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

October 30, 1998

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **METHAMIDOPHOS.** HED Risk Assessment and Disciplinary Chapters for the Reregistration Eligibility Decision (RED) Document. List A Reregistration Case 0043. Chemical No. 101201. DP Barcode: D250644.

FROM: Felecia A. Fort, Chemist
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THRU: Whang Phang, Branch Senior Scientist
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TO: Angel Chiri, Chemical Review Manager
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Special Review and Reregistration Division (7508W)

BACKGROUND

Attached is HED's risk assessment, disciplinary science chapters and other supporting documents for the Methamidophos HED Reregistration Eligibility Decision (RED) as follows:

HED Risk Assessment	Felecia Fort
Hazard Identification Assessment Review Committee Document	Jess Rowland
Toxicology Chapter of the HED RED	Nancy McCarroll
Product and Residue Chemistry Chapters for the HED RED	Felecia Fort
Occupational and Residential Exposure Assessment	Kathryn Boyle
Addendum to Occupational and Residential Exposure Assessment	Felecia Fort
Dietary Exposure and Risk Estimates for Reregistration	Felecia Fort

EXECUTIVE SUMMARY

Methamidophos (O,S-dimethyl phosphoramidothioate) is a restricted use pesticide that is used as an insecticide in agricultural settings. Methamidophos is formulated as a liquid product containing 40 percent active ingredient and is known as Monitor 4. As a result of an agreement between the registrant of methamidophos and EPA, methamidophos currently may be applied only to potatoes, tomatoes, and cotton. All uses other than potatoes and cotton have been deleted from the FIFRA Section 3 labels as of December 31, 1997. Under the same agreement, the use patterns for tomatoes is limited to FIFRA Section 24 (c) labels in 11 States.

This is an uncommon assessment because methamidophos is a metabolite of another registered pesticide, acephate. Consequently, this assessment will encompass the risk of methamidophos from applications of acephate and of methamidophos. An aggregate risk assessment which determines the risk from methamidophos from both acephate and methamidophos application was also conducted. There are no residential uses of methamidophos.

Toxicity endpoints were selected based on cholinesterase (ChE) inhibition of the red blood cell, brain and plasma. Based on the developmental and reproductive toxicity studies reviewed, there does not appear to be any special sensitivity for pre- or post-natal effects. HED has determined that for methamidophos the 10-fold uncertainty factor for the protection of infants and children as required under FQPA would be reduced to 3X. The reason is that although the data did not demonstrate an increase in susceptibility in the test animals, there is an indication of neurotoxic effects in hens and in humans. A developmental neurotoxicity study is needed to properly evaluate the neurotoxicity of this chemical.

RISK CHARACTERIZATION

Dietary Risk - Food

Methamidophos Application only

A **chronic** dietary risk assessment was conducted using anticipated residues and BEAD percent crop treated information. The chronic risk is reported as a percentage of the reference dose (RfD) where %RfD greater than 100 is considered to be above HEDs level of concern. The Anticipated Residue Contribution (ARC) for methamidophos for the general population and non-nursing infants occupies 29% and 17% of the RfD. The most exposed subgroup, children (1 to 6 years) occupies 62% of the RfD. Based on these results, the chronic dietary risk from the uses recommended does not exceed HED's level of concern.

To estimate **acute** dietary exposure, a high end exposure analysis

assuming tolerance level residues and 100% of the crop treated was conducted. . Acute dietary exposure estimates at the 95th percentile of exposure for the general population, children (1 to 6 years), and non-nursing infants resulted in an % aRfD of 1856%, 4406% and 1633%, respectively. These results exceed HED's level of concern regarding acute dietary exposure. A probabilistic assessment of acute dietary exposure to methamidophos could further refine acute dietary risk but was not conducted by HED. It is recommended that the registrant(s) conduct a Monte Carlo analysis to address acute dietary concerns.

Methamidophos is classified as a "not likely" human carcinogen. Therefore a carcinogenic risk assessment for methamidophos is not require.

Occupational Risks

MOEs were calculated for mixer/loader (handler) applications for methamidophos. The calculations of short and intermediate- term dermal risk indicate that even with all possible mitigation measures MOEs of greater than 100, the margin of exposure considered as HED's level of concern, could not be obtained for the following scenarios: (1a) mixing/loading of liquid formulation for aerial application and chemigation (potatoes only); (1b) mixing/loading of liquid formulation for ground boom appplications; and (2) applying sprays with a fixed-wing aircraft. No post-application risk assessment was conducted based on the results of handler exposure risk calculations.

Aggregate Exposure/Risk:

Acephate and Methamidophos Application

For **chronic aggregate risk (food),** chronic exposures to methamidophos from applications of acephate and of methamidophos were combined and compared to the methamidophos reference dose. This assessment was conducted using anticipated residues and BEAD% crop treated information. Results of the chronic exposure analysis show that 65% and 50% of the RfD is consumed for the U.S. population and non-nursing infants, respectively. The most significantly exposed subpopulation, children (1 to 6 years) occupied 106% of the RfD. The results indicate that for the children, HED's level of concern is exceeded. Submission of a tomato processing study so that the appropriate processing factors could be used in the dietary risk analysis further refine the risk. Tomato paste was a significant contributor to the dietary risk. Special studies like

market basket surveys, consumer processing studies, and/or residue decline studies could also further improve the dietary risk numbers .

An **acute aggregate risk (food)** which considers methamidophos from application of acephate and methamidophos was not conducted since HED has concerns for methamidophos from application of methamidophos alone. It is recommended that the registrant (s) conduct a Monte Carlo analysis to address acute dietary concerns.

An **aggregate exposure assessment which quantifies risk from food, water, and residential sources** was not conducted because there are no residential uses of methamidophos and HED has acute and chronic exposure concerns from food alone. An aggregate exposure assessment which quantifies risk from food and drinking water will be conducted when if and when HED no longer has these concerns from food.

Additional Data Requirements

Additional data requirements have been identified in the science chapters. These requirements are indicated below.

Toxicology

There are no data gaps for standard Subdivision F Guideline requirements for Methamidophos; however, the Hazard Identification Assessment Review Committee (HIARC) has determined that a developmental neurotoxicity study in rats is required.

Product Chemistry

Pertinent data requirements have not been satisfied for the Bayer 72% T (EPA Reg. No. 3125-341) and the Valent 72% T (EPA Reg. No. 59630-68). For the Bayer 72% T additional data are required for OPPTS 830.1550, 830.1600-1650, 830.1750, 830.1800, 830.6313-830.6320, 830.7000, 830.7050, and 830.7100. For the Valent 72% T additional data are required for OPPTS 830.1600-1650, 830.1700, 830.1750, 830.1800, 830.6314, 830.6316, 830.6317, 830.7000, 830.7050, 830.7200, 830.7370, and 830.7550-830.7570. All MP data requirements are outstanding for the Bayer 60% FI (EPA Reg. No. 3125-348). Provided that the registrants submit the data required in the attached data summary tables for the 72% Ts and 60% FI, and either certify that the suppliers of beginning materials and the manufacturing processes for the methamidophos MPs have not changed since the last comprehensive product chemistry review or submit complete updated product chemistry data packages, HED has no objections to the reregistration of methamidophos with respect to product chemistry data requirements.

Residue Chemistry

No additional data are required.

Occupational and Residential Exposure

No additional data are required.

SCIENCE ASSESSMENT

Summary of Registered Uses

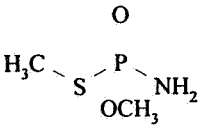
Methamidophos (O,S-dimethyl phosphoramidothioate) is a restricted use pesticide that is used as an insecticide in agricultural settings. Methamidophos is formulated as a liquid product containing 40 percent active ingredient. The product is known as Monitor 4. As a result of an agreement between the registrant of methamidophos and EPA, methamidophos currently may be applied only to potatoes, tomatoes, and cotton. All uses other than potatoes and cotton have been deleted from the FIFRA Section 3 labels as of December 31, 1997. Under the same agreement, the use patterns for tomatoes is limited to FIFRA Section 24 (c) labels in 11 States. Methamidophos can be applied aerially, by groundboom sprayer, and by sprinkler irrigation (i.e., chemigation) to potatoes only. For potatoes, the maximum application rate is 1.0 lb ai/acre (range = 0.5 to 1.0 lb ai/acre), and applications are made according to a 7 to 10 day preventative program or "as necessary". Applications to potatoes must not be made later than 14 days before harvest. For cotton, the maximum application rate is 1.0 lb ai/acre (range = 0.1 to 1.0 lb ai/acre), and 1 to 2 applications can be made per season. The preharvest application interval for cotton is 50 days. For tomatoes, the maximum application rate is also 1.0 lb ai/acre (range 0.75 to 1.0 lb ai/acre) and applications can be made at 5 to 7 day intervals, as necessary, up to 7 days before harvest.

Physical and Chemical Properties Assessment

Identification of Active Ingredient

Methamidophos (O,S-dimethyl phosphoramidothioate) is an acaricide/insecticide registered for use on cotton and potatoes. We note that the registered uses of

methamidophos on broccoli, Brussels sprouts, cabbage, cauliflower, celery, and sugar beets are to be canceled, and the 24(c) registrations labeled for melons, cucumbers, lettuce, alfalfa, Bermuda grass, peppers, clover, and eggplant are pending cancellation, leaving tomatoes as the only remaining food use with methamidophos 24(c) registrations.



Empirical Formula:	$C_2H_8NO_2PS$
Molecular Weight:	141.1
CAS Registry No.:	10265-92-6
Shaughnessy No.:	101201

IDENTIFICATION OF ACTIVE INGREDIENT

Methamidophos is a colorless to white crystalline solid with a strong mercaptan-like odor and a melting point of 46.1 C. Methamidophos is readily soluble (>200 g/L) in water, acetone, dimethylformamide, dichloromethane, and 2-propanol, and is soluble in n-octanol at 50-100 g/L, toluene at 2-5 g/L, and n-hexane at <1 g/L.

MANUFACTURING-USE PRODUCTS

A search of the Reference Files System (REFS) conducted 12/05/97 identified three methamidophos manufacturing-use products (MPs) registered under Shaughnessy No. 101201: the Bayer Corporation 72% technical product and 60% formulation intermediate (T and FI; EPA Reg. Nos. 3125-341 and 3125-348, respectively), and the Valent U.S.A. Corporation 72% T (EPA Reg. No. 59639-68). We note that the Valent 72% T was transferred from Chevron (EPA Reg. No. 62499-21; 10/4/91). Only the registered 72% Ts and 60% FI are subject to a reregistration eligibility decision.

Hazard Assessment

HED has reviewed the toxicology database submitted in support of reregistration of Metamidophos. The submitted studies were found to be acceptable for regulatory purposes and the database is considered adequate to support registration eligibility.

Methamidophos is acutely toxic, causing death shortly after exposure to relatively low oral, dermal, or inhalation doses. Methamidophos is only moderately irritating to the eyes and only mildly irritating to the skin. However, deaths and other signs of systemic toxicity occurred shortly after dermal or ocular application. These findings suggest that Methamidophos is rapidly absorbed via these routes. Other toxic signs observed in animals treated acutely with Methamidophos are consistent with cholinesterase inhibition (ChE) and are typical of the acute toxic signs induced by the organophosphate class of chemicals. They included: tremors, salivation, chromodacryorrhea (bloody tears) and dyspnea (labored breathing).

Table 1. Acute Toxicity of Methamidophos

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral; Rat 95.0% a.i.	00014044	LD_{50} = 15.6 mg/kg ♂ LD_{50} = 13.0 mg/kg ♀	I
81-2	Acute Dermal; Rabbit 75% a.i.	00014049	LD_{50} = 118 mg/kg ♂	I
81-3	Acute Inhalation; Rat 70.5% a.i.	00148449	LC_{50} = 0.052-0.079 mg/L[a] ♂ LC_{50} = 0.062-0.128 mg/L[a] ♀	I
81-4	Primary Eye Irritation; Rabbit 72.3% a.i.; dose: 0.1 mL	00014221	Corneal opacity and pannus present in 2/6 rabbits for 10 days posttreatment. One death 30 min. after dosing	I
81-5	Primary Skin Irritation; Rabbit 73% a.i. dose: 0.1 mL	00014220	PIS = 0.6 but test material was lethal to 5/9 animals within 24 hrs. of treatment	I
81-6	Dermal Sensitization; Guinea Pig 73.8% a.i.	00147929	Not a skin sensitizer (modified Buehler test)	--

[a] 95% Confidence limit

Subchronic Toxicity

Subchronic oral rat study

In a subchronic toxicity study (MRID No. 00014155) on rats, treatment with methamidophos resulted in reduced weight gain and food consumption in male rats. Rats at the

highest dose were quiet and appeared weak; however, cholinergic signs were not observed in either sex. The only clinical effect observed was significantly decreased thymus weights in the females which occurred in the high-dose. Inhibition of plasma and erythrocyte ChE was also observed in all sexes. Brain ChE was not determined.

The systemic LOAEL is 60 ppm (3 mg/kg/day) based on significantly decreased male body weight gain and decreased food consumption and clinical signs in both sexes. The NOAEL is 20 ppm (1.0 mg/kg). The ChE LOAEL = 6 ppm (0.3 mg/kg/day), based on plasma and RBC ChE inhibition in both sexes. The ChE NOAEL is 2 ppm (0.1 mg/kg/day).

Subchronic oral dog study

In a subchronic oral dog study, (MRID No. 00014153), treatment with methamidophos had no effect on appearance, behavior, mortality, food intake, body weight, hematology, clinical chemistry, urinalysis, organ weight or gross necropsy. Plasma and RBC ChE inhibition were observed. Brain ChE determinations and histopathology were not performed.

A LOAEL for systemic effects was not established. The NOAEL is ≥15 ppm (0.375 mg/kg/day). THE ChE LOAEL is 5 ppm (0.125 mg/kg/day), based on plasma and RBC ChE inhibition in both sexes. The ChE NOAEL is 1.5 ppm (0.0375 mg/kg/day).

Subchronic inhalation rat study

In a subchronic inhalation toxicity study (MRID No. 41402401), groups of Wistar rats (10/sex/dose) were exposed by inhalation to methamidophos (73% a.i.) in the form of aerosol (head/nose only) for 6 hrs/day for 3 months. The mean analytical concentrations were 0, 0.0011, 0.0054, or 0.0231 mg/L. No treatment related effects were observed at the low-dose group. The only effect observed in the mid-dose male and female was the inhibition of cholinesterase (ChE) activities in erythrocytes and plasma throughout the treatment period and brain at the end of the study. There was no substantive difference in the magnitude of the response on plasma or erythrocyte ChE inhibition from weeks 1-13. At high doses, slight to moderate muscle tremors and aggressive behavior; decreased body weight gain; decreased food consumption; altered clinical chemistry parameters, and decreased spleen weights were observed. When treatment was discontinued, ChE activities in the erythrocytes and plasma (not determined in the brain) returned to the pretreatment values.

The systemic LOAEL for both sexes is 0.0231 mg/L, based on clinical signs,

decreased body weight gain and feed consumption, altered clinical chemistry parameters, and decreased spleen weights. The NOAEL is 0.005 mg/L. Based on the inhibition of ChE activities in erythrocytes, plasma and brain, the NOAEL and LOAEL for both sexes are 0.001 mg/L and 0.005 mg/L, respectively.

Special Subchronic Toxicity Studies (Cholinesterase Inhibition)

Subchronic oral rat study

The objective of this study (MRID No. 41867201). was to establish a NOAEL for the Methamidophos-induced cholinesterase (ChE) inhibition in plasma, erythrocytes (RBCs) and brain of the rat. In this study, groups of Fischer 344 rats (25/sex/group) received methamidophos (≈78% a.i.) at dietary concentrations of 0, 0.5, 1, 2, or 4 ppm for 56 days. Methamidophos had no effect on body weight gain or food consumption of both sexes. There were no mortalities, and toxic signs usually associated with ChE inhibition were not observed. The only effect, which was seen at all dose levels and all sampling intervals, was the inhibition of ChE activities in the plasma, RBCs and brain.

The inhibition of acetyl and butyryl ChE activity in plasma, and acetyl ChE activity in RBC and brain at 0.5 ppm (0.03 mg/kg/day), for both sexes was considered by the Reference Dose (RfD)/Peer Review Committee on May 29,1992 to define the threshold LOAEL for this chemical. Subsequently, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) revaluated the study on January 20, 1998 and determined that 0.5 ppm (0.03 mg/kg/day) is a NOAEL. The basis for this decision includes: the magnitude of ChE inhibition in the brain at 0.03 mg/kg/day is small; only reached statistical significance at day 56 in females and at day 35 in males; and appeared to be within or close to the detection level of this assay. Consequently, the LOAEL and NOAEL for this study have been determined to be 1 ppm (0.06 mg/kg/day) and 0.5 ppm (0.03 mg/kg/day), respectively, for both sexes.

Subchronic oral human study

In a subchronic oral toxicty study on humans (MRID No. 00015160), volunteers were given mixtures of Methamidophos (Monitor; purity not stated) and Acephate (Orthene) in two ratios, 1:4 or 1:9 (Monitor:Acephate) in gelatin capsules containing corn oil. The group receiving the 1:9 ratio received the equivalent of 0.01, 0.02, 0.03, or 0.4 mg/kg/day of methamidophos. The 1:4 ratio group received methamidophos equivalent to 0.02 or 0.04 mg/kg/day. Each group received increasing levels of the test materials until a significant inhibition of ChE activity occurred (i.e., ChE activity "was greater than two standard deviations below mean pretest activity for two consecutive bleedings"). Dosing human subjects with graded levels of Monitor:Orthene mixtures for a total of 37-73 days had no

effects on RBC ChE activity, hematology, blood chemistry, blood pressure, pulse rate, pupil size, light reflex, eye accommodation, chest sound, muscle tone, knee jerk, tongue tremor or finger tremor. The only effect was the significant inhibition of plasma ChE activities in both groups. All suppressed ChE activity returned to the pretest values during the 7-day recovery period.

Based on the findings, NOAELs and LOAELs were as follows:
1:4 mixture: NOAEL (both sexes) = 0.1 mg/kg/day (≈0.02 mg/kg Methamidophos); LOAEL = 0.2 mg/kg/day (≈0.04 mg/kg Methamidophos)
1:9 mixture: NOAEL (♂) = 0.2 mg/kg/day (≈0.02 mg/kg Methamidophos); LOAEL = 0.3 mg/kg/day (≈0.03 mg/kg Methamidophos)
1:9 mixture: NOAEL (♀) = 0.3 mg/kg/day (≈0.03 mg/kg Methamidophos); LOAEL = 0.4 mg/kg/day (≈0.04 mg/kg Methamidophos)

Chronic Toxicity Studies

Chronic dog study

In a one-year chronic toxicity study, (MRID Nos. 00147938 and 41234304), dogs administered Methamidophos displayed no significant effects on mortality, clinical signs, body weights, food consumption, hematology, clinical chemistry, urinalysis, organ weights, or gross and histologic pathology. The cholinesterase (ChE) data indicate that inhibition of brain, plasma and RBC ChE was dose related in both sexes and occurred at all doses throughout the study.

The systemic NOAEL is >32 ppm (>0.8 mg/kg/day). The ChE LOAEL is 2 ppm (≈0.05 mg/kg/day, lowest dose tested), based on brain, plasma and erythrocyte ChE inhibition. A NOAEL was not established for ChE inhibition.

Combined chronic/carcinogenicity rat study

In a chronic/carcinogenicity toxicity study (MRID Nos. 00148452 and 43248102), methamidophos was administered to rats. Treatment related effects included loose stools, urine stains, rough coats, skin lesions, and body weight decreases. ChE data indicate that inhibition of brain, plasma and RBC ChE was dose related in both sexes and occurred at all doses and sampling times. At the doses tested, there was no treatment-related increase in the tumor incidence when compared to controls. Dosing was considered adequate based on brain, plasma and RBC ChE inhibition.

The systemic LOAEL is 18 ppm (≈0.9 mg/kg/day), based on decreased body weight gain

in males. The systemic NOAEL is 6 ppm (≈0.3 mg/kg/day). The ChE LOAEL is 2 ppm (≈0.1 mg/kg/day, lowest dose tested), based on brain, plasma and erythrocyte ChE inhibition. A NOAEL was not established for ChE inhibition. The oncogenic NOAEL is >54 ppm (≈2.7 mg/kg/day).

Carcinogenicity mouse study

In a carcinogenicity study (MRID Nos. 0014557, 00147937, and 43248101), methamidophos did not produce treatment-related increases in the tumor incidence when compared to controls. Dosing was, therefore, considered adequate based on adverse effects on body weight and feed consumption. Treatment related effects included significant body weight decreases, decreased body weight gain, and significantly lower feed consumption in both sexes.

The systemic LOAEL is 25 ppm (≈3.6 mg/kg/day, highest dose tested), based on decreased body weight gain and feed consumption in males and females. The systemic NOAEL is 5 ppm (≈0.7 mg/kg/day). The oncogenic NOAEL is >25 ppm (>3.6 mg/kg/day).

Developmental Toxicity Studies

Developmental toxicity rat study

In a developmental toxicity study (MRID No. 00148454), CD rats were administered methamidophos (≈71% a.i.) by gavage at dose levels of 0, 0.3, or 3 mg/kg/day on gestation days 6 through 15. Clinical signs (fasciculation, hyperactivity, salivation, lacrimation and polyuria); significantly decreased body weight gain; and significantly lower feed consumption were seen in the high dose group. Reproductive parameters were unaffected by treatment. Treatment-related developmental effects were limited to the high-dose group. Cholinesterase activity was not measured. In addition, compound-related developmental toxicity was also confined to the high-dose group and also manifested as significantly decreased mean body weight and total litter weights. No compound-related increases in fetal malformations or variations were seen.

The maternal toxicity LOAEL is 3.0 mg/kg/day, based on decreased body weight gain and feed consumption during pregnancy and signs indicative of cholinesterase inhibition (i.e., fasciculation, hyperactivity, salivation and lacrimation). The NOAEL is 1.0 mg/kg/day.

The developmental toxicity LOAEL is 3.0 mg/kg/day, based on decreased fetal weight; the NOAEL is 1.0 mg/kg/day.

Developmental toxicity rat study

In another developmental toxicity study (MRID 43906901), pregnant SD rats received methamidophos (76% a.i.) by gavage at dose levels of 0, 0.05, 0.14, or 5.49 mg/kg/day on gestation days 6 through 15. Treatment-related maternal toxicity was observed only in the high-dose group and included clinical signs (tremors, muscle fasciculations and salivation), decreased body weight gain and food consumption, and inhibition of ChE activities of plasma, RBC, and brain. Treatment-related developmental effects were observed only in the high-dose group and included decreased placental and fetal weights (males, females and combined); an increase in skeletal variations (incompletely ossified frontal bones, sacral arches and sternebrae [segments 3, 4] and xiphoid); and unossified metacarpals and sternebrae. Other parameters examined were unaffected in any group.

Based on the above findings, the maternal LOAEL and NOAEL are 5.49 and 0.14 mg/kg/day (analytical values), respectively. The developmental LOAEL and NOAEL are also 5.49 and 0.14 mg/kg/day, respectively.

Developmental toxicity rabbit study

In a developmental toxicity study on rabbits (MRID No. 00041315), Methamidophos (62% a.i.) was administered by gavage to Himalayan rabbits at dose levels of 0.5, or 2.5 mg/kg on gestation days 6 through 18. Treatment-related maternal toxicity was manifested as reduced body weight gain at all dose levels. The response was not dose related but significant at the low and high levels. Reproductive parameters were unaffected by treatment. The number of implants, resporptions, stunted fetuses, fetal deaths, sex distribution, and fetal and placental weights were also unaffected by treatment. Similarly, no compound-related increases in fetal malformations or variations were seen.

The maternal toxicity LOAEL is considered to be <0.1 mg/kg/day (lowest dose tested), based on decreased body weight gain during gestation; a NOAEL was not established.

The developmental toxicity NOAEL is >2.5 mg/kg/day (highest dose tested).

Developmental toxicity rabbit study

In this developmental toxicity study (MRID No. 44040601), the timed-pregnant NW rabbits received methamidophos by gavage at dose levels of 0, 0.2, 0.65, or 2.47 mg/kg/day on gestation day 6 through 18. Maternal toxicity observed in the mid-dose and high-dose groups included decreased body weight gain and decreased absolute (g/day) and relative (g/kg/day) food consumption. The high-dose also caused hyperactivity (thumping of the cage with the hindlimbs) and weight loss. Methamidophos had no effect on fetal development in this study. Plasma and erythrocyte ChE were inhibited at all doses tested.

Based on the above findings, the maternal LOAEL and NOAEL are 0.65 and 0.20 mg/kg/day (analytical values), respectively. The developmental NOAEL is >2.47 mg/kg/day (HDT).

Reproductive Toxicity

The reproduction study in rats (MRID Nos. 00148455 and 41234301) showed that methamidophos at the highest dose tested (33 ppm) produced adverse effects in parental animals including premating body weight decrements, decreased body weight gain in females during gestation and lactation, decreased body weight in F1 males and females. No other treatment-related effects were seen. Effects on reproductive performance at 33 ppm included significant reductions in the number of sperm-positive PO females delivering pups and nonsignificant reduction in the number of sperm-positive F1 females delivering F2b pups. Toxicity to the offspring at 33 ppm consisted of decreases in pup viability for the F1, F2a, and F2b generations and significant reductions in pup weight during lactation in the F1, F2a, and F2b generations.

Parental systemic

NOAEL = 10 ppm (0.5 mg/kg/day)
LOAEL = 33 ppm (1.65 mg/kg/day), based on decreases body weight of males and females during premating and of females during lactation.

Reproductive

NOAEL = 10 ppm (0.5 mg/kg/day)
LOAEL = 33 ppm (1.65 mg/kg/day), based on decreases in the number of sperm positive females giving birth.

Developmental

NOAEL = 10 ppm (0.5 mg/kg/day)
LOAEL = 33 ppm (1.65 mg/kg/day), based on decreases in pup viability and body weight during lactation.

Mutagenicity Studies

The available studies (MRID No. 00098457, 4285470, 42854701, 41461401, 41461401, 41234306, 41234306, 41234305 and 41234305) indicate that Methamidophos is not mutagenic in bacteria but does induce gene mutations in cultured mammalian cells at high S9-activated levels. Similarly, there was evidence of

clastogenicity at high nonactivated concentrations and polyploidy at high S9-activated doses. In contrast, Methamidophos was negative for chromosome aberrations *in vivo* and did not induce UDS *in vitro*. The data suggest, therefore, that the marginal genotoxicity activity seen with the test substance is not expressed *in vivo*. The lack of an oncogenic effect in the rat or mouse long-term feeding studies and the absence of significant reproductive or developmental toxicity that could be associated with a mutagenic mode of action (i.e., germ cell damage, reduced numbers of pregnancies, decreased total implants, increased resorptions) support this conclusion. Based on these considerations, HED concluded that there is no concern for mutagenicity.

Metabolism

In a metabolism study, (MRID No. 00015224), with oral dosing, methamidophos was absorbed, rapidly degraded and/or eliminated within the first 24 hours postdosing. In the ^{14}C studies, 60% of the radioactivity was detected in CO_2 and 11% in urine. Fecal excretion of radiolabel was low. In the ^{32}P studies, ≈70% of the radioactivity was detected in the urine. Fecal excretion of the ^{32}P radiolabel was initially low (2-3%) but increased 3-21 days postdosing (8-21%). The identified metabolites in the urine (O,S-dimethyl-phosphorothioate, methyl dihydrogen phosphate and phosphoric acid) are not considered to be ChE inhibitors. The content of Monitor technical in tissue 14 days posttreatment was <0.004 ppm. There was no difference in the rate of metabolism, excretion or nature of the metabolites between males and females.

Neurotoxicity Studies

Acute oral delayed neurotoxicity study in hens

In an acute oral delayed neurotoxicity study (MRID No. 00041217) which consisted of an acute lethality phase and a neurotoxicity phase, White Leghorn hens were exposed to methamidophos (74% a.i.) in a dose range of 10 to 75.94 mg/kg/day. Neither forced motor activity nor neurotoxic esterase (NTE) were assessed. In the oral lethality phase of the study, deaths (>2 hours-6 days) and other signs of toxicity were observed at ≥22.5 mg/kg or above. Acute signs of poisoning included: muscular weakness, unsteadiness (leg weakness), diarrhea, excessive salivation, anorexia, lateral and sternal recumbency, dyspnea, and cyanotic combs and wattles shortly before death. The higher the dose, the sooner the onset of toxic signs and death. Death was caused by respiratory paralysis. No signs of toxicity were observed at the doses, 15 mg/kg or below.

Based on these findings, the oral LD_{50} in hens = 29.75 mg/kg.

In the neurotoxicity phase of the study, no histopathological lesions typical of delayed neurotoxicity were observed at the lower doses (30 or 50.63 mg/kg). However, 2/10 of the hens died at 30 mg/kg and 4/12 hens died at 50.63 mg/kg.

Subchronic oral delayed neurotoxicity study in hens

In a subchronic delayed neurotoxicity study (MRID No. 40985202), methamidophos was administered orally (by gavage) to White Leghorn hens at dose levels of 0.3, 1, or 3 mg/kg/day. Overall, the data indicate that butyrylcholinesterase (BuChE) inhibition was dose related in the mid- and high-dose groups; the peak response appeared to occur at week 8. Similarly, neurotoxic esterase (NTE) inhibition was dose related. However, ataxia, abnormal motor activity or histological changes in brain, spinal cord and peripheral nerves, generally regarded as indicators of delayed neurotoxicity, were not observed in any hen on the study. Based on the negative results of the forced motor activity tests and microscopic examinations of brain, spinal cord and peripheral nerves, methamidophos did not induce delayed neurotoxicity in hens.

LOAEL = 1 mg/kg/day based on inhibition of plasma BuChE and spinal cord NTE activity.

NOAEL = 0.3 mg/kg/day.

Acute neurotoxicity screening study in rats

In an acute neurotoxicity screening study (MRID No. 43025001), SD rats received a single dose of methamidophos (by gavage) at dose levels of 0.9, 3, or 9 mg/kg. Treated males had slightly decreased motor/locomotion activities and one male had clinical signs (increased sitting/lying, urine, oral and nasal staining). Females at this dose showed slightly reduced motor activity. At higher doses, markedly decreased motor/locomotor activity and clinical sign were observed. Most clinical signs were observed only on the day of dosing and were completely resolved by study day 5. The peak effect on the functional observational battery (FOB) and motor and locomotor activities occurred on day 0. No treatment related gross or histopathological effects were seen; brain weights were unaffected by treatment. Statistically significant and dose-related inhibition of serum, RBC and brain ChE was observed at all doses and in both sexes

The LOAEL is 0.9 mg/kg, based on slightly reduced motor/locomotor activity in males and females and clinical signs in one male consistent with neurotoxicity secondary to cholinesterase inhibition. The study NOAEL is <0.9 mg/kg.

The ChE LOAEL is 0.9 mg/kg, based on inhibition of all measured

activities. The ChE NOAEL is ≤0.9 mg/kg. Although NOAELs were not established, a second rat acute neurotoxicity study on Methamidophos (MRID No. 43345801) demonstrated a LOAEL = 0.7 mg/kg (and threshold ChE NOAEL = 0.3 mg/kg).

Acute neurotoxicity screening study in rats (Supplemental study)

In an acute (supplemental) neurotoxicity screening study, (MRID No. 43345801) *Methamidophos (75.6% a.i.)* was administered to a single dose (by gavage) to SD rats at dose levels 0, 0.3, or 0.7 mg/kg. Relative to the control values, Methamidophos at the low dose (0.3 mg/kg) had no effect on any of the parameters examined. Relative to the control values, the mid-dose (0.7 mg/kg) had no effect on the neurobehavioral parameters examined, but the ChE activities of RBC, plasma, and brain were inhibited significantly.

The results of this study should be considered together with those of another acute neurotoxicity study (MRID No. 43025001) in which a NOAEL for neurobehavioral effects was not determined. Based on the results of both studies, the NOAEL for neurobehavioral effects is 0.7 mg/kg and the LOAEL is 0.9 mg/kg, for males and females. The NOAEL and LOAEL for ChE activities are 0.3 mg/kg and 0.7 mg/kg, respectively.

Subchronic neurotoxicity screening study in rats

In a subchronic neurotoxicity screening study (MRID No. 43197901), Fischer 344 rats received methamidophos in the diet at concentrations 0, 1, 12, or 16 ppmfor 13 weeks. Treatment-related clinical signs in males and females of the high-dose group observed included: muscle fasciculations, increased reactivity, perianal and urine staining, and red and clear lacrimation; tremors were also noted in the high-dose males. Reductions in motor and locomotion activities and decreased forelimb grip strength were also reported. There was no evidence of cumulative toxicity beyond week 8. Reduced activity (sluggish arousal during open field observations) was only seen in the high-dose females. Decreased body weight gain was also recorded for the high-dose males and females. Mid-dose females had an increased incidence of urine stains throughout most of the study. Other treatment-related effects in the mid-dose group were: reduced motor and locomotor activities and decreased body weight gain in the females. No treatment-related effects were observed in the low-dose group. Similarly, treatment with Methamidophos had no adverse effects on the incidence of gross or microscopic

changes or brain weights. The ChE data indicate that inhibition of plasma, brain, and RBC ChE was statistically significant.

Based on these findings, the NOAEL for neurotoxicity is 1 ppm (0.067 mg/kg/day for males and 0.074 mg/kg/day for females). The LOAEL for neurotoxicity is 12 ppm (0.787 mg/kg/day for males and 0.889 mg/kg/day for females).

Based on these findings, the NOAELs and LOAELs for inhibition of ChE (both sexes) were:

RBC: NOAEL = 1 ppm (0.067 mg/kg/day ♂; 0.074 mg/kg/day ♀)
LOAEL = 12 ppm (0.787 mg/kg/day ♂; 0.899 mg/kg/day ♀)

Plasma and brain = NOAEL = <1 ppm (<0.067 mg/kg/day ♂; <0.074 mg/kg/day ♀, lowest dose tested)
LOAEL = 1 ppm

Toxicological Endpoints

Based on the above summarized studies, the Hazard Identification Assessment Review Committee determined that there are toxicological endpoints of concern for Methamidophos (see HIARC document of 2/12/98). These endpoints are shown in Table 2.

Table 2. Methamidophos Endpoints Used For Risk Assessment

Exposure Scenario	NOAEL for use in Risk Assessment	Uncertainty Factor	Endpoint
Acute Dietary Adjusted aRfD = 0.001 mg/kg/day	0.3 mg/kg/day (Acute Neurotoxicity-rat)	300*	Brain ChE inhibition
Chronic Dietary Adjusted RfD = 0.0001 mg/kg/day	0.03 mg/kg/day (8 week toxicity-rat)	300*	Brain ChE inhibition
Short-Term (1-7 days)	1 mg/kg/day (21 day dermal-rat)	100	Brain ChE inhibition
Intermediate-Term Exposure (1 week to several months)	1 mg/kg/day (21-day dermal-rat)	100	Brain ChE inhibition
Long-Term Exposure (several months to lifetime)	Not applicable The use pattern does not indicate potential long-term exposure.	N/A	N/A
Inhalation Exposure (any duration)	0.001 mg/L (90-day inhalation- rat)	100	plasma, brain and erythrocyte ChE inhibition
Carcinogenic	Methamidophos has been classified as a "not likely" human carcinogen. Risk assessment not required.	N/A	N/A
Aggregate Assessment	The dermal and inhalation MOE's may be combined to obtain a total MOE since a common toxicological endpoint (cholinesterase inhibition) was observed.	N/A	N/A
FQPA Considerations	For acephate the 10-fold uncertainty factor to account for the protection of infants and children has been reduced to 3X. Thus, for all scenarios, MOEs equal to or greater than 300 are appropriate.	N/A	N/A

NOAEL - No Observable Effect Level, ChE = Cholinesterase, MOE = Margins of Exposure, N/A = not applicable
Note that only short- and intermediate- term exposure/risk assessments are evaluated in this document. Since the exposures that would result from the uses of methamidophos were determined to be of an intermittent nature (i.e., the frequency and duration of these exposures do not exhibit a chronic exposure pattern), a long-term assessment are appropriate.

*The 300 safety factor which includes a 3X for FQPA, is applicable for dietary and residential exposures.

Dietary Exposure Assessment

The chemistry database is essentially complete. Based on the available plant metabolism data, the methamidophos residue of concern in plant commodities is the parent, methamidophos. Acceptable goat and hen metabolism studies have been submitted and evaluated. The livestock metabolism data indicate that no detectable residues of concern are likely to be present in eggs, milk, and livestock tissues. With regard to livestock, a 40 CFR 180.6(a)(3) [Category 3] situation exists. Therefore, no tolerances on animal commodities are required.

Adequate methods are available for the enforcement of established tolerances. The Pesticide Analytical Manual (PAM) Volume II lists Method I, a GLC method employing thermionic detection, as well as Method A, a confirmatory TLC method. Codex MRLs have been established for residues of methamidophos *per se*.

Pending label amendments for some crops, adequate field trial data are available to reassess the established tolerances for cottonseed, potatoes, and tomatoes. The available data suggest that the tolerance levels for cottonseed and tomato should be raised to 0.2 ppm and 2.0 ppm, respectively. A tolerance for residues of methamidophos in/on cotton gin byproducts must be proposed. The available data support a tolerance level of 10 ppm (see Table 3.).

The registrants are not supporting use of methamidophos on Brussels sprouts, cauliflower, celery, lettuce, and peppers. Because there are registered acephate uses on these crops, methamidophos tolerances for these crops should be moved to 40 CFR §180.315(c). Additionally, the basic producer of acephate (Valent U.S.A. Corporation) has indicated that they will be supporting use of acephate on the following food/feed crops which were not originally on the methamidophos labels: beans (snap, dry, and lima); cranberries; and peppermint/spearmint. Therefore, tolerances for residues of methamidophos in/on these commodities resulting from use of acephate should also be established under 40 CFR §180.315(c). The tolerance expression in this section should read: "Tolerances are established for residues of methamidophos in or on the following raw agricultural commodities as a result of the application of acephate:".

The following tolerances should be revoked as the registrants are not supporting methamidophos uses and there are no registered acephate uses on these commodities: beets, sugar, roots; beets, sugar, tops; broccoli; cabbage; cucumbers; eggplant; and melons.

Table 3. Tolerance Reassessment Summary for Methamidophos.

Commodity	Tolerance Listed Under 40 CFR §180.315	Reassessed Tolerance	Tolerance [1] Listed Under 40 CFR §180.108	Comment *[Correct Commodity Definition]*
Tolerances Listed Under 40 CFR §180.315 (a)				
Beets, sugar, roots	0.02	Revoke	--	The registrants are not supporting methamidophos use on sugar beets and there are no registered acephate uses.
Beets, sugar, tops	0.50	Revoke	--	
Broccoli	1.0	Revoke	--	The registrants are not supporting methamidophos use on broccoli and there are no registered acephate uses.
Brussels sprouts	1.0	1.0	0.5	This tolerance must be moved to §180.315(c).
Cabbage	1.0	Revoke	--	The registrants are not supporting methamidophos use on cabbage and there are no registered acephate uses.
Cauliflower	1.0	0.5	0.5	This tolerance must be moved to §180.315(c).
Cottonseed	0.1 (N)	0.2	--	*[Cotton, undelinted seed]*
Cucumbers	1.0	Revoke	--	The registrants are not supporting methamidophos use on cucumbers and there are no registered acephate uses.
Eggplant	1.0	Revoke	--	The registrants are not supporting methamidophos use on eggplant and there are no registered acephate uses.
Lettuce	1.0	1.0	1	This tolerance must be moved to §180.315(c).
Melons	0.5	Revoke	--	The registrants are not supporting methamidophos use on melons and there are no registered acephate uses.
Peppers	1.0	1.0	1	This tolerance must be moved to §180.315(c).
Potatoes	0.1(N)	0.1	--	
Tomatoes	1.0	2.0	--	

Commodity	Tolerance Listed Under 40 CFR §180.315	Reassessed Tolerance	Tolerance [1] Listed Under 40 CFR §180.108	Comment *[Correct Commodity Definition]*
Tolerance To Be Proposed Under 40 CFR §180.315 (a)				
Cotton, gin byproducts	--	10	--	
Tolerance Listed Under 40 CFR §180.315 (b)				
Celery	1	1.0	1	This tolerance must be moved to §180.315(c).
Tolerances to be Listed Under 40 CFR §180.315 ©				
Beans (succulent and dry form)	--	1.0	1	[*Beans, dry and succulent*]
Brussels sprouts	1.0	1.0	0.5	
Cauliflower	1.0	0.5	0.5	
Celery	1	1.0	1	
Cranberries	--	0.1	0.1	
Lettuce	1.0	1.0	1	[*Lettuce, head*]
Mint hay	--	2	1	[*Mint, tops (leaves and stem)*]
Peppers	1.0	1.0	1	
Soybeans	--	TBD	1	

[1] Tolerances listed in 40 CFR §180.108 are expressed in terms of the combined residues of acephate and methamidophos; several tolerances have limits on methamidophos levels. Tolerance levels listed in this column in italics are for the combined residues of acephate and methamidophos. Unitalicized tolerance levels are the methamidophos limits.

[2] TBD = To be determined. Reassessment of tolerance(s) cannot be made at this time because additional data are required.

[3] Tolerance formerly listed in 40 CFR §186.100, moved to 40 CFR §180.108 (63 FR 2163, 1/14/98).

[4] Tolerance formerly listed in 40 CFR §185.100, moved to 40 CFR §180.108 (63 FR 2163, 1/14/98).

Dietary Exposure (food source)

Dietary exposure assessments were conducted using the DEEM® (Dietary Exposure Evaluation Model) program and was based on the listing of tolerances eligible for reregistration described in this document. The dietary exposure assessment for methamidophos was conducted for exposure to methamidophos from methamidophos application only. A dietary exposure assessment which includes exposure to methamidophos from applications of methamidophos and of acephate is discussed in the aggregate exposure assessment section of this document.

Chronic Dietary Exposure

To assess chronic dietary risk the DEEM® program calculates exposure based on average food consumption estimates (from the USDA 1989-1992 Nationwide Food Consumption Survey (NFCS)) and on tolerances and/or appropriate anticipated residue estimates. Chronic dietary risk is expressed as a percent of the chronic Reference Dose (RfD) and is estimated by the DEEM system from the general U.S. population and 22 subpopulations including infants and children (which typically demonstrate the highest exposure). The toxicological endpoint selected for the chronic dietary assessment is the adjusted RfD, 0.0001 mg/kg/day. This RfD has been revised to include the additional FQPA safety factor of 3X. The chronic dietary assessment for methamidophos includes use of percent crop treated data (BEAD memo by Sherry Wise) and anticipated residues (HED memo by F.Fort, 10/22/98). A percent RfD less than 100 is considered to be below HED's level of concern.

The Anticipated Residue Contribution (ARC) for methamidophos for the general population and non-nursing infants occupies 29% and 17% of the RfD (Table 4). The most exposed subgroup, children (1 to 6 years) occupies 62% of the RfD. Based on these results, the chronic dietary risk from the uses recommended through reregistration, does not exceed HED's level of concern.

Acute Exposure

To assess acute dietary risk, the DEEM program calculated total, one day exposure based on the reported consumption of foods and uses a high end residue estimate (in this case tolerance level residues and 100% crop treated). The high end of the resultant exposure distribution is then compared to the adjusted acute Reference Dose. The acute RfD (aRfD) that was used in this assessment is 0.001 mg/kg/day, which includes the 3X FQPA safety factor adjustment. Acute dietary exposure estimates at the 95th percentile of exposure for the general population, children (1 to 6 years), and non-nursing infants resulted in an % aRfD of 1856%, 4406% and 1633%, respectively (Table 4). These results exceed HED's level of concern regarding acute dietary exposure. A probabilistic assessment of acute dietary exposure to acephate could further refine acute dietary risk but was not conducted by HED. It is recommended that the registrant (s)

conduct a Monte Carlo analysis to address acute dietary concerns.

Carcinogenic Exposure

Methamidophos is classified as a "not likely" human carcinogen. Therefore a carcinogenic risk assessment for methamidophos is not required.

Table 4. Summary of Dietary Risk for Methamidophos

Population Subgroup	Chronic Dietary Risk		Acute Dietary Risk	
	Exposure (mg/kg/day)	% chronic RfD[ab]	Exposure (mg/kg/day)	% acute RfD[ac]
U.S. Population	0.000029	29	0.0186	1856
Children (1 - 6 years)	0.000062	62	0.0440	4406
Non-Nursing Infants (<1 year)	0.000017	17	0.0163	1633

a. A % RfD or %aRfD that is less than 100% is not considered as exceeding HEDs level of concern.
b. Rfd (methamidophos) = 0.0001 mg/kg/day
c. aRfd (methamidophos) = 0.001 mg/kg/day

Non-Dietary Exposure

Occupational Exposure

At this time, products containing methamidophos are intended for occupational uses only. Methamidophos is a restricted use pesticide due to its acute dermal toxicity and residue effects on avian species. As such, it may be sold and used only by certified applicators or persons under their direct supervision. It may not be sold to homeowners. Therefore, a residential assessment for methamidophos was not performed.

Methamidophos was one of the chemicals included in the October 1995 agricultural re-entry generic data call-in. Bayer indicated that it would satisfy the requirement for post-application dermal exposure data through its participation in the Agricultural Re-entry Task Force (ARTF). This data will allow the Agency to estimate re-entry exposures for methamidophos.

It should also be noted that methamidophos is one of 22 chemicals on the United Nations list

of chemicals requiring prior informed consent (PIC) procedures. On this list methamidophos is a PCU (problems under conditions of use), which are pesticides which are not banned or restricted in developed (industrialized) countries, but which have been shown to cause problems when used without the sophisticated application technologies required to mitigate risks.

Occupational Handler Exposure and Risk

EPA has determined that there are potential exposures to mixers/loaders, applicators, and other handlers during usual use-patterns associated with methamidophos. HED has identified the following major methamidophos exposure scenarios for occupational handlers:

- (1a) mixing/loading liquid formulation for aerial and chemigation application,
- (1b) mixing/loading liquid formulation to support groundboom applications;
- (2) applying sprays with a fixed-wing aircraft;
- (3) applying sprays with a helicopter;
- (4) applying sprays with groundboom equipment; and
- (5) flagging aerial spray applications.

Dermal and inhalation exposures were developed using PHED Version 1.1 surrogate data since no chemical-specific data were submitted. Use of surrogate or generic data is appropriate since it is generally believed that the physical parameters of the handling and application process (e.g. the type of formulations, the method of application, and the type of clothing), not the chemical properties of the pesticide, control the amount of dermal and inhalation exposure. Thus, PHED typically allows exposure and risk assessments to be conducted with a much larger number of observations than available from a single exposure study.

Caveats, assumptions, and factors used to complete this exposure assessment are described in detail in Table 11 and in the Occupational and Residential Exposure Assessment attached. Handler exposure assessments are completed by EPA using a baseline exposure scenario and, if required, increasing levels of risk mitigation (PPE and engineering controls) to achieve an appropriate Margin of Exposure. Baseline short and intermediate-term dermal and inhalation exposures (developed using PHED Version 1.1 surrogate data) are presented in Table 5. Baseline risks are presented in Table 6. Tables 7 and 8 present the short- and intermediate-term dermal and inhalation exposures and risks with additional personal protective equipment. Tables 9 and 10 present the short- and intermediate-term dermal and inhalation exposures and risks with engineering controls.

Summary of Combined Dermal and Inhalation Risks from Handler Exposures

The acceptable MOE for combined short- or intermediate-term dermal and inhalation exposure/risk is 100. Few MOEs are equal to or greater than 100 for the exposure scenarios evaluated, even with the use of all available risk mitigation measures. The MOE's above the level of concern are for: (1a) mixing/loading of liquid formulation for aerial application and

chemigation (potatoes only); (1b) mixing/loading of liquid formulation for ground boom appplications; and (2) applying sprays with a fixed-wing aircraft.

Occupational Post-application Exposure and Risk

Calculation of postapplication exposures to methamidophos is being deferred due to the results of the handler exposure calculations. Therefore, post-application exposures were not estimated in this assessment.

FQPA CONSIDERATIONS

Aggregate Exposure

In examining aggregate exposure, FQPA directs EPA to take into account available information concerning exposures from pesticide residues in food and other exposures for which there is reliable information. These other exposures include drinking water and non-occupational exposures, e.g., to pesticides used in and around the home. Risk assessments for aggregate exposure consider both short-, intermediate- and long-term (chronic) exposure scenarios considering the toxic effects which would likely be seen for each exposure duration.

Methamidophos is a food use chemical. There are no residential uses of methamidophos; therefore, the considerations for aggregate exposure are those from food and water exposure. Additionally, since methamidophos is a metabolite of acephate, an aggregate risk assessment which determines the risk from methamidophos from application of acephate and application of methamidophos was conducted.

For **chronic aggregate risk (food),** chronic exposures to methamidophos from application of acephate and application of methamidophos were combined and compared to the methamidophos reference dose. This assessment was conducted using anticipated residues and BEAD % crop treated information. Results of the chronic exposure analysis show that 65% and 50% of the RfD is consumed for the U.S. population and non-nursing infants, respectively. The most significantly exposed subpopulation, children (1 to 6 years) occupied 106% of the RfD. The results indicate that for children, HED's level of concern are exceeded.

An **acute aggregate risk (food)** which considers methamidophos from application of acephate and methamidophos was not conducted since HED already has concerns for methamidophos from application of methamidophos alone. It is recommended that the registrant (s) conduct a Monte Carlo analysis which includes an aggregate assessment which take into

account methamidophos from application of acephate and methamidophos to address acute dietary concerns.

No **aggregate cancer risk** assessment is required because methamidophos is not a carcinogen.

An **aggregate exposure assessment which quantifies risk from food, water, and residential sources** was not conducted because there are no residential uses of methamidophos, and HED has concerns for acute and chronic aggregate exposure from food alone.

Cumulative Exposure To Substances with Common Mechanism of Toxicity.

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

Although at present the Agency does not know how to apply the information in its files concerning common mechanism issues to most risk assessments, there are pesticides as to which the common mechanism issues can be resolved. These pesticides include pesticides that are toxicologically dissimilar to existing chemical substances (in which case the Agency can conclude that it is unlikely that a pesticide shares a common mechanism of activity with other substances) and pesticides that produce a common toxic metabolite (in which case common mechanism of activity will be assumed).

EPA does not have, at this time, available data to determine whether methamidophos has a common mechanism of toxicity with other substances or how to include this pesticide in a

cumulative risk assessment. For the purposes of this reregistration eligibility decision, therefore, EPA has not assumed that methamidophos has a common mechanism of toxicity with other substances.

However, the Agency has determined that methamidophos is a metabolite of a registered pesticide, acephate. Therefore, methamidophos residues resulting from applications of both acephate and methamidophos will be considered in a cumulative risk assessment and compared to appropriate toxicological endpoints for methamidophos. This is described to some extent in the aggregate exposure section of this risk assessment document.

Endocrine Disruption

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

Determination of Safety for Infants and Children

FFDCA section 408 provides that EPA shall apply an additional tenfold margin of safety for infants and children in the case of threshold effects to account for pre-and post-natal toxicity and the completeness of the database unless EPA determines that a different margin of safety will be safe for infants and children. Margins of safety are incorporated into EPA risk assessments either directly through use of a MOE analysis or through using uncertainty (safety) factors in calculating a dose level that poses no appreciable risk to humans. EPA believes that reliable data support using the standard MOE and uncertainty factor (usually 100 for combined inter- and intra-species variability)) and not the additional tenfold MOE/uncertainty factor when EPA has a complete data base under existing guidelines and when the severity of the effect in infants or children or the potency or unusual toxic properties of a compound do not raise concerns regarding the adequacy of the standard MOE/safety factor.

Susceptibility issues: There was no indication of increased susceptibility of the offspring of rats or rabbits to pre- and or postnatal exposure to Methamidophos. In all studies examined, maternal or parental NOAELs were less than or equivalent to offspring NOAELs.

Uncertainty factor: The Committee determined that the **10 x** factor to account for enhanced sensitivity of infants and children (as required by FQPA) **should be reduce to 3 x** and is based on the following weight-of-the-evidence considerations:

1) Evidence of positive effects in the NTE assay in hens in Subchronic Toxicity Studies..

2)In studies from *open literature*, ingestion of Methamidaphos has been shown to result in delayed peripheral neuropathy in humans. Similarly, adult hens developed poly neuropathy but only after ingestion of doses 12-16 times the LD_{50}.

3) The HIARC recognized that the dose levels causing delayed neuropathy in humans are NOT well characterized. Exposures occurred at high doses through accidental occupational poisoning, suicide attempts or ingestion of contaminated vegetables.

4) Based on this evidence, a Developmental Neurotoxicity Study in Rats is **required**.

Table 5: Occupational Handlers' Short- and Intermediate-term Dermal, and Inhalation Exposures to Methamidophos at Baseline

Exposure Scenario (Scen.#)	Baseline Dermal Unit Exposure (mg/lb ai)[a]	Baseline Inhalation Unit Exposure (μg/lb ai)[b]	Maximum Application Rate (lb ai/acre)[c]	Amount Treated per Day (acres)[d]	Baseline Daily Dermal Exposure (mg/day)[e]	Baseline Daily Inhalation Exposure (mg/day)[f]
Mixer/Loader Exposure						
Mixing/Loading of Liquid Formulation for Aerial Application and Chemigation (potatoes only) (1a)	2.9	1.2	1.0	350	1,000	0.42
Mixing/Loading of Liquid Formulation for Groundboom Applications (1b)	2.9	1.2	1.0	80	230	0.096
Applicator Exposure						
Applying Sprays with a Fixed-Wing Aircraft (2)	Not Feasible (see engineering controls)	Not Feasible (see engineering controls)	1.0	350	--	--
Applying Sprays with a Helicopter (3)	Not Feasible (see engineering controls)	Not Feasible (see engineering controls)	1.0	350	--	--
Applying Sprays with Groundboom Equipment (4)	0.014	0.74	1.0	80	1.1	0.059
Flagger Exposure						
Flagging Aerial Spray Applications (5)	0.011	0.35	1.0	350	3.9	0.12

[a] Baseline dermal unit exposure represents long pants, long sleeved shirt, no gloves, open mixing/loading, open cab tractor for groundboom applications, and open flagging.
[b] Baseline inhalation unit exposure represents no respirator.
[c] Maximum application rates are values found in Bayer and Valent Monitor 4 labels. The formulations are 4 pounds active ingredient per gallon of formulation, based on the labels.
[d] Amounts of acreage treated per day are from the HED estimates of acreage that could be treated in a single day for each exposure scenario of concern.
[e] Daily Dermal Exposure (mg/day) = Dermal Unit Exposure (mg/lb ai) * Maximum Application Rate (lb ai/acre) * Amount Treated per Day (acres/day).
[f] Daily Inhalation Exposure (mg/day) = [Inhalation Unit exposure (μg/lb ai)/1,000 μg/mg conversion] * Maximum Application Rate (lb ai/acre) * Amount Treated per Day (acres/day).

Table 6: Occupational Handler Short- and Intermediate-term Dermal and Inhalation Risks from Methamidophos at Baseline					
Exposure Scenario (Scen.#)	Baseline Short- and Intermediate Daily Dermal Dose (mg/kg/day)[a]	Baseline Daily Inhalation Dose (mg/kg/day)[b]	Baseline Short- and Intermediate-term Dermal MOE[c]	Baseline Inhalation MOE[d]	Baseline Short- and Intermediate-term Dermal + Inhalation Total MOE[e]
Mixer/Loader Exposure					
Mixing/Loading of Liquid Formulation for Aerial Application and Chemigation (potatoes only), (1a)	14	0.0060	0.07	45	< 1
Mixing/Loading of Liquid Formulation for Groundboom Applications (1b)	3.3	0.0014	0.3	190	< 1
Applicator Exposure					
Applying Sprays with a Fixed-Wing Aircraft (2)	Not Feasible (see engineering controls)	--	--	--	--
Applying Sprays with a Helicopter (3)	Not Feasible (see engineering controls)	--	--	--	--
Applying Sprays with Groundboom Equipment (4)	0.016	0.00084	63	320	53
Flagging Exposure					
Flagging Aerial Spray Applications (5)	0.056	0.0017	18	160	16

[a] Baseline Daily Dermal Dose (mg/kg/day) = [Daily Dermal Exposure (mg/day) from Table 5] / Body Weight (70 kg)].

[b] Baseline Daily Inhalation Dose (mg/kg/day) = [Daily Inhalation Exposure (mg/day) from Table 5] / Body Weight (70 kg)].

[c] Dermal MOE = NOAEL (1.0 mg/kg/day) / Daily Dermal Dose (mg/kg/day).

[d] Inhalation MOE = NOAEL (0.27 mg/kg/day) / Daily Inhalation Dose (mg/kg/day).

[e]

Total MOE: $\dfrac{1}{\frac{1}{MOE_{Inhalation}} + \frac{1}{MOE_{Dermal}}}$

Table 7: Occupational Handler Short- and Intermediate-term Dermal, and Inhalation Exposures to Methamidophos with PPE

Exposure Scenario (Scen.#)	PPE Dermal Unit Exposure (mg/lb ai)[a]	PPE Inhalation Unit Exposure (μg/lb ai)[a]	Maximum Application Rate (lb ai/acre)[b]	Amount Treated per Day (acres)[c]	PPE Daily Dermal Exposure (mg/day)[d]	PPE Daily Inhalation Exposure (mg/day)[e]
Mixer/Loader Exposure						
Mixing/Loading of Liquid Formulation for Aerial Application and Chemigation (potatoes only) (1a)	0.017	0.12	1.0	350	6.0	0.042
Mixing/Loading of Liquid Formulation for Groundboom Applications (1b)	0.017	0.12	1.0	80	1.4	0.0096
Applicator Exposure						
Applying Sprays with a Fixed-Wing Aircraft (2)	No Data (see engineering controls)	No Data (see engineering controls)	1.0	350	--	--
Applying Sprays with a Helicopter (3)	No Data (see engineering controls)	No Data (see engineering controls)	1.0	350	--	--
Applying Sprays with Groundboom Equipment (4)	0.011	0.074	1.0	80	0.88	0.0059
Flagger Exposure						
Flagging Aerial Spray Applications (5)	0.010	0.035	1.0	350	3.5	0.012

[a] PPE: Scenario 1a and 1b - open mixing/loading, double layer of clothing, chemical resistant gloves (dermal), and an organic vapor removing respirator (inhalation) (i.e., 90% protection factor); Scenario 2 and 3 - no PPE data available; Scenario 4 - open cab, double layer clothing, chemical resistant gloves (dermal), and organic vapor removing respirator (inhalation) (i.e., 90% protection factor); Scenario 5 - double layer of clothing, no gloves, and organic vapor removing respirator (inhalation) (i.e., 90% protection factor.

[b] Maximum application rates are values found in Bayer and Valent Monitor 4 labels. The formulations are 4 pounds active ingredient per gallon of formulation, based on the labels.

[c] Amounts of acreage treated per day are from the HED estimates of acreage that could be treated in a single day for each exposure scenario of concern.

[d] Daily Dermal Exposure (mg/day) = Dermal Unit Exposure (mg/lb ai) * Maximum Application Rate (lb ai/acre) * Amount Treated per Day (acres/day).

[e] Daily Inhalation Exposure (mg/day) = [Inhalation Unit exposure (μg/lb ai)/1,000 μg/mg conversion] * Maximum Application Rate (lb ai/acre) * Amount Treated per Day (acres/day).

Table 8: Occupational Handler Short- and Intermediate-term Dermal and Inhalation Risks from Methamidophos with PPE					
Exposure Scenario (Scen.#)	PPE Short- and Intermediate Daily Dermal Dose (mg/kg/day)[a]	PPE Daily Inhalation Dose (mg/kg/day)[b]	PPE Short- and Intermediate-term Dermal MOE[c]	PPE Inhalation MOE[d]	PPE Short- and Intermediate-term Dermal + Inhalation Total MOE[e]
Mixer/Loader Exposure					
Mixing/Loading of Liquid Formulation for Aerial Application and Chemigation (potatoes only), (1a)	0.086	0.00060	12	450	12
Mixing/Loading of Liquid Formulation for Groundboom Applications (1b)	0.020	0.00014	50	1900	49
Applicator Exposure					
Applying Sprays with a Fixed-Wing Aircraft (2)	--	--	--	--	--
Applying Sprays with a Helicopter (3)	--	--	--	--	--
Applying Sprays with Groundboom Equipment (4)	0.013	0.000084	77	3200	75
Flagging Exposure					
Flagging Aerial Spray Applications (5)	0.050	0.00017	20	1600	20

[a] PPE Daily Dermal Dose (mg/kg/day) = [Daily Dermal Exposure (mg/day) from Table 5] / Body Weight (70 kg)].
[b] PPE Daily Inhalation Dose (mg/kg/day) = [Daily Inhalation Exposure (mg/day) from Table 5] / Body Weight (70 kg)].
[c] Dermal MOE = NOAEL (1.0 mg/kg/day) / Daily Dermal Dose (mg/kg/day).
[d] Inhalation MOE = NOAEL (0.27 mg/kg/day) / Daily Inhalation Dose (mg/kg/day).
[e]

Total MOE: $$\frac{1}{\frac{1}{MOE_{Inhalation}} + \frac{1}{MOE_{Dermal}}}$$

Table 9: Occupational Handler Short- and Intermediate-term Dermal, and Inhalation Exposures to Methamidophos with Engineering Controls

Exposure Scenario (Scen.#)	Engineering Controls Dermal Unit Exposure (mg/lb ai)[a]	Engineering Controls Inhalation Unit Exposure (μg/lb ai)	Maximum Application Rate (lb ai/acre)[b]	Amount Treated per Day (acres)[c]	Engineering Controls Daily Dermal Exposure (mg/day)[d]	Engineering Controls Daily Inhalation Exposure (mg/day)[e]
Mixer/Loader Exposure						
Mixing/Loading of Liquid Formulation for Aerial Application and Chemigation (potatoes only) (1a)	0.0086	0.083	1.0	350	3.0	0.029
Mixing/Loading of Liquid Formulation for Groundboom Applications (1b)	0.0086	0.083	1.0	80	0.69	0.0066
Applicator Exposure						
Applying Sprays with a Fixed-Wing Aircraft (2)	0.0050	0.068	1.0	350	1.8	0.024
Applying Sprays with a Helicopter (3)	0.0019	0.0018	1.0	350	0.67	0.00063
Applying Sprays with Groundboom Equipment (4)	0.0050	0.043	1.0	80	0.040	0.0034
Flagger Exposure						
Flagging Aerial Spray Applications (5)	0.0011	0.035	1.0	350	0.39	0.012

[a] Daily Dermal Eng. Control Dose (mg/kg/day) = [Eng. Control Dermal Unit Exposure (mg/lb ai) * Maximum Application Rate (lb ai/acre) * Amount Treated per Day (acres/day)] / [Body Weight (70 kg)].
[b] Maximum application rates are values found in Bayer and Valent Monitor 4 labels. The formulations are 4 pounds active ingredient per gallon of formulation, based on the labels.
[c] Amounts of acreage treated per day are from the HED estimates of acreage that could be treated in a single day for each exposure scenario of concern.
[d] Daily Dermal Exposure (mg/day) = Dermal Unit Exposure (mg/lb ai) * Maximum Application Rate (lb ai/acre) * Amount Treated per Day (acres/day).
[e] Daily Inhalation Exposure (mg/day) = [Inhalation Unit exposure (μg/lb ai)/1,000 μg/mg conversion] * Maximum Application Rate (lb ai/acre) * Amount Treated per Day (acres/day).

Table 10: Occupational Handler Short- and Intermediate-term Dermal and Inhalation Risks from Methamidophos with Engineering Controls					
Exposure Scenario (Scen.#)	Engineering Controls Short- and Intermediate Daily Dermal Dose (mg/kg/day)[a]	Engineering Controls Daily Inhalation Dose (mg/kg/day)[b]	Engineering Controls Short- and Intermediate-term Dermal MOE[c]	Engineering Controls Inhalation MOE[d]	Engineering Controls Short- and Intermediate-term Dermal + Inhalation Total MOE[e]
Mixer/Loader Exposure					
Mixing/Loading of Liquid Formulation for Aerial Application and Chemigation (potatoes only), (1a)	0.043	0.00041	23	660	22
Mixing/Loading of Liquid Formulation for Groundboom Applications (1b)	0.0099	0.000094	101	2900	98
Applicator Exposure					
Applying Sprays with a Fixed-Wing Aircraft (2)	0.026	0.00034	38	790	36
Applying Sprays with a Helicopter (3)	0.0096	9.0E-6	104	30,000	104
Applying Sprays with Groundboom Equipment (4)	0.0057	0.000049	175	5500	170
Flagging Exposure					
Flagging Aerial Spray Applications (5)	0.0055	0.000175	181	1543	162

[a] Eng. Controls Daily Dermal Dose (mg/kg/day) = [Daily Dermal Exposure (mg/day) from Table 5] / Body Weight (70 kg)].
[b] Eng. Controls Daily Inhalation Dose (mg/kg/day) = [Daily Inhalation Exposure (mg/day) from Table 5] / Body Weight (70 kg)].
[c] Dermal MOE = NOAEL (1.0 mg/kg/day) / Daily Dermal Dose (mg/kg/day).
[d] Inhalation MOE = NOAEL (0.27 mg/kg/day) / Daily Inhalation Dose (mg/kg/day).
[e]

$$\text{Total MOE: } \frac{1}{\frac{1}{MOE_{Inhalation}} + \frac{1}{MOE_{Dermal}}}$$

Table 11: Exposure Scenario Descriptions for the Use of Methamidophos

Exposure Scenario (Number)	Data Source	Standard Assumptions[a] (8-hr work day)	Comments[b]
		Mixer/Loader Descriptors	
Mixing/Loading of Liquid Formulation for Aerial Application and Chemigation (i.e., sprinkler irrigation; (1a)	PHED V1.1	350 acres.	**Baseline:** Hands, dermal, and inhalation - acceptable grades. Hands = 53 replicates; dermal = 25 to 122 replicates; inhalation = 85 replicates. High confidence in hands, dermal, and inhalation data. Single layer, no gloves for dermal. **PPE:** Hands, dermal, and inhalation - acceptable grades. Hands = 59 replicates; dermal = 25 to 122 replicates; inhalation = 85 replicates. High confidence in hands, dermal, and inhalation data. Maximum PPE values calculated from PHED data using a 50% protection factor for the addition of coveralls; a 90% protection factor was used for inhalation PPE. Double layer, gloves for dermal. **Engineering Controls (closed mixing)** Hands, dermal, and inhalation - acceptable grades. Hands = 31 replicates; dermal = 16 to 22 replicates; inhalation = 27 replicates. High confidence in hands, dermal, and inhalation data. Single layer, gloves for dermal.
Mixing/Loading of Liquid Formulation for Groundboom Applications (1b)	PHED V1.1	80 acres.	**Baseline:** Hands, dermal, and inhalation acceptable grades. Hands = 53 replicates; dermal = 25 to 122 replicates; inhalation = 85 replicates. High confidence in hands, dermal, and inhalation data. Single layer, no gloves for dermal. **PPE:** Hands, dermal, and inhalation acceptable grades. Hands = 59 replicates; dermal = 25 to 122 replicates; inhalation = 85 replicates. High confidence in hands, dermal, and inhalation data. Inhalation acceptable grades; 85 replicates; high confidence in data. Maximum PPE values calculated from PHED data using a 50% protection factor for the addition of coveralls; a 90% protection factor was used for inhalation PPE. Double layer, gloves for dermal. **Engineering Controls (closed mixing)**: Hands dermal and inhalation - acceptable grades. Hands = 31 replicates; dermal =16 to 22 replicates; inhalation = 27 replicates. High confidence in hands, dermal and inhalation data. Single layer, gloves for dermal.
		Applicator Descriptors	
Applying Sprays with a Fixed-Wing Aircraft (2)	PHED V1.1	350 acres.	**Baseline:** Not Feasible **PPE:** Not Feasible **Engineering Controls (enclosed cockpit):** "Best Available" grades: Hands = acceptable grades; dermal and inhalation = ABC grades. Hands = 34 replicates; dermal = 24 to 48 replicates; inhalation = 23 replicates. Medium confidence in hands, dermal and inhalation data. Single layer, no gloves for dermal.
Applying Sprays with Helicopter (3)	PHED V1.1	350 acres.	**Baseline:** Not Feasible **PPE:** Not Feasible **Engineering Controls (closed cockpit):** Hands and dermal = ABC grades; inhalation = acceptable grades. Hands = 2 replicates; dermal = 3 replicates; inhalation = 3 replicates. Extremely low confidence in hands, dermal and inhalation data. Single layer, no gloves for dermal.

Table 11: Exposure Scenario Descriptions for the Use of Methamidophos

Exposure Scenario (Number)	Data Source	Standard Assumptions[a] (8-hr work day)	Comments[b]
Applying Sprays with Groundboom Equipment (4)	PHED V1.1	80 acres.	**Baseline:** Hands, dermal, and inhalation = acceptable grades. Hands = 29 replicates; dermal = 32 to 42 replicates; inhalation = 22 replicates. High confidence in hands, dermal and inhalation data. Single layer, no gloves for dermal. **PPE:** Hands = ABC grades; dermal, and inhalation = acceptable grades. Hands = 21 replicates; dermal = 32 to 42 replicates; inhalation = 22 replicates. High confidence in hands, dermal and inhalation data. Maximum PPE values calculated from PHED data using a 50% protection factor for the addition of coveralls; a 90% protection factor was used for inhalation PPE. Double layer, no gloves for dermal. **Engineering Controls (closed cab):** Hands = ABC grades; dermal = ABC grades; inhalation = acceptable grades. Hands = 16 replicates; dermal = 20 to 31 replicates; inhalation = 16 replicates. Medium confidence in hands and dermal; high confidence in inhalation. Single layer, no gloves for dermal.
		Flagger Descriptors	
Flagging Aerial Spray Applications (5)	PHED V1.1	350 acres.	**Baseline:** Hands, dermal, and inhalation = acceptable grades. Hands = 16 replicates; dermal = 16 to 18 replicates; inhalation =18 replicates. High confidence in hands, dermal and inhalation data. Single layer, no gloves for dermal. **PPE:** Hands, dermal, and inhalation = acceptable grades. Hands = 16 replicates; dermal = 16 to 18 replicates; inhalation = 18 replicates. High confidence in hands, dermal, and inhalation data. Maximum PPE values calculated from PHED data using a 50% protection factor (PF) on non-hand dermal data to simulate the use of coveralls (doulble layer) and a 90% PF on inhalation data to simulate the use of a respirator. No gloves for dermal. **Engineering Controls:** The same data are used as for baseline using a 90% PF on dermal data and a 90% PF on inhalation data to simulate the use of a closed cab.

[a] Standard Assumptions based on an 8-hour work day as estimated by HED. BEAD data were not available.

[b] These grades are based on Quality Assurance/Quality Control data provided as part of the exposure studies. A replicate refers to data acquired during one complete work cycle. All handler exposure assessments in this document are based on the "Best Available" data as defined by HED SOP for meeting Subdivision U Guidelines (i.e., completing exposure assessments.) Best available grades are assigned as follows: matrices with grades A and B data (which is defined as acceptable grade data) and a minimum of 15 replicates; if not available, then grades A, B, and C data and a minimum of 15 replicates; if not available, then all data (all grades) regardless of the quality and number of replicates. High quality data with a protection factor take precedence over low quality data with no protection.

Data confidence as reported in the Table refers to both the quality and the quantity (number of replicates) of data for each PHED run. Each study in PHED has been graded from A to E. A high confidence run is grades A and B data and 15 or more replicates per body part. Any combination of A and B grade data are listed as acceptable grades data in the tables. A medium confidence run is grades A, B, and C data and 15 or more replicates per body part. Any combination of A, B, and C grade data are listed as ABC grade data in the tables. A low confidence run is all grades (any run that includes D or E grade data) or has less than 15 replicates per body part.

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