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MEMORANDUM

SUBJECT: **CHLORETHOXYFOS. Revised Preliminary Risk Assessment**
Chemical Number 129006. DP Barcode D257108.

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Attached please find the revised preliminary risk assessment for chlorethoxyfos. This document contains revisions made in response to comments received during the 60-day public comment period for the preliminary risk assessment.

REVISED PRELIMINARY RISK ASSESSMENT

CHLORETHOXYFOS

June 22, 1999

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency

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Executive Summary

A revised preliminary risk assessment for the chlorethoxyfos reregistration eligibility decision (RED) is presented. Based on this preliminary assessment, acute and chronic dietary (food only) risk estimates do not exceed HED's level of concern. Tier 2 (PRZM-EXAMS) surface water and ground water (SCI-GROW) estimated environmental concentrations (EECs) do not exceed HED drinking water levels of comparison (DWLOC) for both acute and chronic aggregate dietary exposure. Thus, aggregate acute and aggregate chronic risk estimates do not exceed HED's level of concern. Occupational risk estimates do not exceed HED's level of concern. Currently, there are no registered uses for chlorethoxyfos that could result in residential exposures.

Chlorethoxyfos (O,O-diethyl-O-(1,2,2,2-tetrachloroethyl)phosphorothioate) is an organophosphate insecticide registered for the control of corn rootworms, wireworms, cutworms, seed corn maggot, white grubs and symphylans on corn. Chlorethoxyfos has no other registered uses (i.e., there are no registered uses that could result in residential exposures).

E.I du Pont Nemours and Company, Inc, has registrations for the active ingredient chlorethoxyfos technical 86% (352-553) and the formulated granular products Fortress® 5G (352-552) and Fortress® 2.5G (352-579). Applications are made with ground equipment in a band over the row or in the furrow at planting. Use is limited to only one application per year, at a maximal rate of 0.1625 lb ai/A. Fortress® 5G will only be available in a SmartBox™, which is a completely enclosed, tamper-proof delivery system.

HAZARD

The toxicology data base provides overwhelming evidence confirming that chlorethoxyfos, like other organophosphates, has anticholinesterase activity in all species tested, including dogs, rabbits, rats, mice, and hens. When the toxicological database for chlorethoxyfos is examined in its entirety, it can be seen that chlorethoxyfos is a potent, highly toxic organophosphate with a steep dose response curve. Females generally appear to be more sensitive than males. In some animal studies, treatment-related death was observed without accompanying clinical signs or without obvious outward signs of organophosphate toxicity.

Chlorethoxyfos technical is placed in Toxicity Category I for acute oral, dermal, inhalation, and primary eye and dermal irritation potential. Mortality was observed both in the primary eye irritation and primary skin irritation studies at low doses. In an acute neurotoxicity study, a single oral administration to rats resulted in cholinergic signs and inhibition of cholinesterase activity in both sexes at the lowest dose tested but no neuropathology. There was no evidence of organophosphate induced delayed neurotoxicity (OPIDN) in hens given single oral doses of chlorethoxyfos. The requirement for a subchronic neurotoxicity study in rats was waived since several other toxicity studies in the database provided adequate evidence for the absence of neuropathology.

In subchronic and chronic studies conducted with mice, rats and dogs, systemic toxicity was manifested as mortality, cholinergic signs (tremors), inhibition of plasma, red blood cell and/or brain cholinesterase activity and decreases in body weight and/or body weight gains. In a six month feeding study in dogs conducted to assess the ocular toxicity potential of chlorethoxyfos, no treatment-related abnormalities were found by histopathology or in most of the techniques used to assess visual system structure and function. In a repeated exposure inhalation toxicity study, statistically significant depression in plasma, RBC and brain cholinesterase activity was seen in female rats following a 7-day exposure period.

Chlorethoxyfos was non-mutagenic both *in vivo* and *in vitro*. Chlorethoxyfos is classified as a Group D chemical; not classifiable as to human carcinogenicity based on the lack of evidence of carcinogenic potential in mice and rats. There was no evidence of increased susceptibility following *in utero* exposures to rats and rabbits. Also, following pre/post natal exposure to rats there was no evidence of abnormalities in the development of the fetal nervous system in these studies.

The inhibition of cholinesterase activity was the toxicity endpoint selected for acute and chronic dietary (oral) as well as short- and intermediate-term (dermal and inhalation) risk assessments. An Uncertainty Factor (UF) of 100 was applied to the dose selected for risk assessment to account for inter-species variation (10x) and intra-species extrapolation (10x). The additional 10x factor for the protection of infants and children as required by the Food Quality Protection Act (FQPA) of 1996 was removed based on the: 1) completeness of the toxicology database; 2) lack of increased susceptibility in developmental and reproductive toxicity studies; 3) use of adequate data (actual, surrogate, and/or modeling outputs) to satisfactorily assess dietary exposure as well as screening level drinking water exposure assessment; and 4) lack of uses that could result in residential exposures. As per current OPP policy, an RfD modified by an FQPA safety factor is referred to as a Population Adjusted Dose (PAD). Because the FQPA safety factor was removed, the acute and chronic RfD is equal to the acute and chronic PAD. Therefore, in this document risk estimates will be expressed in terms of percent of RfD occupied.

EXPOSURE AND RISK ASSESSMENTS

Exposure and risk assessments were conducted for chlorethoxyfos for the following exposure routes and durations: acute dietary, chronic dietary, occupational short- and intermediate-term dermal, and short- and intermediate-term inhalation. Because there is just a single early application of chlorethoxyfos, long term dermal or inhalation exposures are not anticipated. The acute and chronic dietary assessments capture exposure estimates for the general public. The latter assessments are for occupational exposures. The different risk assessments were conducted separately based on different hazards identified as toxicological endpoints.

Risk estimates are expressed either as a percentage of the RfD (for dietary risk estimates) or as a margin of exposure (MOE). The percent of the RfD occupied is the exposure (mg/kg/day)

divided by the RfD (mg/kg/day), multiplied by 100.

$$\%RfD = \frac{\text{exposure (mg/kg/day)} \times 100}{RfD \text{ (mg/kg/day)}}$$

The MOE is the NOAEL (mg/kg/day) divided by the exposure (mg/kg/day).

$$MOE = \frac{NOAEL \text{ (mg/kg/day)}}{Exposure \text{ (mg/kg/day)}}$$

For purposes of this risk assessment, risk estimates greater than 100% of the RfD and MOEs less than 100 exceed HED's level of concern.

Acute Aggregate Exposure and Risk Estimate

Acute aggregate exposure and risk estimates do not exceed HED's level of concern. The acute aggregate risk assessment considers both acute food and water exposure.

Acute dietary (food) risk estimates for chlorethoxyfos do not exceed HED's level of concern. For the acute dietary risk assessment, the toxic endpoint selected was the no observed adverse effect level (NOAEL) of 0.06 mg/kg/day based on plasma cholinesterase inhibition at a lowest observed adverse effect level (LOAEL) of 0.6 mg/kg/day observed on day 3 of a six month ocular toxicity in dogs study (feeding study). An uncertainty factor of 100 was applied to the NOAEL to calculate the acute RfD (0.0006 mg/kg/day). A probabilistic acute dietary exposure analysis was conducted. For the US population and all other population subgroups, at the 99.9th percentile exposure, 2% or less of the acute RfD was occupied. The acute dietary exposure analysis was conducted for chlorethoxyfos using anticipated residues derived from field trials and percent of crop treated information (supplied by BEAD). HED notes that no detectable residues of chlorethoxyfos were found in any of the corn residue field trials.

The acute drinking water level of comparison (DWLOC) for chlorethoxyfos is 6 ppb for children 1-6 years old, 18 ppb for adult females, and 21 ppb for adult males. The acute (day 0) PRZM-EXAMS estimated environmental concentration (EEC) for chlorethoxyfos in surface water is 0.4 ppb. For ground water, the SCI-GROW EEC is 0.002 ppb. These levels do not exceed the acute DWLOC, therefore HED concludes that aggregate acute risk estimates do not exceed the level of concern.

Chronic Aggregate Exposure and Risk Estimates

Chronic aggregate exposure and risk estimates do not exceed HED's level of concern. The chronic aggregate risk assessment considers both chronic food and water exposure.

Chronic dietary (food) risk estimates for chlorethoxyfos do not exceed HED's level of concern. For the chronic dietary risk assessment, the toxic endpoint selected was the no

observed adverse effect level (NOAEL) of 0.06 mg/kg/day based on plasma cholinesterase inhibition at a lowest observed adverse effect level (LOAEL) of 0.6 mg/kg/day observed in the 1-year chronic feeding study in dogs, the 90-day feeding study in dogs, and the six month ocular toxicity in dogs study (feeding study). An uncertainty factor of 100 was applied to the NOAEL to calculate the chronic RfD (0.006 mg/kg/day). For the US population and all population subgroups, less than 0.1% of the chronic RfD was occupied. The chronic dietary (food) exposure analysis was conducted for chlorethoxyfos assuming tolerance level residues and percent of crop treated information. HED again notes that no detectable residues of chlorethoxyfos were found in any of the corn residue field trials.

The chronic DWLOC is 6 ppb for children 1-6 years old, 18 ppb for adult females, and 21 ppb for adult males. The chronic (60-day) PRZM-EXAMS estimated environmental concentration (EEC) for chlorethoxyfos in surface water is 0.08 ppb. For ground water, the SCI-GROW EEC is 0.002 ppb. These levels do not exceed the chronic DWLOC, therefore HED concludes that aggregate chronic risk estimates do not exceed the level of concern.

Short- and Intermediate-Term Aggregate Exposure and Risk Estimate

There are no registered uses for chlorethoxyfos that could result in residential exposures at the present time. Therefore, a short and intermediate-term aggregate risk assessment for the general public is not required.

Occupational Exposure and Risk Estimates

Loader/Applicator

Short- and intermediate-term dermal and inhalation risk estimates do not exceed HED's level of concern. Combined loader and applicator MOEs (dermal + inhalation) range from 320 to 1,800.

Short and intermediate-term dermal and inhalation risk assessments were conducted for occupationally exposed individuals. The short- and intermediate-term dermal toxicity endpoint is the NOAEL of 1.25 mg/kg/day obtained from a 21-day dermal toxicity study in rats, with an LOAEL of 3.75 mg/kg/day based on red blood cell (RBC) cholinesterase inhibition. The short-term inhalation toxicity endpoint is the NOAEL of 0.000508 mg/L (0.13 mg/kg/day) obtained from a 7-day inhalation toxicity study in rats, with the LOAEL of 0.001924 mg/L (0.50 mg/kg/day) based on plasma, RBC, and brain ChEI. The intermediate-term inhalation endpoint is based on the same study as the chronic dietary endpoint (i.e., NOAEL of 0.06 mg/kg/day for cholinesterase inhibition).

HED's worker exposure estimates are based on chemical specific studies (MRID# 425592-22 (2.5G), and MRID# 443998-02 (for 5G)); which monitored the chlorethoxyfos exposure of loaders and applicators who were operating an open-cab tractor for Fortress® 2.5G and, an enclosed-cab tractor for Fortress® 5G while applying chlorethoxyfos at the maximum

label rate. The combined loader and applicator total dermal and inhalation risk estimates for both products do not exceed HED's level of concern.

Post-Application Exposure

Minimal post-application exposure is anticipated during activities such as scouting or harvesting, as chlorethoxyfos is incorporated into the soil, is not water soluble, degrades readily, is not systemic in the plant, and harvesting of corn is primarily mechanical in nature.

I. Hazard Assessment

A. Toxicology Assessment

The toxicology database for chlorethoxyfos is complete. The toxicology profile is presented in Table 1. Chlorethoxyfos is acutely toxic via the oral, dermal and inhalation routes of exposure, is too toxic to test for eye and skin irritation, and is not a dermal sensitizer. It did not induce OPIDN in hens nor neuropathology in rats following a single oral doses. The principal toxicological effects in mice, rats, and dogs following subchronic and chronic oral (dietary) exposure was inhibition of plasma, red blood cell and/or brain cholinesterase activity. In a study that examined the ocular toxicity potential, there was no treatment-related histopathology or abnormalities in most of the techniques used to assess visual system structure and function. Repeated dermal applications for 21-days resulted in inhibition of plasma, erythrocyte and brain cholinesterase activity. There was no evidence of carcinogenicity in mice and rats when tested at doses that were judged to be adequate to assess carcinogenicity. Chlorethoxyfos was non mutagenic both *in vivo* and *in vitro*. Chlorethoxyfos is classified as a Group D chemical; not classifiable as to human carcinogenicity based on the lack of carcinogenic potential which is supported by the lack of mutagenic activity. There was no evidence of increased susceptibility of rat or rabbit fetuses following *in utero* exposure in prenatal developmental toxicity studies, no offspring toxicity was seen at the highest dose tested in the two-generation reproduction toxicity study, and there was no evidence of abnormalities in the development of the fetal nervous system in these studies.

Table 1. Toxicity Profile of Chlorethoxyfos

Study Type	MRID No.	Results	Toxicity Category
Acute Oral	40883711	LD ₅₀ = 4.8 mg/kg (Males) 1.8 mg/kg (Females)	I
Acute Dermal	40883715	LD ₅₀ = 18.5 mg/kg (Males) 12.5 mg/kg (Females)	I
Acute Inhalation	40883716	LC ₅₀ ≥ 0.008 mg/L	I

Primary Eye Irritation	40883717	0.1 mL too toxic; 0.05 mL caused deaths within 4 hrs.	I
Primary Skin Irritation	40883718	0.5 mL too toxic to test	I
Dermal Sensitization	40883719	Non-sensitizing	NA
Acute Delayed Neurotoxicity	40898702	Negative for OPIDN	NA
Acute Neurotoxicity	44234601	LOAEL (ChE Inhibition) = 0.75 mg/kg/day (M) LOAEL (ChE Inhibition) = 0.25 mg/kg/day (F) No neuropathology	NA

Study Type	MRID No.	Results
7-Day - Inhalation Toxicity-Rat	44382101	NOAEL (ChE Inhibition)= 0.000508 mg/L (0.13 mg/kg/d) LOAEL (ChE Inhibition) = 0.001924 mg/L (0.5 mg/kg/d)
21-Day Dermal Toxicity-Rat	44399801	NOAEL (ChE Inhibition) = 1.25 mg/kg/day LOAEL (ChE Inhibition) = 3.75 mg/kg/day
Subchronic-Feeding-Mouse	41290629	NOAEL (systemic) = 8.89 mg/kg/day LOAEL (systemic) = >8.89 mg/kg/day (HDT) NOAEL (ChE Inhibition)= Not established. LOAEL (ChE Inhibition)= 2.19 mg/kg/day (LDT)
Subchronic-Feeding-Rat	41290627	NOAEL (systemic) = 0.357 mg/kg/day LOAEL (systemic) = 0.784 mg/kg/day NOAEL (ChE Inhibition)=0.093 mg/kg/day LOAEL (ChE Inhibition)= 0.472 mg/kg/day
Subchronic-Feeding-Rat	42559215	NOAEL (systemic) = 0.635 mg/kg/day LOAEL (systemic) = 1.23 mg/kg/day NOAEL (ChE Inhibition)=0.080 mg/kg/day LOAEL (ChE Inhibition)= 0.635 mg/kg/day
Subchronic-Feeding-Dog	40898703 40898704	NOAEL (systemic) = 0.185 mg/kg/day LOAEL (systemic) = 1.820 mg/kg/day NOAEL (ChE Inhibition)=0.017 mg/kg/day LOAEL (ChE Inhibition)= 0.185 mg/kg/day
Six Month-Feeding-Dog	42559221	NOAEL (systemic) = 0.061 mg/kg/day LOAEL (systemic) = 0.578 mg/kg/day NOAEL (ChE Inhibition) = Not established LOAEL (ChE Inhibition) = 0.061 mg/kg/day
Chronic-Feeding-Dog	41736833	NOAEL (systemic) = 0.616 mg/kg/day LOAEL (systemic) = 2.24 mg/kg/day NOAEL (ChE Inhibition)=0.063 mg/kg/day LOAEL (ChE Inhibition)= 0.616 mg/kg/day

Study Type	MRID No.	Results
Chronic toxicity/Carcinogenicity-Rat	41736837	NOAEL (systemic) = 0.311 mg/kg/day LOAEL (systemic) = >0.311 mg/kg/day (HDT) NOAEL (ChE Inhibition)=0.154 mg/kg/day LOAEL (ChE Inhibition)= 0.311 mg/kg/day No evidence of carcinogenicity
Carcinogenicity-Mouse		NOAEL (systemic) = 3.25 mg/kg/day LOAEL (systemic) = 14.9 mg/kg/day No evidence of carcinogenicity
Developmental Toxicity-Rat	40898705	Maternal NOAEL = 0.25 mg/kg/day LOAEL = 0.50 mg/kg/day Developmental NOAEL = 0.25 mg/kg/day LOAEL = 0.50 mg/kg/day
Developmental Toxicity-Rabbit	41290633 42559219	Maternal NOAEL = 0.76 mg/kg/day LOAEL = 1.38 mg/kg/day Developmental NOAEL = 1.38 mg/kg/day LOAEL = 2.1 mg/kg/day
Reproductive Toxicity	41736836	Parental/Systemic NOAEL = 0.296 mg/kg/day LOAEL = 0.607 mg/kg/day Offspring NOAEL = 0.607 mg/kg/day (HDT) LOAEL >0.607 mg/kg/day (HDT)
Gene Mutation - <i>Salmonella</i>	40883726	Non-mutagenic (±)activation.
Gene Mutation - HGPRT	40883727	Non-mutagenic (±)activation.
Mouse Lymphoma	40883728	Non-mutagenic (±)activation.
Micronucleus Assay	40883729	Non-mutagenic (±)activation.
DNA Repair Assay	40883730	Non-mutagenic (±)activation.
CHO Assay	40883731	Non-mutagenic (±)activation.
Metabolism-Rat	42559220 41290635	Greater than 95% of the administered radioactivity was recovered by 7 days post-dosing. Radioactivity eliminated in the urine (60-66%), feces (13-26%), expired air (11%) and tissues/ carcass (5-6%). Trichloroacetic acid, dichloroacetic acid, trichloroethanol and trichloroethanol's glucuronide conjugates (the major urinary metabolite) detected in the urine and feces. Unchanged parent was the major fecal metabolite in females, but was not detected in males.

B. Dose Response Assessment

1. Determination of Susceptibility

The Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base and concluded that: 1) the toxicology data base is complete; 2) neurotoxicity studies did not show evidence of OPIDN in hens, neuropathology was not seen either in the acute neurotoxicity study with rats or in the other toxicity studies, and there was no evidence of abnormalities in the development of the fetal nervous system in the pre/post natal studies; 3) there was no evidence of increased susceptibility in the prenatal developmental toxicity studies in rats and rabbits and in the two-generation reproduction study in rats; and 4) the weight-of-the evidence did not indicate the need for a developmental neurotoxicity study in rats.

The FQPA Safety Factor Committee evaluated the hazard and exposure data of chlorethoxyfos and determined that the **FQPA safety factor** for the protection of infants and children should be **removed** based on the following factors:

- i. In prenatal developmental toxicity studies following *in utero* exposure in rats and rabbits, there was no evidence of developmental effects being produced in fetuses at lower doses as compared to maternal animals nor was there evidence of an increase in severity of effects at or below maternally toxic doses.
- ii. In the pre/post natal two-generation reproduction study in rats, there was no evidence of enhanced susceptibility in pups when compared to adults (i.e., effects noted in offspring occurred at maternally toxic doses or higher).
- iii. Adequate actual data, surrogate data, and/or modeling outputs are available to satisfactorily assess dietary and residential exposure and to provide a screening level drinking water exposure assessment.

2. Toxicology Endpoint Selection

The toxicology endpoints selected for dietary and non-dietary risk assessments are presented in Table 2.

Table 2. Toxicology Endpoints Selected for Risk Assessments

Exposure Duration	Exposure Route	Dose	Endpoint	Comments
Acute	Dietary	Acute RfD= 0.0006 mg/kg	Plasma cholinesterase inhibition (ChEI)	NOAEL=0.06 mg/kg/day based on plasma ChE inhibition seen on day 3 in 6-month ocular toxicity study in dogs and an Uncertainty Factor of 100 applied. No FQPA Safety Factor.
Chronic	Dietary	Chronic RfD= 0.0006 mg/kg/day	Plasma, RBC and/or brain ChEI following subchronic and chronic exposures	The NOAEL=0.061 mg/kg/day for ChEI is based on the <u>combined results</u> of the 90-day, 6-month and 1-year studies in dogs. An Uncertainty Factor of 100 applied. No FQPA Safety Factor.
Short-Term (1-7 Days)	Dermal	Dermal NOAEL = 1.25 mg/kg/day	RBC ChEI	A MOE of 100 is adequate for occupational exposure risk assessments. There are no residential uses.
Intermediate-Term (7 days-several months)	Dermal	Dermal NOAEL = 1.25 mg/kg/day	RBC ChEI	A MOE of 100 is adequate for occupational exposure risk assessments. There are no residential uses.
Long-Term (several months to life-time)	Dermal	None	None	Based on the use pattern (1 application/year), there is no potential long-term dermal exposure. Therefore, this risk assessment is not required.
Short-Term (1-7 Days)	Inhalation	Inhalation NOAEL 0.00058 mg/L (0.13 mg/kg/day)	Plasma, RBC, and brain ChEI	The rat 7- day study is based on 6 hours of exposure per day. A MOE of 100 is adequate for occupational exposure risk assessments. There are no residential uses.
Intermediate-Term (7 days - several months)	Inhalation	Oral NOAEL= 0.06 mg/kg/day	Plasma cholinesterase inhibition	Inhalation study duration only 7 days. Not appropriate for this exposure period. Therefore, the oral NOAEL was selected. A MOE of 100 is adequate for occupational exposure risk assessments. There are no residential uses.
Long-Term (several months to life-time)	Inhalation	None	None	Based on the use pattern (1 application/year), there is no potential long-term dermal exposure. Therefore, this risk assessment is not required.

For acute dietary risk assessment, the HIARC did not select the acute neurotoxicity study in rats because cholinesterase inhibition was seen in both sexes at the lowest dose tested at the 1-day measurement; a NOAEL was not established for the principal effect. Consequently, the use of a LOAEL from this study would require an additional 3x uncertainty factor yielding an acute RfD of 0.0008 mg/kg/day ($0.25 \text{ mg/kg/day} \div 300 = 0.0008 \text{ mg/kg/day}$) which approximates the acute RfD of 0.0006 mg/kg/day derived from the NOAEL of 0.6 mg/kg/day (on day 3 of the 6 month dog ocular toxicity study) and the conventional 100x uncertainty factor. Since it is preferable to use a NOAEL than a LOAEL and additional factors, the dog study with a NOAEL was selected for deriving the acute RfD.

The inhalation NOAEL dose per unit body weight (mg/kg/day) is derived by multiplying the

Sprague-Dawley rat dose per liter times the respiratory rate (rate) and dividing by rat weight:

$$\frac{0.000508 \text{ mg/l} * (10.3 \text{ l/hr Sprague-Dawley rat inhalation rate}) * (6 \text{ hour exposure/day})}{0.236 \text{ kg (Sprague-Dawley rat body weight)}} = 0.13 \text{ mg/kg/day}$$

II. Exposure Assessment

A. Registered Uses

Chlorethoxyfos is registered for the control of corn rootworms, wireworms, cutworms, seed corn maggot, white grubs and symphylans on corn. Chlorethoxyfos is sold in the US by E.I du Pont Nemours and Company under the trade names Fortress® 5G (352-552) and Fortress® 2.5G (352-579). Fortress® is a granular soil insecticide for use on field corn, sweet corn, popcorn and corn grown for seed. The maximal amount of chlorethoxyfos applied per acre is 0.1625 lb ai/A. Applications are to be made with ground equipment in a T-band or in the furrow at planting. Fortress® is restricted to one application per year. Fortress® 5G is only available in a SmartBox™, which is a completely enclosed, tamper-proof delivery system.

B. Dietary Exposure

Tolerances are established (40 CFR §180.486) for residues of chlorethoxyfos in corn commodities as follows:

field corn grain	0.01 ppm
field corn forage	0.01 ppm
field corn fodder	0.01 ppm
popcorn grain	0.01 ppm
popcorn fodder	0.01 ppm
sweet corn (K + CWHR)	0.01 ppm
sweet corn forage	0.01 ppm

The nature of residue in corn and animals is adequately understood (Attachment 5, J. Stokes memo of 4/11/95). The HED Metabolism Assessment Review Committee has concluded that the residue of concern is the parent compound, chlorethoxyfos. In the corn metabolism study, no residues of the parent were found in corn commodities even after treatment at a 10x rate (MRID 41290601).

Tolerances are not required at this time for residues in milk and livestock tissues. The metabolism of chlorethoxyfos in the goat was extensive. No significant residues of parent or its oxygen analog were found. All metabolites detected were the result of re-incorporation of radioactivity in to natural products (MRID 41290602 and 41736804).

Adequate field trial data were submitted to support the established tolerances (MRID 41736815 and 417368-18). Field trials also showed no residues (<0.01 ppm) of parent in any of the corn raw agricultural commodities analyzed. On the basis of the results from both wet and

dry corn processing studies (MRID 41290616 and 41736819), HED concludes that no food/feed additive tolerances are required. Based upon non-detectable chlorethoxyfos residues measured in field corn, popcorn, and sweet corn commodities (<0.01 ppm) one-half the limit-of-detection ($\frac{1}{2}$ LOD = 0.005 ppm) was used for the anticipated residue values in the acute dietary exposure analysis.

Based upon non-detectable chlorethoxyfos residues measured in field corn, popcorn, and sweet corn commodities (<0.01 ppm) and the results of the goat metabolism study, finite transfer of chlorethoxyfos residues is not expected to meat, fat, meat byproducts, milk, or eggs. No tolerances for meat, fat, meat byproducts, milk, or eggs are necessary. There are no CODEX, Canadian, or Mexican limits established for chlorethoxyfos. Therefore, no compatibility problem exists.

Adequate methodology is available for analysis and enforcement of chlorethoxyfos residues (MRID 41290603). Chlorethoxyfos has been tested through the FDA Multiresidue protocols A - E. Chlorethoxyfos residues are recovered by Protocols C, D, and E, but not by Protocols A and B.

1. Acute Dietary (Food) Exposure

The Dietary Exposure Evaluation Model (DEEM™) was used to evaluate the dietary exposure based on individual consumption data from USDA 1989-1992 Nationwide Continuing Surveys of Food Intake by Individuals (CSFII). HED's level of concern for acute dietary risk is greater than 100% of the aRfD.

The acute Tier 3 probabilistic analysis includes anticipated residues set at one-half the limit of detection ($\frac{1}{2}$ LOD = 0.005 ppm) based upon non-detectable chlorethoxyfos residues (<0.01 ppm) measured in field corn, pop corn, and sweet corn commodities and Biological Economic Analysis Division's (BEAD's) percent crop treated data (% CT). Because BEAD estimated less than 1% of crop treated, in accordance with current policy, HED defaulted to 1% crop treated.

Table 3 summarizes the results of the probabilistic acute dietary exposure analysis. At the 99.9th percentile exposure, all population subgroups have 2% or less of the aRfD occupied.

Table 3. Acute Probabilistic Dietary Exposure Results for Chlorethoxyfos.

Subgroups	95 th Percentile Exposure (% aRfD)	99 th Percentile Exposure (% aRfD)	99.9 th Percentile Exposure (% aRfD)
U.S. Population	0.000000 (0.03)	0.000000 (0.06)	0.000003 (0.5)
Non-nursing infants (< 1 year old)	0.000001 (0.08)	0.000001 (0.12)	0.000001 (0.2)

Children (1-6 years old)	0.000000 (0.06)	0.000001 (0.10)	0.000012 (2.0)
Females (13-19 years old/not pregnant/not nursing)	0.000000 (0.03)	0.000000 (0.04)	0.000001 (0.1)
Males (13-19 years old)	0.000000 (0.03)	0.000000 (0.06)	0.000005 (0.9)

2. Chronic Dietary (Food) Exposure

The Dietary Exposure Evaluation Model (DEEM™) was used to evaluate the dietary exposure based on individual consumption data from USDA 1989-1992 Nationwide Continuing Surveys of Food Intake by Individuals (CSFII). HED's level of concern for chronic dietary risk is greater than 100% of the cRfD.

Tolerance level residues were assumed and percent of crop treated information (1%) was incorporated into this analysis. Table 4 summarizes the results of the chronic dietary exposure analysis. All population subgroups have less than 1% of the cRfD occupied.

Table 4. Chronic Dietary Exposure Results for Chlorethoxyfos.

Subgroups	Chronic Total Exposure (mg/kg/day)	Chronic Risk (% cRfD)
U.S. Population	0.000000	0.0%
Non-nursing infants (< 1 year old)	0.000000	0.1%
Children (1-6 years old)	0.000000	0.1%
Females (13-19 years old/not pregnant/not nursing)	0.000000	0.0%
Males (13-19 years old)	0.000000	0.0%

C. **Drinking Water Exposure**

1. Acute and Chronic DWLOC

The acute and chronic DWLOC for the children 1-6 years old is 6 ppb, for adult females it is 18 ppb, and for adult males it is 2 ppb..

Based on the acute and chronic dietary exposure estimates presented in Tables 3 and 4, drinking water levels of comparison (DWLOCs) were calculated using the formulas presented

below. A human health DWLOC is the concentration of a pesticide in drinking water which would result in unacceptable aggregate risk, after having already factored in all food exposures and other non-occupational exposures for which OPP has reliable data.

$$DWLOC_{acute} \text{ (ug/L)} = \frac{[\text{acute water exposure (mg/kg/day)} \times (\text{body weight, kg})]}{[\text{consumption (L/day)} \times 10^{-3} \text{ mg/}\mu\text{g}]}$$

where acute water exposure (mg/kg/day) = aRfD - acute food exposure (mg/kg/day)

$$DWLOC_{chronic} \text{ (ug/L)} = \frac{[\text{chronic water exposure (mg/kg/day)} \times (\text{body weight, kg})]}{[\text{consumption (L/day)} \times 10^{-3} \text{ mg/}\mu\text{g}]}$$

where chronic water exposure (mg/kg/day) = [RfD - (chronic food exposure) (mg/kg/day)]

The Agency's default body weights and consumption values used to calculate DWLOCs are as follows: 70 kg/2L of water per day (adult male) and 10 kg/1L of water per day (child).

1. Surface Water

EFED (R. Matzner, 11/23/98) provided estimated environmental concentrations (EECs) for chlorethoxyfos in surface water. Based on PRZM-EXAMS modeling, the following EECs for surface water were calculated:

Table 5. PRZM-EXAMS (Tier 2) modeling results for chlorethoxyfos in surface water.

Application Method	Acute (High) Concentration (ppb)	Chronic (60-day) Concentration (ppb)
In-Furrow	0.006	0.012
T-Band	0.427	0.080

2. Ground Water

EFED (R. Matzner, 11/23/98) provided estimated environmental concentrations (EECs) for chlorethoxyfos in ground water. Based on SCI-GROW modeling the groundwater concentration of chlorethoxyfos was estimated to be 0.002 ppb.

D. Occupational Exposure

Chlorethoxyfos can be applied with ground equipment in a T-band or in the furrow at planting. Fortress® is restricted to one application per year. DuPont has registered two products which present potential exposure for loaders, applicators, and other handlers during normal use-patterns associated with chlorethoxyfos: Fortress® 2.5G granules in 50 lb bags and Fortress® 5G SmartBox™.

Fortress® 2.5G granules are supplied in 50 lb bags, which are opened and loaded manually into hoppers mounted on mechanical planters. Due to chlorethoxyfos being in Toxicity Category I for inhalation (MRID # 40883716, $LC_{50} \geq 0.008\text{mg/L}$) and because of its high vapor pressure (1.7×10^{-3} mm Hg), the product label requires organic vapor/pesticide respirators. The amount of Fortress® 2.5G granules applied per acre varies from 5 to 6.5 lbs product per acre depending on row spacing.

Fortress® 5G SmartBox™ is a completely enclosed, tamper-resistant delivery system. This system is designed to significantly reduce worker exposure to this pesticide. Although in field studies worker exposures were dramatically reduced compared to mixing and applying loose granules, some problems were reported with the equipment. Such problems should be monitored by the Registrant establishing a registry of incident reports. The amount of Fortress® 5G SmartBox™ applied per acre varies from 2.5 to 3.25 lbs product based on row spacing.

Loader exposure estimates from Fortress® 5G in the SmartBox™ are based on wearing long-sleeved shirt, long pants, shoes plus socks and waterproof gloves. Loaders of Fortress® 2.5G are based on wearing coveralls over long-sleeved shirt, long pants, shoes plus socks and waterproof gloves, plus an organic vapor with pesticide prefilter or pesticide canister respirator. Applicator risk is based on the use of an open-cab tractor for Fortress® 2.5G and, an enclosed-cab tractor for Fortress® 5G. The label also requires protective eyewear for both loaders and applicators. The label should also state that contaminated eyes should be flushed for a minimum of 15 minutes. Current labels specify that the post-application reentry interval (REI) for Fortress® is 48 hours, or 72 hours if annual rainfall is less than 25 inches. Coveralls, shoes plus socks, and waterproof gloves are required for early reentry into the treated area.

A summary of exposure estimates and risk assessments for occupational handlers is included as Tables 6 and 7.

HED's worker exposure estimates are based on chemical specific studies which monitored the chlorethoxyfos exposure of applicators who were operating an open-cab tractor for Fortress® 2.5G and, an enclosed-cab tractor for Fortress® 5G while applying Fortress® 5G at the maximum label rate per acre of corn.

The combined loader and applicator total dermal and inhalation risks for both products do not exceed HED's level of concern. For Fortress® 5G in the SmartBox™ (Table 6) the total short-term $MOE_{total} = 1800$ and total intermediate-term, $MOE_{total} = 1200$. For Fortress® 2.5G granular (Table 7) the total short-term $MOE_{total} = 420$ and total intermediate-term, $MOE_{total} = 320$.

Post Application Exposure

Minimal post-application exposure is anticipated during activities such as scouting or harvesting, as chlorethoxyfos is incorporated into the soil, is not water soluble, degrades readily, is not systemic in the plant, and harvesting of corn is primarily mechanical in nature.

Chlorethoxyfos Exposure Scenario Tables

Table 6. Occupational Handler Exposure Estimate and Risk Assessment Summary Chlorethoxyfos [DuPont Fortress 5G SmartBox]

		DERMAL			INHALATION				Combined MOE (With PPE)
		(With minimum PPE)*			(With no respirator)				
Application Scenario	(lb ai/day)	UE ^b mg/lb a.i.	ADD ^c (mg/kg/day)	Short-& interm.- term MOE ^d	UE ^e mg/day	ADD ^f (mg/kg/day)	Short-term MOE ^d	Interm.-term MOE ^d	MOE Total ^g
SmartBox™ using a closed-cab tractor and planter [loader]	29.25	0.0002	0.000084	15,000	9.6X10 ⁻⁵	1.4 X10 ⁻⁶	93,000	43,000	S-T 13,000 I-T 11,000
[applicator]	29.25	0.00081	0.00034	3,700	0.0019	2.7 X10 ⁻⁵	4800	2200	S-T 2100 I-T 1400
[combined] ^h	29.25	0.0010	0.00042	3,000	0.0020	2.8 X10 ⁻⁵	4600	2100	S-T 1800 I-T 1200

* The minimum PPE for loaders is coveralls over long sleeve shirt and long pants, shoes, socks, eye protection, and waterproof gloves. The minimum PPE for applicators in the cab is long sleeve shirt, long pants, and shoes with socks. The minimum PPE for applicators outside the cab is coveralls over long sleeve shirt and long pants, shoes with socks, waterproof gloves and protective eyewear.

^b UE = Dermal Unit Exposure is the amount of exposure measured in terms of mg a.i./lb a.i. handled

^c ADD(mg/kg/day) [dermal]: = unit exposure (UE) from studies in mg/lb a.i. handled * 29.25 lb a.i./day / 70 kg wt;

^d MOE = NOAEL/ADD; For Dermal (short- & intermediate-term time periods)-NOAEL = 1.25 mg/kg/day; For short-term inhalation-NOAEL = 0.13 mg/kg/day (Based on 7-day inhalation study); For intermediate-term inhalation-NOAEL = 0.06 mg/kg/day (based on an oral study, assume 100% absorption). Inhalation NOAEL = 0.13 mg/kg/day = 0.000508 mg/l X (10.3 l/hr sprague-Dawley inhalation rate) X (rat exposed 6hrs/day) divided by 0.236 kg (Sprague-Dawley rat body weight).

^e UE = The Inhalation Unit Exposure factor is based on the respiratory rate of 29 liters/minute. Loader exposure was 0.25 hours/day (=435 liters); applicator 7.75 hours/day (=13,485 liters)

UE (loader) = (0.22 nanograms ai/liter) X (1 X 10⁶ mg/nanogram) X 435 liters/day = 9.6×10^{-5} mg/day; UE (applicator) = (0.14 nanograms ai/liter) X (1 X 10⁶ mg/nanogram) X 13,485 liters/day = 0.0019 mg/day.

^f ADD(mg/kg/day) [inhalation] = UE is divided by avg body weight for ADD: mg/day / 70kg = mg/kg/day (The total dose).

^g MOE Total is based upon the following formula: the inverse of the sum of the inverses of the dermal and inhalation MOEs:

$1 / (1/\text{MOE}_{\text{dermal}} + 1/\text{MOE}_{\text{inhalation}})$; these MOE have a common endpoint. ¹ = Short-term, and ² = intermediate-term

^h Loader/Applicator = 1 person performing both loading and application of the pesticide to the crop/commodity.

These estimates are based on data from a study (MRID#443998-02) which used 3.25 lb. product/acre (equivalent to 0.1625 lb a.i./acre)

Table 7. Occupational Handler Exposure Estimate and Risk Assessment Summary Chlorethoxyfos [DuPont Fortress 2.5G Granules]

		DERMAL			INHALATION				Combined MOE (With PPE)
		(With PPE)*			(With Mixer/Loader Wearing Organic Vapor Respirator)				
Application Scenario	(lb ai/day)	UE ^b mg/lb a.i.	ADD ^c (mg/kg/day)	Short-& interm.-term MOE ^d	UE ^e mg/day	ADD ^f (mg/kg/day)	Short-term MOE ^d	Interm.-term MOE ^d	MOE Total ^g
Fortress 2.5G™ using an open cab tractor and planter [loader]	29.25	0.0024	0.0010	1300	0.001	1.4 E-5	9300	4300	S-T 1100 I-T 990
[applicator]	29.25	0.0029	0.0012	1000	0.0047	6.7 E-5	1900	900	S-T 660 I-T 470
[combined] ^h	29.25	0.0053	0.0022	570	0.0057	8.1 E-5	1600	740	S-T 420 I-T 320

* The PPE is at maximum for loaders; which is, an organic/vapor respirator, coveralls over long sleeve shirt, long pants, shoes, socks, eye protection, and waterproof gloves.

The PPE is at minimum for applicators; which is, an organic/vapor respirator, long sleeve shirt, long pants, and shoes with socks.

The minimum PPE for applicators outside the tractor is coveralls over long sleeve shirt and long pants, shoes with socks, waterproof gloves and protective eyewear.

^b UE = Unit Exposure is the amount of exposure measured in terms of mg a.i./lb a.i. handled

^c ADD(mg/kg/day) Dermal: = unit exposure (UE) from studies in mg/lb a.i. handled * 29.25 lb a.i./day / 70 kg wt;

^d MOE = NOAEL/ADD; For Dermal (short- & intermediate-term time periods)-NOAEL = 1.25 mg/kg/day; For short-term inhalation-NOAEL=0.13 mg/kg/day (Based on 7-day inhalation study); For intermediate-term inhalation- NOAEL =0.06 mg/kg/day (based on an oral study, assume 100% absorption). Inhalation NOAEL= 0.13 mg/kg/day =0.000508 mg/l X (10.3 l/hr sprague-Dawley inhalation rate) X (rat exposed 6hrs/day) divided by 0.236 kg (Sprague-Dawley rat body weight).

^e UE =Unit Exposure factor is based on the respiratory rate of 29 liters/minute. Loader exposure was 0.3 hours/day (=522 liters); applicator 7.7 hours (=13,400 liters).

UE (loader) = (37.5 nanograms ai/liter) X (1X10⁻⁶ mg/nanogram) X 522 liters/day= 0.02 mg/day X 0.5 (% 5G)= 0.01 mg/day X 0.10 (with the use of an organic vapor respirator)=0.001mg/day, UI:

(applicator) = (0.7 nanograms ai/liter) X (1X10⁻⁶ mg/nanogram) X (13,400liters/day)=0.0094 mg/day X 0.5 (% 5G) = 0.0047 mg/day

^f ADD(mg/kg/day) [inhalation] = The UE divided by avg body weight; for ADD: (mg/day) / 70kg = mg/kg/day (total dose)

^g MOE Total is based upon the following formula: the inverse of the sum of the inverses of the dermal and inhalation MOEs:

$1 / (1/MOE_{dermal} + 1/MOE_{inhalation})$; these MOE have a common endpoint

^h Loader/Applicator = 1 person performing both loading and application of the pesticide to the crop/commodity.

Note: The study data (MRID# 425592-22) is based on using 5G; the study data indicates 5.5 lb. product/acre (equivalent to 0.275 lb a.i./acre). For 2.5G data, the 5G study data was used, but the values were cut in half because the 2.5G product ingredients is half the 5G product ingredients, which equals 2.75 lb. product/acre (equivalent to 0.1375 lb a.i./acre).

E. Residential Exposure

There are no registered uses that would result in residential exposures at the present time.

III. Aggregate Risk Estimates and Risk Characterization

A. Aggregate Acute Risk Estimate

The acute dietary (food) risk estimates for chlorethoxyfos do not exceed HED's level of concern. Tier 2 (PRZM-EXAMS) surface water and ground water (SCI-GROW) estimated environmental concentrations (EECs) do not exceed HED drinking water levels of comparison (DWLOC) for acute aggregate dietary exposure. Thus, aggregate acute risk estimates do not exceed HED's level of concern.

B. Short and Intermediate-Term Aggregate Risk Estimate

Because chlorethoxyfos does not have any registered uses that could result in residential exposures, aggregate short and intermediate-term risk assessments are not required.

C. Chronic Aggregate Risk Estimate

The chronic dietary (food) risk estimates for chlorethoxyfos do not exceed HED's level of concern. Tier 2 (PRZM-EXAMS) surface water and ground water (SCI-GROW) estimated environmental concentrations (EECs) do not exceed HED drinking water levels of comparison (DWLOC) for chronic aggregate dietary exposure. Thus, aggregate chronic risk estimates do not exceed HED's level of concern.

D. Occupational Risk Estimates

HED's worker exposure estimates are based on chemical specific studies (MRID# 425592-22 (2.5G), and MRID# 443998-02 (for 5G)). The combined loader and applicator total dermal and inhalation risks for both products do not exceed HED's level of concern. For Fortress® 2.5G granular (Table 7) the total short-term $MOE_{total} = 420$ and total intermediate-term, $MOE_{total} = 320$. For Fortress® 5G in the SmartBox™ (Table 6) the total short-term $MOE_{total} = 1800$ and total intermediate-term, $MOE_{total} = 1200$.

IV. Data Needs

There are no data gaps for chlorethoxyfos, however, HED makes the following recommendations:

1. Fortress® 5G SmartBox™ is a completely enclosed, tamper-resistant delivery system. This system is designed to significantly reduce worker exposure to this pesticide. Although in field studies worker exposures were dramatically reduced compared to mixing and applying loose granules, some problems were reported with the equipment. **Such problems should be monitored by the Registrant establishing a registry of incident reports.**
2. Product labels require protective eyewear for both loaders and applicators. The label should also state that contaminated eyes should be flushed for a minimum of 15 minutes.