8-21-95

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

AUG 21 1995

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: HED Risk Assessment for Chlorethoxyfos (Fortress®)

FROM: Steve Robbins, Chemical Manager SR 8/21/95
Registration Section
Risk Characterization and Analysis Branch
Health Effects Division (7509C)

THROUGH: Karen Whitby, Acting Chief
Risk Characterization and Analysis Branch
Health Effects Division (7509C)
and
Stephanie Irene, Acting Director
Health Effects Division (7509C)

TO: Dennis Edwards, Product Manager Team 19
Insecticide-Rodenticide Branch
Registration Division (7505C)

As requested, HED has completed a risk assessment for use of chlorethoxyfos (2.5G and 5G formulations) on corn. All the studies described below have been found acceptable except as noted. The Hazard Assessment section of this document is from Karen Hamernik in TB I, the Occupational/Residential Exposure Assessment from Charles Lewis in OREB, the Dietary Exposure Assessment, Product Chemistry and Tolerance assessment from Jerry Stokes in CBTS, and the Dietary Risk Assessment from Brian Steinwand in SAB.

I. BACKGROUND

E. I. du Pont de Nemours and Company, Inc. is pursuing the registration of the new active ingredient chlorethoxyfos technical 86% (352-LLG) and the formulated product Fortress® 5G (352-LLE) and Fortress® 2.5G (352-LTO). The proposed use of this organophosphate insecticide is for the control of corn rootworms, wireworms, cutworms, seed corn maggots, white grubs and symphylans on corn.

The Health Effects Division has evaluated the chlorethoxyfos study data. A summary of the findings and an assessment of human health risk resulting from the proposed use of chlorethoxyfos are provided in this document.

II. USE PATTERN

Fortress® is a granular soil insecticide for use on field corn, sweet corn, popcorn and seed corn. The amount of Fortress® applied per acre varies from 2.5 to 3.25 lbs based on row spacing. 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 will only be available in a SmartBox™, which is a completely enclosed, tamper-proof delivery system.

III. PRODUCT CHEMISTRY

Common Name: Chlorethoxyfos

Chemical Name: O,O-diethyl-O-(1,2,2,2-tetrachloroethyl)phosphorothioate

Molecular Formula: $C_6H_{11}Cl_4O_3PS$

CAS Registry No.: 54593-83-8

Solubility: PAI: 2.09 ppm in water at 25°C
PAI: at least 20 g per 100 mL at 20°C in: acetone, acetonitrile, dichloromethane, ethyl acetate, hexane, methanol, or xylene

Melting Point: NA (TGAI is a liquid)

Vapor Pressure: PAI: 1.7×10^{-3} mm Hg at 25°C

Physical Description: The TGAI is a light brown to dark brown liquid which has a strong, objectionable odor characteristic of sulfur-containing compounds.

IV. HAZARD ASSESSMENT

A. Acute Toxicity

Acceptable acute oral, dermal, inhalation, eye irritation, dermal irritation, and skin sensitization data were submitted for chlorethoxyfos, Fortress® Technical. Toxicity category I was assigned for acute oral, dermal, inhalation, eye irritation, and skin irritation. Fortress Technical is not a dermal sensitizer.

Acceptable acute oral, dermal, inhalation, eye irritation, dermal irritation, and skin sensitization data were submitted for the 5.0% a.i. chlorethoxyfos formulation, Fortress® 5G. Toxicity category I was assigned to the 5.0% Fortress® 5G, for the acute oral and inhalation studies. Toxicity category III was assigned for acute dermal and primary eye irritation. Toxicity category IV was assigned for primary skin irritation. Fortress® 5G is not a dermal sensitizer.

B. Subchronic Toxicity

A 90-day toxicity study (MRID# 412906-27, HED# 008330) was conducted in rats (Crl:CD BR) with chlorethoxyfos administered at 0, 0.1, 1.0, 5, or 10 ppm (equivalent to 0, 0.007, 0.071, 0.357, or 0.784 mg/kg/day for males; 0, 0.010, 0.093, 0.472, or 1.10 mg/kg/day for females). The systemic NOEL is 5 ppm (0.357 mg/kg/day). The systemic LOEL is 10 ppm (0.784 mg/kg/day) based on mortality, tremors, and clinical signs. A LOEL for tremors of 0.1 ppm (0.010 mg/kg/day) lowest dose tested was based on single to multiple observations of tremors in 2 out of 10 females (tremors were not observed at 1.0 ppm in females but were observed in more females and/or with earlier onset at 5.0 and 10 ppm. Tremors were first observed in males at 10 ppm. The NOEL for cholinesterase inhibition is 1.0 ppm (0.093 mg/kg/day). The cholinesterase inhibition LOEL is 5 ppm (0.472 mg/kg/day) based on inhibition of plasma cholinesterase (25-30%) on days 45 and 90 for females. This was considered to be part of a dose-related decreasing trend. At 10 ppm plasma

2

cholinesterase inhibition was statistically significant, 37% (at 90 days) and 42% (at 45 days) for males and 69% (at 90 days) and 77% (at 45 days) for females. There was no treatment-related inhibition of red blood cell (RBC) cholinesterase. Brain cholinesterase activity was not measured.

A special 90-day feeding study (MRID# 425592-15) with chlorethoxyfos in female rats (Crl:CD BR) only, was conducted to address the particular issues of the lack of a NOEL for cholinesterase inhibition in the rat and the need to find or confirm a NOEL for tremors. Chlorethoxyfos was administered via the diet for 90 days at dose levels of 0, 0.1, 1.0, 8.0, 12.8, or 16.0 ppm (equivalent to 0, 0.008, 0.080, 0.635, 1.23, or 1.63 mg/kg/day). Plasma and RBC cholinesterase were measured on days 1, 7, 14, 21, 28, 45, and 90 (not fasted). Brain (homogenate) cholinesterase was measured at termination (not fasted). The acute NOEL for cholinesterase inhibition is 8 ppm (0.635 mg/kg/day), the acute LOEL for cholinesterase inhibition is 12.8 ppm (1.23 mg/kg/day), based on statistically significant decreases in plasma cholinesterase of 53% and RBC cholinesterase of 13% on day 1 of treatment. The subchronic NOEL for cholinesterase inhibition is 1 ppm (0.080 mg/kg/day). The subchronic LOEL for cholinesterase inhibition is 8 ppm (0.635 mg/kg/day) based on statistically significant decreases in plasma (38-46%) and/or RBC (12-21%) cholinesterase on days 7, 14, 21, 28, 45, and 90, and decreases in brain cholinesterase (14%) on day 90. Further decreases in these blood and brain cholinesterase, activities were noted with increasing doses. The systemic NOEL is 8 ppm (0.635 mg/kg/day), while the systemic LOEL is 12.8 ppm (1.23 mg/kg/day) based on mortality, clinical signs of toxicity, body weight and weight gain decreases, and a reduced food efficiency. Tremors (additional observations for tremors were included in the study design) were observed in this study starting at 12.8 ppm (1.23 mg/kg/day). A dose-related increase in keratitis of the cornea was noted at the two highest dose levels (occurred mostly in moribund or animals found dead). No treatment-related retinal or optic nerve lesions were noted.

In a 90-day feeding study in the dog (Beagle 4 to 5 months old) (MRID#s 408987-03 and 408987-04; HED# 007112), chlorethoxyfos was administered at dose levels of 0, 0.5, 5, or 50 ppm (equivalent to 0, 0.017, 0.185, or 1.820 mg/kg/day for males and 0, 0.019, 0.186, or 1.840 mg/kg/day for females). Plasma and RBC cholinesterase was measured twice pretest and on days 45 and 90 (fasted). Brain cholinesterase (caudate n., cerebellum/medulla and cerebrum) were measured at termination. The cholinesterase inhibition NOEL is 0.5 ppm (0.017 mg/kg/day). The cholinesterase inhibition LOEL is 5 ppm (0.185 mg/kg/day) based on statistically significant brain (33%) (caudate n.) in females only at termination, and plasma (38-43%) cholinesterase inhibition in both sexes at days 45 and 90. Greater inhibition was seen at the high dose. RBC cholinesterase may have been inhibited in high dose males and/or females but due to data variability even in pretest group mean values it was not clear. The systemic NOEL is 5 ppm (0.185 mg/kg/day). The systemic LOEL is 50 ppm (1.820 mg/kg/day) based on, in females, tremors (one female), diarrhea, transient decreases in mean body weight, elevated ALT and lower serum calcium, total protein, and albumin (males also).

In a 90-day feeding study in the mouse (Crl:CD-1 (ICR) BR approx. 6 weeks old at start) (MRID# 412906-29; HED# 008330), chlorethoxyfos was administered at dose levels of 0, 7.5 (compromised), 15, 30, or 60 ppm (equivalent to 0, compromised, 2.19, 4.27, or 8.89 mg/kg/day for males and 0, compromised, 2.82, 5.78, or 10.7 mg/kg/day for females). Analysis of 7.5 ppm concentration showed unacceptable variation of 7-100% (average about 75% of nominal) due to homogenization problems. Plasma and RBC cholinesterase were measured at termination. Brain cholinesterase was not assayed. The cholinesterase inhibition NOEL could not be determined. The cholinesterase inhibition LOEL is 7.5 ppm (non-reliable - mg/kg/day equivalent could not be reliably determined due to compromise of dosing) (lowest dose tested (LDT)). Plasma cholinesterase was inhibited about 21% (males) and 37% (females)(LDT). This inhibition was considered to be statistically significant and increased with increasing dose. Also dosing was compromised at 7.5

ppm. RBC cholinesterase was inhibited in males (20-30%) at 15 ppm and above. This inhibition was also considered to be statistically significant. The systemic NOEL is 60 ppm (8.89 and 10.7 mg/kg/day for males and females respectively) (HDT), while the systemic LOEL is greater than 60 ppm (8.89 mg/kg/day). At 60 ppm, increase in unilateral colored discharge (often statistically significant), enophthalmus, and phthisis of eye relative to other groups and control, not obviously explainable by relationship to orbital sinus bleeding alone.

A six-week subchronic feeding study in the rat (Crl:CD BR, 36 days old at start) and mouse (Crl:CD-1 (ICR) BR, 43 weeks old at start) (MRID# 412906-32; HED# 008330) was used to aid in the dose setting for a longer term study. In this study chlorethoxyfos was administered at dose levels of 0, 0.1, 1, 5, or 10 ppm for the rat (10/animals/sex/group) (equivalent to 0, 0.009, 0.091, 0.477, or 0.958 mg/kg/day for males and 0, 0.014, 0.132, 0.660, or 1.33 mg/kg/day for females). The cholinesterase inhibition NOEL is 1 ppm (0.132 mg/kg/day). The cholinesterase inhibition LOEL is 5 ppm (0.660 mg/kg/day) based on brain cholinesterase inhibition of 6% (females) which is statistically significant. In addition, brain 52% (females), 25% (males), plasma 72% (females), 49% (males), and RBC 24% (females), 30% (males) cholinesterase activities were decreased at 10 ppm (0.958 mg/kg/day). The decreases were statistically significant.

The dose levels for mice (10 animals/sex/group) were 0, 0.1, 10, 15, or 100 ppm (equivalent to 0, 0.018, 1.98, 2.85 or 19 mg/kg/day for males and 0, 0.028, 2.94, 3.98, or 31.9 mg/kg/day for females). Plasma and brain (homogenate) cholinesterase were assayed at termination (prandial state unknown). There were no values for RBC cholinesterase provided due to technical difficulties. The cholinesterase inhibition NOEL is 0.1 ppm (0.018 mg/kg/day). The cholinesterase inhibition LOEL is 10 ppm (1.98 mg/kg/day) based on plasma cholinesterase inhibition in males (51%) and females (61%) which was statistically significant. In addition brain cholinesterase decreased in 15 ppm males (10%) and 100 ppm males (85%) and females (79%). The decreases were found to be statistically significant. The systemic NOEL is 15 ppm (2.85 mg/kg/day). The systemic LOEL is 100 ppm (19 mg/kg/day) based on decreases in food consumption (36%) and food efficiency (62%) in males which were found to be statistically significant. No clinical signs were observed in males or females.

C. Carcinogenicity/Chronic Toxicity

2yr in rats

In a combined chronic toxicity/carcinogenicity study (MRID# 417368-37) chlorethoxyfos was administered to rats (Crl:CD BR, about 35 days old at start) via the diet at dose levels of 0, 0.1, 0.8, 4, or 8 ppm (equivalent to 0, 0.004, 0.031, 0.154, or 0.311 mg/kg/day for males and 0, 0.005, 0.042, 0.208, or 0.416 mg/kg/day for females). Plasma and RBC cholinesterase were measured at 3, 6, 12, 18, and 24 months (fasted). Brain (homogenate) cholinesterase was measured at termination of the study. The cholinesterase inhibition NOEL is 4 ppm (0.154 mg/kg/day for males and 0.208 mg/kg/day for females). The cholinesterase inhibition LOEL is 8 ppm (0.311 mg/kg/day for males and 0.146 mg/kg/day for females) based on statistically significant inhibition of plasma cholinesterase (36%, month 12, for females) and RBC cholinesterase (9-15%, month 6, 12, for males) and 12-24%, month 12 and 24, for females). There was no brain cholinesterase inhibition. The systemic NOEL is 8 ppm (0.311 mg/kg/day for males and 0.416 mg/kg/day for females). The systemic LOEL is greater than 8 ppm (0.311 mg/kg/day for males and 0.416 mg/kg/day for females). There were no systemic effects. The dose selection was based on mortality and other signs at 10 ppm and above in two 90-day rat feeding studies. A slight increase in kidney tumors which was not found to be statistically significant ($p \leq 0.05$) in the high dose group of male rats.

The incidence of kidney tumors appeared to be slightly increased but was not statistically significant ($p \leq 0.05$) by the statistical methods used by the study authors. Consequently,

Toxicology Branch I, determined that a weight of the evidence evaluation by the Health Effects Division's Carcinogenicity Peer Review Committee (CPRC) might be required. The registrant was informed and provided additional information and a formal response to the issue. The original diagnosis of tumor type for all three males was kidney carcinoma (malignant). Subsequently, upon reevaluation, the registrant classified the tumor type in two of the males as carcinoma, kidney (metastatic) and the tumor type in the third male as nephroblastoma, malignant, kidney.

On February 2, 1995, an ad hoc group consisting of Mr. William Burnam and Drs. Esther Rinde and Kerry Dearfield (SAB) and Drs. Karl Baetcke and Karen Hamernik (Toxicology Branch I), met to discuss the necessity of taking the issue to the CPRC. The conclusion of the group was that further testing would not be useful and that the available 2-year study in the rat was adequate for carcinogenicity testing. In addition, the group determined that the data did not warrant further consideration by the CPRC. The group recommended that the test material be classified as a "Group D", not classifiable as to human carcinogenicity, because of the inadequacy of evidence. The nature of the effect in the male rat kidney, made it difficult to clearly interpret the data as showing either the presence or absence of a carcinogenic effect.

Reevaluation of the individual animal pathology data showed one high dose female (animal No. 423577) with lymphocytic leukemia in numerous organs, which matched up with the incidences at different organ sites noted in the histopathology summary table. This type of neoplasm (lymphocytic leukemia), under this circumstances, was considered to be of no biological significance since it was found (in multiple sites) in a single animal. It should be noted also that lymphocytic leukemia was not found in any group of females at interim sacrifice.

D. Developmental Toxicity

In the developmental toxicity study in the rat (Crl:CD BR, females were 63 days old at the start) (MRID# 408987-05; HED# 007112, chlorethoxyfos suspended in 0.5% aqueous methylcellulose was administered by gavage at doses of 0, 0.05, 0.25, 0.50 or 0.60 mg/kg/day. The maternal toxicity NOEL is 0.25 mg/kg/day, while the maternal toxicity LOEL is 0.50 mg/kg/day. The maternal toxicity LOEL was based on increased mortality and decreased mean body weight gain during gestation days 13 - 17. The developmental NOEL is 0.25 mg/kg/day, while the developmental LOEL is 0.50 mg/kg/day. The developmental LOEL is based on decreases in the number of live fetuses per litter.

In the developmental toxicity study in the rabbit (N. Zealand White, females were 26 weeks old at the start) (MRID#s 412906-33 and 425592-19; HED# 008330), chlorethoxyfos suspended in 0.5% aqueous methylcellulose was administered by gavage at doses of 0, 0.76, 1.38, 2.1 or 3.1 mg/kg/day. The maternal NOEL is 0.76 mg/kg/day while the maternal LOEL is 1.38 mg/kg/day. The maternal LOEL was based on treatment related mortality associated with cholinesterase inhibition. The developmental NOEL is 1.38 mg/kg/day, while the developmental LOEL is 2.1 mg/kg/day. The developmental LOEL is based on a statistically significant increase in the average number of early resorptions per litter relative to controls. This is supported by an increase in the number of litters with at least one early resorption per total litters observed (relative to controls and lower dose groups). There was no evidence of teratogenicity.

E. Reproductive Toxicity

In the two generation reproductive toxicity study in the rat (Crl:CD BR, F_0 43 days old at start) (MRID# 417368-36), chlorethoxyfos was administered at doses of 0, 0.25, 1, 4, or 8 ppm (equivalent to 0, 0.018, 0.074, 0.296 or 0.607 mg/kg/day for males and 0, 0.022, 0.091, 0.357 or 0.776 mg/kg/day for females). The parental NOEL is 4 ppm (0.296 mg/kg/day for males and 0.357

mg/kg/day for females) while the parental LOEL is 8 ppm (0.607 mg/kg/day for males and 0.776 mg/kg/day for females). The parental LOEL is based on increased incidence of tremors during lactation. The reproductive NOEL is 8 ppm while the reproductive LOEL is greater than 8 ppm. There were no findings in this study of possibly treatment related staining/wetness of the perineum and inguinal areas in pups.

F. Mutagenicity

A Salmonella gene mutation study (MRID# 408837-26; HED# 007112) showed that chlorethoxyfos was not mutagenic even up to cytotoxic doses of 5000 μg/plate in the presence or absence of metabolic activation.

A Chinese hamster ovary (CHO) cell gene mutation (HGPRT) study (MRID# 408837-27; HED# 007112) showed that chlorethoxyfos was not mutagenic even at severely cytotoxic doses in the absence (30 μg/ml) or presence (65 μg/ml) of metabolic activation.

A mouse lymphoma L5178Y cell gene mutation (TK) study (MRID# 408837-28; HED# 007112) showed that chlorethoxyfos was not mutagenic even at severely cytotoxic doses (320 μg/ml) under both activating and non-activating conditions.

In an *in vivo* micronucleus assay (MRID# 408837-29; HED# 007112) in male and female mice (Crl: CD-1 (ICR) BR) (chromosome aberrations) no statistically significant increases in micronuclei were found even in animals treated with toxic doses of chlorethoxyfos.

A DNA repair assay (MRID# 408837-30; HED# 007112) in cultured rat hepatocytes (other effects) showed that chlorethoxyfos did not cause DNA damage in two trials when tested up to the limit of solubility, even at cytotoxic concentrations of 200 μg/ml in the first trial and 100 μg/ml in the second trial.

An *in vitro* chromosomal aberration study (MRID# 408837-31; HED# 007112) showed that chlorethoxyfos did not induce chromosomal aberrations in the presence or absence of metabolic activation even at cytotoxic concentrations (160 μg/ml).

G. Metabolism

The metabolism of chlorethoxyfos was studied in rats (MRID#s 425592-20 and 412906-35; HED#s 011373 and 008330) administered a single oral high dose of 1 to 1.5 mg/kg of purified radiolabeled chlorethoxyfos to male and female rats. Greater than 95% of the administered radioactivity was recovered by 7 days post dosing. Sixty to 66% of the radioactivity was eliminated in the urine, 13 to 26% in the feces, about 11% was found in the expired air, and 5 to 6% in the tissues and carcass. Trichloroacetic acid, dichloroacetic acid, trichloroethanol and trichloroethanol's glucuronide conjugate (the major urinary metabolite) were detected in the urine and feces. Unchanged parent was the major fecal metabolite in females, but was not detected in males. Chlorethoxyfos is activated by conversion to the oxon. Acceptable rationales for waiver of the single and multiple low dose and i.v. studies were provided.

H. Other Significant Toxicity Studies

In the six month ocular toxicity study in the dog (MRID# 425592-21), chlorethoxyfos was administered in the diet at doses of 0, 2, 20, or 60 ppm (equivalent to 0, 0.061, 0.578, or 1.880 mg/kg/day for males and 0, 0.062, 0.619, or 1.852 mg/kg/day for females). Plasma and RBC cholinesterase were measured pretest, days 2 and 3, weeks 1, 6, 13, and 26 (non-fasted). Brain

(pons, cerebellum, hippocampus, caudate n.) and retinal and extraocular muscle cholinesterase were measured at termination (fasted). The acute cholinesterase inhibition NOEL is 2 ppm (0.061 mg/kg/day for males and 0.062 mg/kg/day for females) while the acute cholinesterase inhibition LOEL is 20 ppm (0.578 mg/kg/day for males and 0.619 mg/kg/day for females). The acute cholinesterase inhibition LOEL is based on plasma cholinesterase inhibition of 38% (males) and 30% (females, which is statistically significant) on day 2 of treatment. On day 3 of treatment plasma cholinesterase inhibition of 40% (males) was considered to be statistically significant. The subchronic to chronic cholinesterase inhibition NOEL is less than 2 ppm (LDT) while the subchronic to chronic cholinesterase inhibition LOEL is 2 ppm (threshold response) (0.061 mg/kg/day for males and 0.062 mg/kg/day for females). The subchronic to chronic cholinesterase inhibition LOEL is based on plasma cholinesterase inhibition of 12 to 21% in both sexes at weeks 1, 6, 13 and 26 (the 21% inhibition in females, at week 6 is statistically significant). Further dose related decreases in plasma cholinesterase at higher doses at all time points were observed and were mostly statistically significant for both sexes. At 20 ppm (0.578 mg/kg/day for males and 0.619 mg/kg/day for females) cerebellum cholinesterase inhibition (19-20%) was noted in both sexes, while retinal cholinesterase inhibition, 15% in males and 31% in females, was not statistically significant but was considered to be of toxicology concern due to dose related trends. The trends, at 60 ppm (1.880 mg/kg/day for males and 1.852 mg/kg/day for females), were further decreases in cholinesterase in all brain areas of 24 to 63% (mostly statistically significant in both sexes) and retinal cholinesterase (52-56% statistically significant in both sexes). Possible effects on RBC cholinesterase activity (both sexes) at 20 and 60 ppm were evident, but not clear cut, because although decreases at some time points were statistically significant , dose response curves were very shallow. There were no effects on ocular muscle cholinesterase at any dose. The systemic NOEL is 2 ppm (0.061 mg/kg/day for males and 0.062 mg/kg/day for females) while the systemic LOEL is 20 ppm (0.578 mg/kg/day for males and 0.619 mg/kg/day for females) based on a statistically significant increase in incidence of watery stool in each sex. The ocular toxicity NOEL is 60 ppm (1.880 mg/kg/day for males and 1.852 mg/kg/day for females) while the ocular toxicity LOEL is greater than 60 ppm based on the absence of histopathology or clear evidence of electroretinogram (ERG) abnormalities with the techniques used.

V. DOSE RESPONSE ASSESSMENT

A. RfD Committee Review

The Health Effects Division RfD/Peer Review Committee met on November 3, 1994 to discuss and evaluate the toxicology data base submitted in support of Fortress® (Chlorethoxyfos) registration and to establish the reference dose (RfD).

The Committee recommended that a Reference Dose for this chemical be established based upon the combined subchronic and chronic toxicity studies in dogs (MRID#s 425592-21, 417368-33, 408987-03, and 408987-04) with an overall NOEL of 2 ppm (0.061 mg/kg/day for males and 0.062 mg/kg/day for females) based on cholinesterase inhibition. At this level (2 ppm), plasma cholinesterase was inhibited 12 to 21% in both males and females in the six month study. The 2 ppm level was, therefore, considered to be a threshold NOEL. In the 90 day feeding study, plasma and brain cholinesterase inhibition in females and plasma cholinesterase inhibition in males were observed at 5 ppm. An uncertainty factor (UF) of 100 was applied to account for inter-species extrapolation and intra-species variability. On this basis, the RfD was calculated to be 0.0006 mg/kg/day.

B. Cancer Classification

Chlorethoxyfos is classified in Group D, "not classifiable as to human carcinogenicity" (refer to section IV C of this document).

C. Additional Toxicological Endpoints for Risk Assessment

Based upon a review by the Less Than Lifetime (LTL) committee of the toxicology database for chlorethoxyfos, toxicology endpoints of concern have been identified for use in risk assessments corresponding to the categories below. A brief capsule of the study is presented for use in preparation of risk assessments.

Acute Dietary Endpoint (One Day)

Study selected - 6-Month Ocular Toxicity Study in Dogs - MRID No.: 425592-21

Summary: The critical endpoint for acute dietary risk assessment is the $NOEL_{acute}$ of 2 ppm (≈0.06 mg/kg/day) based on decreased plasma cholinesterase inhibition at the next higher dose (the $LOEL_{acute}$). At the $LOEL_{acute}$ of 20 ppm (0.578 mg/kg/day [males] and 0.619 mg/kg/day [females]), plasma cholinesterase activity was decreased 38% in males and 30% (statistically significant) in females on day 2 of treatment. On day 3 of treatment, at this dose level (20 ppm), plasma cholinesterase was statistically significantly inhibited in both sexes by 40% (males) and 35% (females). Therefore the endpoint and dose for use in the risk assessment is a NOEL of 0.06 mg/kg/day.

Short Term Occupational Endpoint (One to Seven Days)

Study selected - 6-Month Ocular Toxicity Study in Dogs - MRID No.: 425592-21

Summary: On study day 7, plasma cholinesterase was inhibited 62% in males and was statistically significantly inhibited 55% in females at the LOEL of 20 ppm (0.578 mg/kg/day [males] and 0.619 mg/kg/day [females]). These values were part of a dose-related decreasing trend. Therefore the endpoint and dose for use in the risk assessment is a NOEL of 0.06 mg/kg/day.

Intermediate Term Occupational Endpoint (One Day to Several Months)

Study selected - 6-Month Ocular Toxicity Study in Dogs - MRID No.: 425592-21

Summary: Same study and dose level (NOEL = 2 ppm or ≈ 0.06 mg/kg/day) as for acute dietary endpoint. At LOEL of 20 ppm (0.578 mg/kg/day - males and 0.619 mg/kg/day - females), there was significant (statistically or toxicologically) inhibition of plasma cholinesterase at weeks 1, 6, 13, and 26 (both sexes) and of brain (cerebellar) and retinal cholinesterase at week 26. Therefore the endpoint and dose for use in the risk assessment is a NOEL of 0.06 mg/kg/day.

Dermal and Inhalation Absorption

Due to the lack of data the following assumption regarding the dermal and inhalation absorptions were made. Based on a comparison of the dermal (LD_{50}) studies for the technical and the 5G end-use product, the dermal absorption is likely to be far less than 100%. DuPont (at the meeting with EPA on 7/26/95) recommended a dermal absorption factor of 20%. HED is using an

interim dermal absorption factor of 50%. This is a more conservative estimate because it is based on a comparison of the technical and 5G dermal LD_{50}s. Cholinesterase inhibition (RBC, plasma or brain) was not measured in these studies and is considered to be the most sensitive toxicological endpoint for this organophosphate. This chemical is known to be a very potent cholinesterase inhibitor. For the purposes of a full Section 3 registration, an acceptable dermal toxicity study is required.

HED did determine, as a consequence of the meeting with Dupont on July 26, 1995, that the risk assessment should be conducted using 1) an estimate of inhalation exposure with the assumption of an inhalation absorption factor of 100%, and 2) a dermal exposure with a dermal absorption factor of 50%. For the purposes of risk assessment, the toxicity endpoint for both the dermal and inhalation exposure is the 6-month dog (oral exposure) ocular toxicity study having a NOEL of 0.06 mg/kg/day. It should be noted that the LOEL in this study is based on statistically significant plasma cholinesterase inhibition on days 2 and 3 of treatment. Based on the similarity of the dermal and oral LD_{50}s for the technical, it is appropriate to use the oral toxicity endpoint with the dermal exposure to estimate risk (margins of exposure). The plasma cholinesterase inhibition observed in this study was also used as the endpoint of concern to estimate MOEs by the inhalation route of exposure. The support for this rationale is the absence of an inhalation toxicity study and the fact that the oral LD_{50} and inhalation LC_{50} for the technical and 5G are both category I. On this basis, we have NO reason to believe that chlorethoxyfos is less potent in terms of toxicity by the inhalation route. An inhalation toxicity study must be submitted for full Section 3 registration. The protocol for this study should be approved by the Agency.

VI. DIETARY EXPOSURE AND RISK CHARACTERIZATION

A. Dietary Exposure

The major components identified in the plant include trichloroacetic acid (TCA), D-glucose, and oxalate. Neither the parent chlorethoxyfos or its oxygen analog are detected in any above-ground portion of the plant at any time during the growing period. Detectable residues (limit of detection, 0.01 ppm) of the parent, oxygen analog, or TCA are not expected in corn grain at the normal label rate. Residues of TCA are not expected in corn grain at the normal label rate. Residues of TCA in fodder or stover at the maximum label rate are expected to be $\leq$0.03 ppm.

The metabolism of chlorethoxyfos in the goat was extensive. No significant residues of parent or its oxygen analog were found. The major metabolite of the orally administered 14C chlorethoxyfos in the goat was 14C-CO_2 which was exhaled. The major components excreted in the urine were biosynthetic intermediates like 14C-glycine, 14C-serine, 14C-glycine conjugates of benzoic acid and phenyl acetic acid. The main residue in milk was 14C-lactose. Thus all metabolites detected were the result of re-incorporation of radio activity in to natural products.

An analytical method has been validated by the EPA lab (Beltsville) for residues of chlorethoxyfos in corn grain, forage, and fodder.

The Metabolism Committee met on April 11, 1995 and discussed the results of metabolism studies and field trials for chlorethoxyfos as delineated in the J. Stokes briefing paper. No residues of the parent or oxon were found in corn commodities even after treatment at a 10x rate. Field trials also showed no residues (<0.01 ppm) of parent or oxon. Low levels (up to 0.03 ppm) of trichloroacetic acid (TCA) were found in fodder or stover. Detectable levels of TCA (>0.01 ppm) are not expected in corn grain. TCA is a rat metabolite of chlorethoxyfos and a non-genotoxic carcinogen in mice. It was concluded that there is no toxicological concern with TCA at the low levels found in corn fodder. It was also decided that the oxon need not be included in the tolerance

since detectable residues were not found following the 10x application. HED/CBTS will inform the Registration Division that additional validation data are not required for the oxon. It was also noted that the issue of including the oxon will need to be revisited if future uses such as foliar applications result in significantly higher residues. Tolerances are not required at this time for residues in milk and livestock tissues. The nature of the residues in plants and animals are understood. The residue of concern is chlorethoxyfos.

B. Dietary Risk Characterization

1. Acute Dietary Exposure/Risk

The acute dietary exposure analysis estimates the distribution of single-day exposures for the overall U.S. population and certain subgroups. The analysis evaluates individual food consumption as reported by respondents in the USDA 1977-78 Nationwide Food Consumption Survey (NFCS) and accumulates exposure to the chemical for each commodity. Each analysis assumes uniform distribution of chlorethoxyfos in the commodity supply.

The Acute Dietary Margin of Exposure (MOE) is a measure of how close the high end exposure comes to the NOEL, and is calculated as the ratio of the NOEL to the exposure (NOEL/exposure = MOE). Generally, acute dietary margins of exposure greater than 100 tend to cause no dietary concern when the data are compared to an endpoint from an animal study. The highest MOE for high end exposure in this analysis is 1,500 for females (13+ years). The lowest MOE for any population sub group is 375 for Infants (<1 year). The results of this analysis indicate that chlorethoxyfos in the diet represents no serious risk concern for acute exposure.

2. Chronic Dietary Exposure/Risk

A chronic dietary exposure analysis was conducted for chlorethoxyfos at the proposed permanent tolerances for the following commodities: corn, fresh, includes sweet - 0.01 ppm; corn, grain, field and pop - 0.01 ppm; corn, forage, field and sweet - 0.01 ppm; corn fodder, field and pop - 0.01 ppm to estimate the Theoretical Maximum Residue Contribution (TMRC) for the general population and 22 subgroups. The Reference Dose (RfD) used in the analysis is 0.0006 mg/kg bwt/day, based on a NOEL of 0.0610 mg/kg bwt/day from one year, 90-day and 6-month dog feeding studies with an uncertainty factor of 100 that demonstrated brain ChE inhibition in females. The RfD was established by the HED RfD committee. Chlorethoxyfos is classified as a Group D chemical, not classifiable as to human carcinogenicity, because of the inadequacy of evidence. As a new chemical, tolerances for chlorethoxyfos have yet to be published in the CFR. Tolerance level residues and 100 percent crop treated assumptions were made for the proposed commodities for this chronic dietary exposure analysis. Anticipated residues and percent crop treated information were not available for this analysis.

Chronic Exposure Analysis - (If the new tolerances on corn are approved)

Subgroup	Exposure (mg/kg/day)	%RfD
U.S. Population	0.000006	1.0
Children (1-6 years old)	0.000015	2.4

The chronic analysis for chlorethoxyfos is a worst case estimate of dietary exposure with all residues at tolerance level and 100 percent of the commodities assumed to be treated with chlorethoxyfos. Even without refinements, the chronic dietary exposure to chlorethoxyfos appears

to result in minimal risk for this petition on corn at 0.01 ppm and does not exceed the RfD for any of the population subgroups.

VII. OCCUPATIONAL EXPOSURE AND RISK CHARACTERIZATION

A. Occupational Exposure

A worker exposure study (MRID 425592-22) was submitted by DuPont and does satisfy the Subdivision U guideline requirements for the Fortress® 5G product tested during the study. However, in a meeting with the registrant on July 26, 1995, HED/OREB was informed that the Fortress® 5G product tested was a prototype and therefore different than the current Fortress® 2.5G product. HED/OREB has estimated exposure to loaders and applicators of Fortress® 2.5G based on the exposure data contained in the previously submitted DuPont study. HED/OREB has assumed that the exposure potential from the current Fortress® 2.5G product is the same as for the product tested during the study. Currently, no exposure data are available for Fortress® 5G applied with the SmartBox™.

Current estimates of exposure for Fortress® 2.5G assume loaders will wear long-sleeved shirt, long pants, waterproof gloves, shoes plus socks, coveralls, protective eyewear[1] and an organic vapor (OV) respirator.

Loaders working with the SmartBox™ must wear long-sleeved shirt, long pants, waterproof gloves, shoes plus socks, protective eyewear, and an OV respirator.

Applicators of both Fortress® 2.5G and Fortress® 5G (SmartBox™) must wear long-sleeved shirt, long pants, and shoes plus socks while operating a closed cab tractor. For either formulation, if the applicator exits the cab to make a repair or adjustment to the planter, the following PPE must be worn: waterproof gloves, coveralls, and protective eyewear. After completing the repairs/adjustments, but before reentering the cab, this PPE must be removed and placed in a chemical resistant bag. The bag must not be placed in the cab.

As currently labelled, Fortress® 5G (SmartBox™) is applied differently than that of the original Fortress® 5G formulation used for the exposure study. As a result, the PPE requirements may be more restrictive than might have been required if the exposure study had been conducted using the new technology (SmartBox™). On the other hand, as mentioned above, the formulation used during the original exposure study was a prototype and different from that of the current products. As a result, the additional PPE required for the Fortress® 5G (SmartBox™) product are prudent until the data outlined later in this review are provided by the registrant.

The new closed loading system for the SmartBox™ should theoretically result in minimal exposure to the handler. However, HED/OREB does not have data to verify this assumption. HED believes that until data are provided for the closed system, the PPE discussed above is required.

---

[1] The use of eye protection while handling Fortress® 5G (SmartBox™) and Fortress® 2.5G is not required by WPS based on the current toxicity values for the products (Tox Cat. III for Eye Irritation). However, the labels for both of these products require use of eye protection. HED does not currently have data that would permit the quantification of the degree of protection provided by this additional PPE.

DETAILED CONSIDERATIONS:

Head-space:

During HED's review of data collected in the exposure study submitted by DuPont, it was noted that for the loader component, inhalation exposure was 50% of total exposure. However, exposure values for hands was only 4% of total exposure. Normally, one would expect insignificant exposure from inhalation and a higher rate for hands. However, since the product is essentially being used as a fumigant (vapor pressure 1.7×10^{-3}), during the loading process, significant volatilization of the formulation was evidently occurring. This volatilization is apparent from the value obtained from the air sampling devices worn by the workers. Furthermore, this concern is the basis for the requirement for the OV respirator.

Because of the volatile nature of chlorethoxyfos, HED/Toxicology Branch has expressed a concern for handlers being subjected to high concentrations of active ingredient when bags are opened (24 bags [50 lbs each] would be required for treatment of 180 acres[2]). Based on the results of the exposure study, it would appear that some portion of the chemical collected by the personal air samplers was most likely due vapor trapped in the head-space of the bag. Unfortunately, HED has no way of determining what portion of the exposure occurred during the other tasks performed during loading.

Consequently, HED believes it is imperative that a loader wear an approved organic vapor respirator during the loading process. Use of a dust/mist respirator would not provide the protection afforded by an OV respirator. Use of an OV respirator could reduce inhalation exposure by 90% (OREB Science Peer Review, April 4, 1994).

Cross contamination:

1. Loaders

The clothing scenario proposed by HED/OREB for handlers should provide adequate protection during loading. However, HED/OREB is very concerned about the potential contamination of the tractor cab following loading of the 2.5G product. PPE contaminated with chlorethoxyfos during loading could contaminate the cab. Data from the submitted study seem to indicate that this phenomena could occur. Therefore, loaders must remove the waterproof gloves, protective eyewear, OV respirator, and coveralls prior to entering the cab. The PPE that are removed must not be used again until properly cleaned.

Based on the type of 15-row described by as typical, HED/OREB has assumed that one loading operation will be required per day to treat 180 acres. Therefore, only one set of PPE would be required per day for loading.

---

[2] The 2.5G formulation will be marketed in 50 pound bags. DuPont has estimated that 180 acres will be treated per day (Using information provided by Dr. Yuen-shaung Ng, Biological and Economic Analysis Division (BEAD), OREB has confirmed this estimate). Therefore, at an application rate of 6.5 lb product per acre, 23 bags would be opened during the loading process (6.5 lb 2.5G/A x 180 A ÷ 50 lb 2.5G/bag = 22.4 bags).

2. Applicators.

After entering the cab, if the applicator exits the cab to make a repair or adjustment to the planter, a set of coveralls, protective eyewear, and waterproof gloves are to be used other than that used during the loading process. Upon completion of the task, the PPE must be removed and stored in a chemical resistant bag outside the tractor prior to reentering the cab. HED believes that this precaution could reduce exposure once the applicator has reentered the cab.

Fortress® 5G (SmartBox™) Exposure Study.

To answer the questions concerning potential inhalation exposure to workers during loading and application, a Subdivision U guideline exposure study is required for Fortress® 5G applied using the Smartbox™ system. The study must be conducted as outlined in Subdivision U and special consideration of the following issues in the design of the study protocol are needed.

1). Chlorethoxyfos concentrations, in the air and dermal exposure to loaders, during the transfer of the 5G product using the SmartBox™ system.

The original exposure study was conducted with Fortress® 5G loaded into conventional planter equipment. HED can use this information to estimate exposure to loaders of Fortress® 2.5G formulation. Unfortunately, no data are available for Fortress® 5G when used in the Smartbox™. HED is aware that the system should result in reduced dermal and inhalation exposure, however, since the product is volatile, there is a potential for exposure when material is transferred into the delivery system. Workers wearing a personal air sampler during this process could provide the information necessary to justify removal of an OV respirator requirement.

2). Chlorethoxyfos concentration inside the tractor cab during application of the 5G product.

Currently, there is no way for OREB to ascertain from the submitted study, the source of exposure occurring during application. Workers wearing a personal air sampler as well as a separate air sampler located in the cab could provide this needed information.

Fortress® 2.5G Estimates of Exposure.

TABLE 1 contains the estimates of exposure, expressed as μg/kg bw/day, for loaders and applicators of Fortress® 2.5G. These values are based on DuPont's exposure study.

TABLE 1. Inhalation and dermal estimates of exposure (μg/kg bw/day) for loaders and applicators of Fortress® 2.5G.

Task	Routes of Exposure (μg/kg bw/day)	
	Inhalation	Dermal
Loading	0.10	0.50
Application	0.25	0.48

Fortress® 5G (Smartbox™) Estimates of Exposure.

As indicated earlier, OREB does not have exposure data specific for Fortress® 5G when loaded and applied using the new Smartbox™ technology. However, based on several factors, OREB feels that this system of handling Fortress® 5G, could reduce worker exposure, particularly during the loading process.

1. Loading

Use of Fortress® 2.5G in a conventional planter will require a loader to open 24 bags of product. Based on the exposure study, 50% of total exposure reported during the loading process was from the air sampler. The remainder of the exposure was apparently from dermal exposure. Use of an OV respirator could reduce the inhalation component of the loader exposure by 90%.

Use of the Smartbox™ does not require loaders to open bags of product. According to DuPont, the loader only has to place the transfer box containing the formulation, obtained from the Dealer, on the Smartbox™ unit mounted on the planter. After the box has been attached and is in place, product is transferred into the lower unit. Theoretically, the loader should not come in contact with any of the product. This system should reduce loader dermal and inhalation exposure. However, since exposure to organic vapors is a concern, until the registrant provides inhalation data for workers involved with this task, an OV respirator will be required for workers loading Fortress® 5G (Smartbox™). In addition, a complete loader/applicator exposure study, based on Subdivision U Guidelines, is required for Fortress® 5G (Smartbox™).

2. Application.

For the exposure study previously conducted using conventional planters, applicators wore coveralls during the entire application period. Repairs and adjustments to equipment necessitated that the applicator exit the cab and make adjustments. In some instances, hoppers were clogged with foreign materials requiring the applicator to remove them by hand. Other problems involved clogged planters. Consequently, workers may have become contaminated outside the cab and then contaminated the inside of the tractor after reentering. HED believes that by requiring removal of coveralls, protective eyewear, and waterproof gloves after making repairs or adjustments, but before reentering the cab when applying the 2.5G product, problems with cross contamination should be reduced.

Use of the Smartbox™ should negate the need for an applicator to unclog hoppers. Planters will undoubtedly need adjustments during application, however, the chance for exposure should be less than that of the 2.5G product. In addition, applicators must wear coveralls, protective eyewear, and waterproof gloves while outside the cab making adjustments or repairs to the planter. This PPE will be removed prior to reentering the cab, thereby reducing potential contamination of the cab.

PPE Requirements.

TABLE 2 contains the PPE requirements for both Fortress® 2.5G and Fortress® 5G (SmartBox™). These requirements are based on the DuPont exposure study conducted on Fortress® 5G (open loading, conventional planter).

TABLE 2. PPE requirements for Fortress® 2.5G and Fortress® 5G (SmartBox™) applied from a closed cab tractor.		
Task	Formulation	
	Fortress® 2.5G	Fortress® 5G (SmartBox™)
Loading	Coveralls, long-sleeved shirt, long pants, shoes plus socks, waterproof gloves, protective eyewear, and OV respirator.	Long-sleeved shirt, long pants, shoes plus socks, waterproof gloves, protective eyewear, and OV respirator.
Application (In cab)	Long-sleeved shirt, long pants, and shoes plus socks.	Long-sleeved shirt, long pants, and shoes plus socks.
Application (Outside cab)	Coveralls, long-sleeved shirt, long pants, shoes plus socks, waterproof gloves, and protective eyewear.	Coveralls, long-sleeved shirt, long pants, shoes plus socks, waterproof gloves, and protective eyewear.

Calculations

Lbs ai/day

Application rate 0.1625 lb ai/A (from MRID 435503-06) x 180 acres treated per day with ground equipment (from meeting with DuPont August 8, 1995) = **29.25 lb ai/day.**

Estimates of Exposure

Fortress® 2.5G

Loaders - Dermal

2.4 μg/lb ai applied (open loading, wearing long-sleeved shirt, long pants, coveralls, waterproof gloves, and shoes plus socks) x 50% (dermal absorption[3]) x 29.25 lb ai/day ÷ 70 kg bw = **0.5014 μg ai/kg bw/day.**

Loaders - Inhalation

0.24 μg/lb ai applied (open loading, 90% reduction of reported value based on **loader wearing OV respirator)** x 29.25 lb ai/day ÷ 70 kg bw = **0.10029 μg ai/kg bw/day.**

[3] Personal communication, K. Baetcke, TB/HED, August 10,1995.

Applicators - Dermal

2.3 μg/lb ai applied (closed cab, applicator wearing long-sleeved shirt, long pants, coveralls, waterproof gloves, and shoes plus socks) x 50% (dermal absorption) x 29.25 lb ai/day ÷ 70 kg bw = **0.4805 μg ai/kg bw/day.**

Applicators - Inhalation

0.6 μg/lb ai applied (closed cab, applicator **not wearing OV respirator**) X 29.25 lb ai/day ÷ 70 kg bw = **0.25071 μg ai/kg bw/day.**

B. Occupational Risk Characterization

Using the toxicology endpoints (section V above) and the exposure (section VII above) the following MOEs were calculated.

Table 3: **Dermal Margins of Exposure (MOEs) assuming 50% Absorption**

	Endpoint NOEL (μg/kg/day)	**Dermal Exposure** (μg/kg/day)	**MOE**
Fortress 2.5G			
Applicator	60.00	0.48	120
Mixer/Loader	60.00	0.50	125
M/L/A	60.00	0.98	61

Table 4: **Inhalation Margins of Exposure (MOEs) assuming 100% Absorption**

	Endpoint NOEL (μg/kg/day)	**Inhalation Exposure** (μg/kg/day)	**MOE**
Fortress® 2.5G (respirator for M/L only)			
Applicator	60.00	0.25	240
Mixer/Loader (respirator)	60.00	0.10	600
M/L/A	60.00	0.35	171

Table 5: **Total (Dermal + Inhalation) Margins of Exposure (MOEs)**

	Endpoint NOEL (μg/kg/day)	Total Exposure (μg/kg/day)	MOE
Fortress® 2.5G (respirator for M/L only)			
Applicator	60.00	0.73	82
Mixer/Loader	60.00	0.60	100
M/L/A	60.00	1.33	45

The MOEs expressed above are based on numerous assumptions (e.g., dermal absorption, inhalation toxicity, and exposure values inside the tractor cab). Another significant unknown variable is the contribution of the organic vapor to either the dermal or inhalation exposure. Because of the nature and number of these assumptions, the MOEs may overstate the actual risk. In particular, it is likely that dermal absorption will be significantly less than 50%. It is felt that the clothing scenario proposed by HED/OREB for handlers should provide adequate protection during loading. However, HED/OREB is very concerned about the potential contamination of the tractor cab following loading of the 2.5G product. Coveralls, protective eyewear, and waterproof gloves contaminated with chlorethoxyfos during loading could contaminate the cab. Therefore, handlers of the 2.5 product must remove the waterproof gloves, protective eyewear, and coveralls required for loading prior to entering the cab. The PPE that are removed must not be used again until properly cleaned. After entering the cab, if the applicator must exit the cab to make a repair or adjustment to equipment, a different set of coveralls, protective eyewear, and waterproof gloves are to be used. Upon completion of the task, the PPE must be removed and stored in a chemical resistant bag outside the tractor prior to reentering the cab.

PPE for handlers cannot be reused

PPE for Applicators can be reused

The following is the summary of HED's recommendations for registration of chlorethoxyfos:

I. Outstanding Data Needed for Full Registration of Chlorethoxyfos: [Note: Prior Agency approval of protocols should be obtained for all studies listed.]

1. A repeat-dose dermal toxicity study (that includes monitoring of cholinesterase) conducted with the chlorethoxyfos 5G product.

2. A repeat-dose inhalation toxicity study (that includes monitoring of cholinesterase) conducted with the technical material.

3. An exposure study for Fortress® 5G with measurements of chlorethoxyfos concentrations in the air and dermal exposure to loaders during the transfer of the SmartBox™ (with 5G product) system. Plus, a study in which the measurement of chlorethoxyfos concentration inside the tractor cab during application of the 5G product while the applicator is being monitored for both dermal and inhalation exposure.

Submission of these new data (see **Dermal and Inhalation Toxicity** under section V, C; and **Fortress® 5G (SmartBox™) Exposure Study** under section VII, A) will result in an Agency reassessment of the risk and PPE requirements.

II. Labeling Requirements:

1. Both end-use product labels (5G and 2.5G) must reflect Toxicity Category I labeling due to the steep slope of the dose response curve, the volatility of the technical (high vapor pressure), and the high potential for inhalation exposure to the active ingredient (via especially the 2.5G product).

2. PPE REQUIREMENTS:

PPE requirements for Fortress® 2.5G and Fortress® 5G (SmartBox™) applied from a closed cab tractor.

Task	Formulation	
	Fortress® 2.5G	Fortress® 5G (SmartBox™)
Loading	Coveralls, long-sleeved shirt, long pants, shoes plus socks, waterproof gloves, protective eyewear, and OV respirator.	Long-sleeved shirt, long pants, shoes plus socks, waterproof gloves, protective eyewear, and OV respirator.
Application (In cab)	Long-sleeved shirt, long pants, and shoes plus socks.	Long-sleeved shirt, long pants, and shoes plus socks.
Application (Outside cab)	Coveralls, long-sleeved shirt, long pants, shoes plus socks, waterproof gloves, and protective eyewear.	Coveralls, long-sleeved shirt, long pants, shoes plus socks, waterproof gloves, and protective eyewear.

3. OTHER LABEL CONDITIONS

a) PPE used for loading the 2.5 G product must be removed prior to entering the cab and not used again until properly cleaned.

b) PPE worn by the applicator outside the cab during repairs or adjustments to the planter must be removed prior to reentering the cab and stored in a chemical resistant bag outside the tractor prior to reentering the cab.