (1990) 0, 20, 80, 300 ppm (diet) males F0 (1.3, 5.0, 19)/ F1 (1.4, 5.9, 23) mg/kg/day females F0 (1.5, 6.0, 24)/ F1 (1.5, 6.1, 26) mg/kg/day 10 weeks prior to mating Acceptable/guideline	Maternal toxicity NOAEL <20 ppm (1.5 mg/kg/day) Maternal toxicity LOAEL = 20 ppm (1.5 mg/kg/day), based on decreased RBC cholinesterase (F0 ♂ 8%*/♀ 12%**; F1 ♂ 6%/♀ 16%**). @ 80 ppm: F0 ♂ 38%/♀ 48%; F1 ♂ 48%/♀ 59% @ 300 ppm: F0 ♂ 74%/♀ 82%; F1 ♂ 85%/♀ 80% Reproductive/offspring NOAEL = 20 ppm (1.5 mg/kg/day) Reproductive/offspring LOAEL =80 ppm (6.1 mg/kg/day), based on decreased fertility (both generations/both litters) Offspring NOAEL = Offspring LOAEL = decreased lactation index, decreased number of live pups/litter, decreased pup weight. At 300 ppm, (19/24 mg/kg/day), 3 F0 females (day 28) showed tremors; one F1 dam displayed convulsions and hypothermia and decreased activity (day 173), one F1 female displayed muscle weakness and 2 F1 females displayed tremors on day 109.
870.4100 Chronic toxicity Rat (Crl:CD(SD) BR)	MRID 41916401 (1991) 0, 20, 40, 200, 400 ppm males 0, 1.1, 1.8, 9.4, 23 mg/kg/day females 0, 1.1, 2.1, 10.9, 27 mg/kg/day	NOAEL < 20 ppm (1.1 mg/kg/day) LOAEL = 20 ppm (1.1 mg/kg/day), based on RBC cholinesterase inhibition in males (16%*) Both sexes showed 19% inhibition at 40 mg/kg/day Males showed 20% and 34% brain inhibition at 200 ppm and 400 ppm, respectively at 6 months Females showed 27% and 43% brain inhibition at 200 ppm and 400 ppm, respectively at 6 months BMD analysis performed (sexes combined) RBC: BMD_{10}=0.659; $BMDL_{10}$=0.420

Toxicology Profile of Phosmet		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.4100 Chronic toxicity Dog (beagle)	MRID 00076436 (1967) diet (104 weeks) 0, 20, 40, 400 ppm 0, 0.5, 1, 10 mg/kg/day	NOAEL = 40 ppm (1 mg/kg/day) LOAEL = 400 ppm (10 mg/kg/day), based on RBC (>70%) and brain (>40%) cholinesterase inhibition in both sexes Systemic NOAEL = 400 ppm (10 mg/kg/day) HDT
870.4200 Carcinogenicity mouse (B6C3F1)	MRIDs 00141659, 00160114, 40595501 (1984) 0, 5, 25, 100 ppm (diet) Acceptable/guideline	NOAEL < 5 ppm LOAEL = 5 ppm, based on brain cholinesterase inhibition (both sexes; 29%/28%) Systemic NOAEL = 5 ppm Systemic LOAEL = 25 ppm, based on convulsions (males), hepatocellular carcinoma/adenocarcinoma combined in males
870.7600 Dermal penetration - rat	MRID 40122201 (1987)	Poorly absorbed when applied to shaved skin; 10% absorption
In vitro dermal absorption	Epidermal membranes (rat and human); phosmet applied as (1) an undiluted concentrate at 700 g phosmet/kg (7000 $\mu g/cm^2$), which represents worker mixer/loader exposure, or as (2) a 7 g phosmet/L aqueous dilution (70 $\mu g/cm^2$), which represents worker applicator and re-entry exposure.	**Rat:** The mean percentage of absorbed radioactivity in the receptor fluid was 0.19% for the undiluted concentrate and 11.7% for the aqueous dilution. Mean amount of applied dose remaining in the rat epidermis was 0.01% for the undiluted concentrate and 0.5% for the aqueous dilution. **Human**: The mean percentage of absorbed radioactivity in the receptor fluid was 0.07% for the undiluted concentrate and 1.69% for the aqueous dilution. Mean amount of applied dose remaining in the human epidermis was <0.01% for the undiluted concentrate and 0.15% for the aqueous dilution. correction factor = 4.5 (to account for difference in permeability between rats and humans skin).
870.7485 Metabolism rat (Crl:CD(SD) BRVAF/Plus)	MRID 41296001 (1989) MRID 41425701 (1990) 1 and 25 mg/kg	Phosmet is rapidly absorbed, distributed, metabolized, and eliminated in rats after a single low and high and repeat low dose. Most of radiolabel was recovered within 24 hours in urine (69-83%) and feces (4.5-9.9%) for all groups. Highest levels in liver and whole blood; peak blood levels occurred 0.5 hour following low and high dose.
Bacterial reverse mutation test 870.5100	MRID 00164884 (1986) Salmonella typhimurium TA100, TA1535	Positive w/ & w/out S9
Mammalian micronucleus test mouse bone marrow 870. 5395	MRID 40199401 (1987)	No clastogenic effect at 17 mg/kg in bone marrow cells 24, 48, or 72 hr after dosing;
In vitro mammalian cytogenetics assay in mammalian cells (mouse lymphoma multiple endpoint test) 870.5375	MRID 00164886 (1987)	Positive for structural chromosomal aberrations w/out S9 Positive for SCE w/ & w/out S9
Mouse lymphoma forward mutation	MRID 00164885 (1987)	Positive w/ & w/out S9
DNA damage assay in human fibroblast	MRID 00164887 (1987)	Negative w/ & w/out S9
Morphological transformation of BALB/3T3 cells	MRID 00164888 (1986)	Positive

Executive Summaries

Comparative cholinesterase assay - Acute

EXECUTIVE SUMMARY: In a comparative cholinesterase (dose-response) study (MRID 47087401), phosmet (93.4% a.i.; Lot #4312)] was administered to 10 adult Crl:CD (SD) rats/sex/dose and 10 Crl:CD (SD) postnatal day (PND) 11 pups/sex/dose *via* gavage at dose levels of 0 (0.5% aqueous carboxymethylcellulose), 2.5, 5, or 10 mg/kg bw. At four hours post dose, red blood cell (RBC), plasma, and brain acetylcholinesterase levels were determined.

All adult rats and PND 11 pups survived to scheduled sacrifice, and there were no treatment-related clinical signs.

In the adult rat, acetylcholinesterase activity was reduced only at the 10 mg/kg dose level. Both sexes of adult rats displayed a comparable response with respect to RBC cholinesterase inhibition (males 39%**/females 37%), but plasma cholinesterase inhibition was observed only in the female (31%*). Brain cholinesterase inhibition was observed in both sexes, with the female displaying the greater response (males 18%**/females 27%**).

In the PND 11 pups, a dose-related increase in cholinesterase inhibition was observed in all compartments in both sexes. The magnitude of the inhibition in each compartment at a given dose was comparable between the sexes; *e.g.,* 49%** *vs* 45%**; 55%** *vs* 53%**; and 53%** *vs* 51%** inhibition (males *vs* females) in the RBC, plasma, and brain compartments, respectively, at 10 mg/kg, and the magnitude of the response was similar regardless of the compartment. At the low dose (2.5 mg/kg), the PND 11 pups displayed a statistically (female)/biologically-significant (both sexes) inhibition in brain cholinesterase activity (males 11%; females 17%*).

The NOAEL for adult rats (both sexes) is 5 mg/kg, based on RBC, plasma, and brain cholinesterase inhibition following an acute oral dose of 10 mg/kg (LOAEL). This adult rat NOAEL is consistent with the NOAEL from the guideline acute neurotoxicity study (4.5 mg/kg) in adult rats. **The NOAEL for PND 11 pups could not be determined, based on brain cholinesterase inhibition at all dose levels following acute oral exposure. The LOAEL for PND 11 pups is 2.5 mg/kg.** The PND 11 pup is more sensitive to phosmet with respect to cholinesterase inhibition in all three compartments than the adult rat. A comparison of the LOAEL for PND 11 pups (2.5 mg/kg) with the LOAEL for adult rats (10 mg/kg) indicates a 4-fold difference in response between these two age groups.

A benchmark dose (BMD) analysis of the comparative cholinesterase study was performed on RBC and brain cholinesterase data. The estimated dose at which 10% cholinesterase inhibition is observed (BMD_{10}) and the lower 95% confidence intervals ($BMDL_{10}$) were estimated by fitting the cholinesterase activity data to an exponential dose response model using generalized nonlinear least squares. The BMD_{10} was selected

because it is generally at or near the limit of sensitivity for discerning a statistically significant decrease in cholinesterase activity across the blood and brain compartments and is a response level close to background cholinesterase activity.

BMD_{10} / $BMDL_{10}$ for Acute CCA Study				
Age group	**RBC**		**Brain**	
	***BMD_{10}**	***$BMDL_{10}$**	***BMD_{10}**	***$BMDL_{10}$**
Adult	7.092	3.56	6.826	5.122
pup	2.4	1.4	1.9	1.2

*BMD_{10} / $BMDL_{10}$ are for combined sexes; 4 hours post dose

This study of RBC, plasma, and brain cholinesterase activities following acute oral treatment with phosmet in adult and neonatal rats is classified **Acceptable/Nonguideline.** It does not satisfy any guideline requirement; however, it does satisfy the data requirement for phosmet for comparative cholinesterase activity between adult and young rats.

Comparative cholinesterase assay - Subchronic

EXECUTIVE SUMMARY: In a comparative cholinesterase (dose-response) study (MRID 47695401), phosmet (93.4% a.i.; Lot #4312) was administered to 10 adult Crl:CD (SD) rats/sex/dose and 10 Crl:CD (SD) postnatal day (PND) 11 pups/sex/dose *via* gavage at dose levels of 0 (0.5% aqueous carboxymethylcellulose), 1.25, 2.5, or 5 mg/kg/day for 7 consecutive days. On the last day of dosing, red blood cell (RBC), plasma, and brain samples were collected from each animal at approximately four hours post dose, and cholinesterase activity was determined for each compartment.

All adult rats and neonatal pups survived to scheduled sacrifice, and there were no treatment-related clinical signs. Body weights and body-weight gains were comparable among the groups for both age groups.

In the adult rats, both sexes displayed statistically-significant RBC cholinesterase inhibition four hours after the last of seven oral doses of 1.25 mg/kg/day (males 25%; females 21%), 2.5 mg/kg/day (males 15%; females 16%), and 5 mg/kg/day (males 43%; females 38%). However, a dose-response effect was not evident: the magnitude of the inhibition in both sexes at the mid-dose level was lower than that observed at the low-dose level. Both sexes displayed a statistically-significant inhibition of brain cholinesterase activity at 5 mg/kg/day (males 14%; females 20%) compared to the control values, with the female displaying the a slightly greater response. There was a dose-related reduction in plasma cholinesterase activity in both sexes, although statistical significance was attained only in the high-dose male group (30%)/female group (25%). No plasma cholinesterase inhibition was observed in either sex at the low-dose level.

In the PND 17 pups, there was a dose-related, statistically-significant, reduction in RBC cholinesterase activity in both sexes four hours after the last of seven oral doses of 1.25

mg/kg/day (males 24%; females 20%), 2.5 mg/kg/day (males 40%; females 49%), and 5 mg/kg/day (males 64%; females 56%). Inhibition was comparable between the sexes at all dose levels. Brain cholinesterase activity was reduced significantly in the PND 17 pups (both sexes) at doses of 1.25 mg/kg/day (males 10%; females 16%), 2.5 mg/kg/day (males 32%/females 36%), and 5.0 mg/kg/day (males 54%; females 57%). There was a dose-related, statistically-significant, reduction in plasma cholinesterase activity at doses of 1.25 mg/kg/day (females 20%), 2.5 mg/kg/day (males 32%; females 41%), and 5.0 mg/kg/day (males 56%; females 55%). At 1.25 mg/kg, male pups displayed a 10% inhibition of plasma cholinesterase activity, which was not statistically significant, and the magnitude of the male pup response is not considered biologically significant.

<u>For repeat exposures</u> (7 days' duration),

The adult LOAEL for brain cholinesterase inhibition is 5 mg/kg/day;
The adult NOAEL for brain cholinesterase inhibition is 2.5 mg/kg/day.
The adult LOAEL for RBC cholinesterase inhibition is 1.25 mg/kg/day.
The adult NOAEL for RBC cholinesterase inhibition is < 1.25 mg/kg/day
The adult LOAEL for plasma cholinesterase inhibition is 5 mg/kg/day.
The adult NOAEL for plasma cholinesterase inhibition is 2.5 mg/kg/day.
The pup LOAEL for brain cholinesterase inhibition is 1.25 mg/kg/day;
The pup NOAEL for brain cholinesterase inhibition is <1.25 mg/kg/day.
The pup LOAEL for RBC cholinesterase inhibition is 1.25 mg/kg/day.
The pup NOAEL for RBC cholinesterase inhibition is < 1.25 mg/kg/day
The pup LOAEL for plasma cholinesterase inhibition is 1.25 mg/kg/day (females), 2.5 mg/kg/day (males).
The pup NOAEL for plasma cholinesterase inhibition is <1.25 mg/kg/day (females), 1.25 mg/kg/day (males).
The overall adult LOAEL for cholinesterase inhibition is 1.25 mg/kg/day for red blood cells; the adult NOAEL was not determined (<1.25 mg/kg/day).
The overall pup LOAEL for cholinesterase inhibition is 1.25 mg/kg/day for brain, RBC, and plasma; the pup NOAEL was not determined (<1.25 mg/kg/day).

A benchmark dose (BMD) analysis of the comparative cholinesterase study was performed on RBC and brain cholinesterase data. The estimated dose at which 10% cholinesterase inhibition is observed (BMD_{10}) and the lower 95% confidence intervals ($BMDL_{10}$) were estimated by fitting the cholinesterase activity data to an exponential dose response model using generalized nonlinear least squares. The BMD_{10} was selected because it is generally at or near the limit of sensitivity for discerning a statistically significant decrease in cholinesterase activity across the blood and brain compartments and is a response level close to background cholinesterase activity.

BMD_{10} / $BMDL_{10}$ for Repeat CCA Study				
Age group	**RBC**		**Brain**	
	***BMD_{10}**	***$BMDL_{10}$**	***BMD_{10}**	***$BMDL_{10}$**
Adult	1.194	0.601	3.856	2.840
pup	0.360	0.163	0.822	0.640

*BMD_{10} / $BMDL_{10}$ are for combined sexes; 4 hours post dose

This study of brain, RBC, and plasma cholinesterase activities following repeat oral treatment with phosmet in adult and neonatal rats is classified **Acceptable/Nonguideline.** It does not satisfy any guideline requirement; however, it does satisfy the data requirement for phosmet for a comparative cholinesterase activity assay between adult and young rats following repeat exposure.

Neurotoxicity studies - Acute

EXECUTIVE SUMMARY: In an acute neurotoxicity study in rats [MRID 44673301], Phosmet (94.4% purity) was administered to Sprague Dawley rats (30/sex/group) at 0, 3.0, 4.5, or 22.5 mg/kg as one dose, orally, by gavage. Body weights were recorded weekly, and clinical observations were recorded daily. Cholinesterase activity was measured in plasma, red blood cells, and brain at time of peak effect (approximately 3 hours post-dosing) on day 0, and on days 7 and 14 post-dosing, in 6 animals/sex/group. Neurobehavioral assessment (functional observation battery and motor activity testing) was performed in 12 animals/sex/group prior to the start of testing, at the time of peak effect, and on days 7 and 14 post-dosing. Brain weights were determined on days 0, 7, and 14 (nonperfused animals, 6/sex/group). At study termination, 12 animals/sex/group were perfused in situ, and brain weight, length, and width were measured. Of the perfused animals, 5/sex from the control and high dose groups were subjected to histopathological evaluation of brain and peripheral nervous system.

No effects of treatment were seen in the 3.0 or 4.5 mg/kg groups. At 22.5 mg/kg, there were decreases in plasma cholinesterase in both sexes, at the time of peak effect only (decreased 46% in females, 57% in males). Red blood cell cholinesterase was also decreased at the time of peak effect in both sexes (88% in females, 75% in males); inhibition persisted on days 7 (25%) and 14 (40%) for females only. Brain cholinesterase was inhibited in both sexes at all three time points (for males and females, respectively; 61 and 70% on day 0, 15 and 20% on day 7, and 9 and 17% on day 14). The only other effect of treatment was a decrease in motor activity seen in both sexes at the time of peak effect on day 0. No treatment-related changes were seen in FOB parameters or in neuropathological findings.

The NOAEL is 4.5 mg/kg, and the LOAEL was 22.5 mg/kg, based on cholinesterase inhibition [plasma, red blood cell, and brain] and decreased motor activity in both sexes.

The study is classified as acceptable (guideline), and it satisfies the guideline requirement

for an acute neurotoxicity study in rats (870.6200).

A benchmark dose (BMD) analysis of the comparative cholinesterase study was performed on RBC and brain cholinesterase data. The estimated dose at which 10% cholinesterase inhibition is observed (BMD_{10}) and the lower 95% confidence intervals ($BMDL_{10}$) were estimated by fitting the cholinesterase activity data to an exponential dose response model using generalized nonlinear least squares. The BMD_{10} was selected because it is generally at or near the limit of sensitivity for discerning a statistically significant decrease in cholinesterase activity across the blood and brain compartments and is a response level close to background cholinesterase activity.

BMD_{10} / $BMDL_{10}$				
Study/Time Point	**RBC**		**Brain**	
	***BMD_{10}**	***$BMDL_{10}$**	***BMD_{10}**	***$BMDL_{10}$**
Acute neurotox (day 0)				
males	4.24	2.667	8.718	6.73
females	3.25	2.089	7.824	6.043

*BMD_{10} / $BMDL_{10}$ (3 hours post dose)

Neurotoxicity studies - Subchronic

EXECUTIVE SUMMARY: In a subchronic oral neurotoxicity study [MRID 44811801], Phosmet [97.3% a.i.] was administered for 90 days to 32 Crl:CD(SD)IGS BR rats/sex/dose at nominal dietary concentrations of 0, 25, 50, and 150 ppm. **Actual mean dietary concentrations of Phosmet based on analysis of weekly batches of diet were 0, 21.6, 39.7, and 136 ppm (equivalent to achieved doses of 0/0, 1.5/1.6, 2.7/3.1, and 9.4/11.0 mg/kg/day [M/F]).** Cholinesterase activity levels were determined using modified Ellman method in the blood and brains of 2 rats/sex/dose during the pretest and 6 rats/sex/dose during study weeks 3, 7, and 13. The remaining 12 rats/sex/dose were subjected to the functional observational battery (FOB) and motor activity measurements during the pretest period and study weeks 3, 7, and 12 and were then perfused *in situ* at study termination. Five rats/sex from the control and high-dose groups were used for neuropathological examination.

No rats died during the study. No changes in appearance or behavior, body weights or body-weight gains, or food consumption were observed in any of the treated groups when compared to concurrent controls. Results of the FOB indicated no treatment-related findings during the home cage, handling, open field, sensory, neuromuscular, physiological, and locomotor activity observations. There were no adverse effects on mean ambulatory, total motor activity, or gross neurological findings. No treatment-related effects were observed on brain weight in non-perfused and perfused animals.

In general, whole blood and red blood cell (RBC) cholinesterase activity levels were decreased in all dose groups of both sexes. Plasma and regional brain cholinesterase activities were decreased in all dose groups of the treated females. The details are summarized below:

In the 22 ppm group, mean RBC cholinesterase activity was significantly decreased ($p<0.01$) in the males at week 13 (919%) and females at week 7 (942%). Significant decreases ($p<0.05$ or 0.01) were also observed at week 13 in mean plasma cholinesterase activity in the females (929%), mean whole blood cholinesterase in both sexes (916%-19%), and cholinesterase activity of the olfactory bulb (936%) and brain stem (921%) regions in the females.

In the 40 ppm group, the following significantly decreased)$p<0.05$ or 0.01) mean cholinesterase activity levels were observed: (I) plasma cholinesterase in the males at week 3 (921%) and females at weeks 3 and 13 (927%-46%); (ii) RBC cholinesterase in the males at weeks 3, 7, and 13 (926%-39%) and females at week 7 (938%); (iii) whole blood cholinesterase at weeks 3, 7, and 13 in both sexes (924%-36%); (iv) whole blood cholinesterase at week 7 in the females (920%) and at weeks 3 and 7 in the males (911%-17%).

In the 136 ppm group, the following decreased ($p<0.05$ or 0.01) mean cholinesterase activity levels were observed: (I) plasma cholinesterase at weeks 3, 7, and 13 in both sexes (923%-71%); (ii) RBC cholinesterase at weeks 3, 7, and 13 in males (965%-70%) and at weeks 3 and 7 in females (966%-89%); (iii) whole blood cholinesterase in both sexes (959%-74%) at weeks 3, 7, and 13; (iv) whole brain cholinesterase in both sexes (943%-68%) at weeks 3 and 7; and (v) in all six brain regions in the females (936%-67% and in all brain regions except the olfactory region in the males (927%-52%) at week 13.

The LOAEL is 22 ppm (equivalent to 1.5/1.6 mg/kg/day [Male/Female], the LDT), based on dose-related decreases in plasma, RBC, whole blood, and brain cholinesterase activity levels. The NOAEL was not established.

The study is classified as acceptable (guideline), and it satisfies the guideline requirement for a subchronic neurotoxicity study in rats (870.6200).

A benchmark dose (BMD) analysis of the comparative cholinesterase study was performed on RBC and brain cholinesterase data. The estimated dose at which 10% cholinesterase inhibition is observed (BMD_{10}) and the lower 95% confidence intervals ($BMDL_{10}$) were estimated by fitting the cholinesterase activity data to an exponential dose response model using generalized nonlinear least squares. The BMD_{10} was selected because it is generally at or near the limit of sensitivity for discerning a statistically significant decrease in cholinesterase activity across the blood and brain compartments and is a response level close to background cholinesterase activity.

	BMD_{10} / $BMDL_{10}$			
Study/Time Point	**RBC**		**Brain**	
	***BMD_{10}**	***$BMDL_{10}$**	***BMD_{10}**	***$BMDL_{10}$**
Subchronic neurotox				
3-week	1.949	1.036	2.794	2.22
13-week	0.927	0.48	-	-

*BMD_{10} / $BMDL_{10}$ are for combined sexes; 4 hours post dose

Dermal studies

EXECUTIVE SUMMARY: An *in vitro* dermal absorption study (MRID No. 47262501) was conducted using rat and human skin mounted in an *in* vitro static diffusion cell model. Epidermal membranes from rat and human skin (6 skins/formulation/species) were administered Imidan® 70, which contains the active ingredient [^{14}C]-phosmet. The test material was applied as (1) an undiluted concentrate at 700 g phosmet/kg (7000 μg/cm^2), which represents worker mixer/loader exposure, or as (2) a 7 g phosmet/L aqueous dilution (70 μg/cm^2), which represents worker applicator and re-entry exposure. Penetration and absorption were followed using [^{14}C]- phosmet (>96% radiochemical purity). The applied formulation remained in contact with the skins for 6 hours, and the skins were monitored for 18 hours post dose.

Rat skin was shown to be more permeable to [^{14}C]- phosmet than human skin (Summary Tables 1 and 2). During the exposure period, [^{14}C]- phosmet penetrated through rat skin ~5.7-fold faster than through human skin following application of the undiluted concentrate and ~4.2-fold faster following application of the aqueous dilution. During the post-exposure period, the rate of penetration was reduced for both species and formulations, but the rate for the rat skin remained greater than for the human skin [7.6-fold (undiluted concentrate) and 15-fold (aqueous dilution)]. Cumulative absorption following the 6-hour exposure period was 1.4-fold (undiluted concentrate) and 4.1-fold (aqueous dilution) greater for the rat compared to the human skin. Cumulative absorption during the 18-hour post-exposure period was 2.6-fold (undiluted concentrate) and 6.9-fold (aqueous dilution) greater for the rat compared to the human skin. The absorbed dose (receptor fluid plus skin) was greater [2.9-fold (undiluted concentrate) and 7.2-fold (aqueous dilution) for rat skin than for human skin.

Summary Table 1. *Undiluted Concentrate*			
	RAT	**HUMAN**	**Rat/Human ratio**
penetration rate, 0-6 hr (µg equivalents/cm^2/h)	0.63	0.11	5.7
penetration rate, 6-24 hr (µg equivalents/cm^2/h)	0.38	0.05	7.6
cumulative absorption, 6 hours (µg equivalents/cm^2)	6.86	4.75	1.4
cumulative absorption, 24 hours (µg equivalents/cm^2)	14.4	5.63	2.6
background level of [^{14}C] phosmet (µg equivalents/cm^2)	3.06	2.93	1.0
absorbed dose (receptor fluid only), 24 h (%)	0.19	0.07	2.7
absorbable dose (absorbed + skin), 24 h (%)	0.20	0.07	2.9

Summary Table 2. Aqueous Dilution			
	RAT	**HUMAN**	**Rat/Human ratio**
penetration rate, 0-6 hr (µg equivalents/cm^2/h)	0.25	0.06	4.2
penetration rate, 6-24 hr (µg equivalents/cm^2/h)	0.15	0.01	15
cumulative absorption, 6 hours (µg equivalents/cm^2)	1.77	0.43	4.1
cumulative absorption, 24 hours (µg equivalents/cm^2)	4.57	0.66	6.9
background level of [^{14}C] phosmet (µg equivalents/cm^2)	0.05	0.05	1.0
absorbed dose (receptor fluid only), 24 h (%)	11.7	1.69	6.9
absorbable dose (absorbed + skin), 24 h (%)	12.2	1.70	7.2

Rat Epidermis: The mean total recovery of applied radioactivity was ~85% for the undiluted concentrate and ~89% for the aqueous dilution (Summary Table 3). Most of the applied radioactivity was recovered in the skin washes with a mean recovery of 74% for the undiluted concentrate and in the skin washes (mean recovery of 47%) and tape strips (mean recovery of 19%) for the aqueous dilution. The mean percentage of absorbed radioactivity in the receptor fluid was 0.19% for the undiluted concentrate and 11.7% for the aqueous dilution. Mean amount of applied dose remaining in the rat epidermis was 0.01% for the undiluted concentrate and 0.5% for the aqueous dilution.

Human Epidermis: The mean total recovery of applied radioactivity was ~87% (undiluted concentrate) and ~104% (aqueous dilution). Most of the applied radioactivity was recovered in the skin washes with a mean recovery of 71% for the undiluted concentrate and 86% for the aqueous dilution. The mean percentage of absorbed radioactivity in the receptor fluid was 0.07% for the undiluted concentrate and 1.69% for the aqueous dilution. Mean amount of applied dose remaining in the human epidermis was <0.01% for the undiluted concentrate and 0.15% for the aqueous dilution.

Summary Table 3: Dermal Penetration (percentage of the applied dose)				
Matrix analyzed	Rat		Human	
	Undiluted concentrate	Aqueous dilution	Undiluted concentrate	Aqueous dilution
Absorbed/Absorbable dose				
receptor fluid	0.19±0.04	11.7±6.71	0.07±0.01	1.69±0.60
tape-stripped skin	0.01±0.01	0.5±0.34	<0.01±<0.01	0.34±0.49
Total absorbable	0.20±0.04	12.2±7.01	0.07±0.01	2.03±0.98
Unabsorbed dose				
skin wash	74.3±6.07	47.3±11.0	71.1±7.29	86.4±9.33
Total unabsorbed	85.1±1.82	77.1±17.0	86.2±3.33	101.8±3.84
Total recovered	85.3±1.79	89.3±15.1	86.5±3.23	103.8±3.41

HED COMMENTS: This study is **acceptable/nonguideline**. There are no EPA guidelines for *in vitro* penetration studies, but the study meets the OECD guidelines. The study demonstrates that rat skin is more permeable than human skin. However, it is important to note that there is considerable regional variability in permeability of human skin; *i.e.,* abdominal skin (used in this study) exhibits lower permeability than other potentially-exposed parts of the body (*e.g.,* head and neck). Additionally, the variability of absorbed/absorbable dose within the 6 replicates (both species) is unacceptably high, which reduces the confidence in the comparability of the study results. Also, tape strip data for both the rat and human skin show extremely high variability. Although the amount removed by tape stripping was included in the unabsorbed dose by the author, only the amount in the first 2 tape strips is considered as part of the unabsorbed dose. However, the actual amount in the last 3 tape strips is relatively small and does not add significantly to the absorbable amount.

Given the weaknesses of the *in vitro* study, a strict quantitative use of the *in vitro* data is not recommended. However, this *in vitro* study on rat and human skin provides supplemental data for consideration in determining an appropriate dermal absorption factor for use in the dermal risk assessment.

EXECUTIVE SUMMARY: In a dermal absorption study [MRID 40122201], Phosmet [Imidan 50-WP, 50%] was applied to the shaved back of 4 male Sprague-Dawley (CD) rats/dose. Dilutions used were 1:2, 1:10, and 1:100 applied at a rate of 300 µL/rat. Administered doses were 2.67, 0.52, and 0.058 mg/cm^2 skin. The dosing solutions contained 20-50 µCi of labeled compound. The radioactive test material had a specific activity of 26.6 mCi/mmol and was 97% pure. Phosmet was poorly absorbed when applied to the shaved skin of rats. The percent of radioactive dose found in the carcass, skin, urine, feces, and blood (combined) after 24 hours was 0.9, 3.8, and 11.8% of the administered doses of 2.67, 0.52 and 0.058 mg/cm^2 skin, respectively. The skin at the dosing site contained much of the radioactivity. The amount in the carcass and excreta reached a maximum at 24 hours and accounted for 7.9. 1.7, and 0.3% of the administered radioactivity at the low-, mid-, and high-doses, respectively. Excretion of the absorbed radioactivity was primarily urinary; 0.1% of the high-dose (1:2 dilution), 1.1% of the mid-dose (1:10 dilution), and 5.4% of the low-dose (1:100 dilution) radiolabel was found

in the urine between 10 and 24 hours. Much lower amounts were found in the feces.

The study is classified Acceptable/guideline, and it satisfies the guideline requirement (870.7600) for a dermal penetration study.

Attachment 2. Immunotoxicity DCI Justification

Guideline Number: 870.7800 **Study Title: Immunotoxicity**
Rationale for Requiring the Data
This is a new data requirement under 40 CFR Part 158 as a part of the data requirements for registration of a pesticide (food and non-food uses). The Immunotoxicity Test Guideline (OPPTS 870.7800) prescribes functional immunotoxicity testing and is designed to evaluate the potential of a repeated chemical exposure to produce adverse effects (i.e., suppression) on the immune system. Immunosuppression is a deficit in the ability of the immune system to respond to a challenge of bacterial or viral infections such as tuberculosis (TB), Severe Acquired Respiratory Syndrome (SARS), or neoplasia. Because the immune system is highly complex, studies not specifically conducted to assess immunotoxic endpoints are inadequate to characterize a pesticide's potential immunotoxicity. While data from hematology, lymphoid organ weights, and histopathology in routine chronic or subchronic toxicity studies may offer useful information on potential immunotoxic effects, these endpoints alone are insufficient to predict immunotoxicity.
Practical Utility of the Data
How will the data be used? Immunotoxicity studies provide critical scientific information needed to characterize potential hazard to the human population on the immune system from pesticide exposure. Since epidemiologic data on the effects of chemical exposures on immune parameters are limited and are inadequate to characterize a pesticide's potential immunotoxicity in humans, animal studies are used as the most sensitive endpoint for risk assessment. These animal studies can be used to select endpoints and doses for use in risk assessment of all exposure scenarios and are considered a primary data source for reliable reference dose calculation. For example, animal studies have demonstrated that immunotoxicity in rodents is one of the more sensitive manifestations of TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) among developmental, reproductive, and endocrinologic toxicities. Additionally, the EPA has established an oral reference dose (RfD) for tributyltin oxide (TBTO) based on observed immunotoxicity in animal studies (IRIS, 1997). **How could the data impact the Agency's future decision-making?** If the immunotoxicity study shows that the test material poses either a greater or a diminished risk than that given in the interim decision's conclusion, the risk assessments for the test material may need to be revised to reflect the magnitude of potential risk derived from the new data. If the Agency does not have this data, a 10X database uncertainty factor may be applied for conducting a risk assessment from the available studies.

Attachment 3. International Residue Limit Status Sheet

INTERNATIONAL RESIDUE LIMIT STATUS			
Chemical Name: *N*-(mercaptomethyl) phthalimide *S*-(O,O-dimethyl phosphorodithioate)	Common Name: Phosmet	9 Proposed tolerance X Reevaluated tolerance 9 Other	Date: 9/9/08
Codex Status (Maximum Residue Limits)		U. S. Tolerances	
☐ No Codex proposal step 6 or above ☐ No Codex proposal step 6 or above for the crops requested		Petition Number: PP#8F7383 *DP#: 355156* Other Identifier:	
Residue definition (step 8/CXL): phosmet (only)		Reviewer/Branch: D.Davis and M. Metzger/RRB1	
		Residue definition: phosmet and its oxygen analog	

Crop (s)	MRL (mg/kg)	Crop(s)	Tolerance (ppm)
Tree nuts	0.2	Almond	0.3
		Almond, hulls	50
		Pistachios	0.3

Limits for Canada	Limits for Mexico
☐ No Limits √ No Limits for the crops requested	☐No Limits √ No Limits for the crops requested
Residue definition: phosmet	Residue definition: fosmet

Crop(s)	MRL (mg/kg)	Crop(s)	MRL (mg/kg)

Notes/Special Instructions: S.Funk, 09/22/08.

13544

R183803

Chemical Name: Phosmet

PC Code: 059201
HED File Code: 14000 Risk Reviews
Memo Date: 7/1/2010
File ID: 00000000
Accession #: 000-00-0135

HED Records Reference Center
7/21/2010