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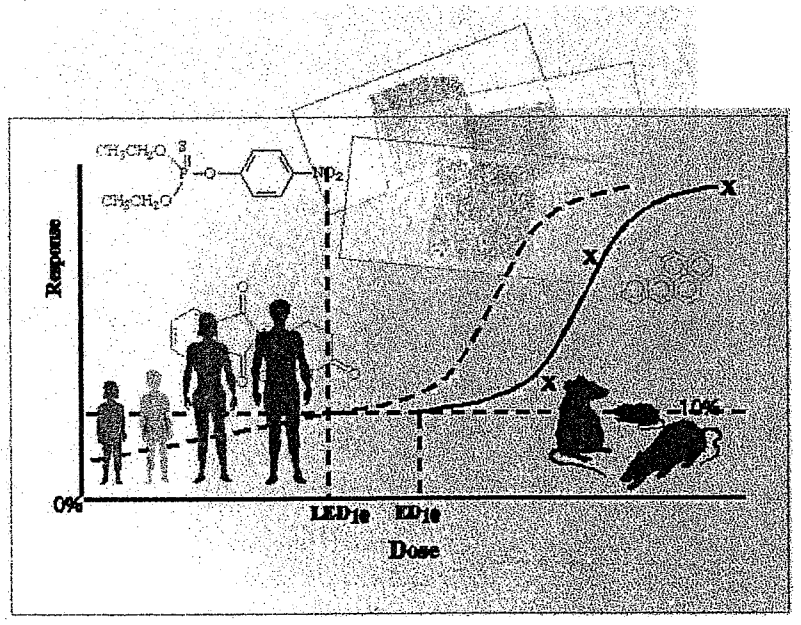
TRP

HUMAN HEALTH RISK ASSESSMENT

Tribufos



U.S. Environmental Protection Agency
Office of Pesticide Programs
Health Effects Division (7509C)

Robert Travaglini, Risk Assessor
September 14, 1999

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HUMAN HEALTH RISK ASSESSMENT

Tribufos

Phase 5

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I. Executive Summary

The Health Effects Division (HED) has evaluated the tribufos database and determined that the data are adequate to support reregistration. The toxicological database is adequate to support reregistration, although some data gaps exist. Residue chemistry data requirements are substantially complete.

Tribufos, also known as DEF, is an organophosphate defoliant/desiccant used on cotton. It is primarily used to defoliate/desiccate cotton in preparation for machine harvesting. It is also used as a defoliant to reduce or prevent losses from boll rot organisms and in conjunction with ultimate insecticide application to accelerate the aging of cotton leaves. Tribufos is manufactured and sold in the United States by Bayer Corporation (formerly Miles-Mobay Corporation, Inc.).

Hazard Assessment

The toxicology database provides strong evidence confirming that tribufos, like other organophosphates, has anticholinesterase activity in all species tested, which include hen, mice, rats, dogs and rabbits. By the oral and dermal routes technical tribufos is placed in Toxicity Category II and by the inhalation route, Category III. No data are available on the eye irritation potential of tribufos. Dermal irritation is mild to moderate, placed in Toxicity Category IV. Tribufos is not a dermal sensitizer. Inhibition of plasma, erythrocyte and/or brain cholinesterase (ChE) activity occurs by all routes (oral, dermal and inhalation) and duration (acute, subchronic and chronic) of exposures.

In addition to its ChE inhibitory effects, tribufos displayed organophosphate-type delayed neurotoxicity in the hen. Tribufos also displayed toxicity of the visual system in the rat following either oral or inhalation exposure. The irreversible visual system toxicity is manifested histopathologically by bilateral retinal atrophy (obliteration) after 12 months of exposure and atrophy of the optic nerves after 24 months of exposure in a lifetime feeding study in the rat.

Tribufos is not a developmental or a reproductive toxicant. There was no evidence of increased susceptibility to rat or rabbit fetuses following *in utero* exposures or in the offsprings following pre/post natal exposure to rats.

In accordance with the Proposed Guidelines for Carcinogen Risk Assessment (April 23, 1996), the HED Cancer Peer Review Committee (CPRC) has classified tribufos as an "unlikely human carcinogen" since all tumor increases occurred only at the highest dose tested (48.02 mg/kg/day in males and 63.4 mg/kg/day in females) and were accompanied by severe toxicity indicative of ChE inhibition. The CPRC concluded that tribufos is a "likely human carcinogen" at high doses, based on increases in tumors in: both sexes of the CD-1 mouse; the liver of male mice; in the lung of female mice; and in the small intestine in both sexes of mice. The CPRC recommended a non-quantitative approach (i.e., non-linear, Margin-of-Exposure) for the purpose of risk characterization utilizing the most sensitive toxic endpoint. The CPRC did not recommend a low-dose linear approach (i.e., q_1^*) because of the severe accompanying toxicity, typical of orangophosphate chemicals, which occurred at all doses in the mouse. HED determined that the most sensitive endpoint for chronic toxicity was plasma ChE inhibition in the one-year dog study, for which the NOAEL was 0.1 mg/kg/day. In addition, there was no apparent concern for mutagenicity, and no structural analogs of concern were identified.

The metabolism of tribufos in rats indicates that >90% of the administered dose was excreted in 72 hours and there was no significant tissue residue. Absorbed material was extensively and completely metabolized.

HED's Food Quality Protection Act (FQPA) Safety Factor Committee following review of the hazard and exposure data has recommend that the 10X Safety Factor to account for enhanced sensitivity of infants and children (as required by FQPA) should be retained. Although no increased susceptibility was seen following *in utero* exposure and pre/post natal exposures, the 10X Safety Factor is retained because of data gaps for acute and subchronic neurotoxicity studies in the rat and the concern for the developmental neurotoxic potential of tribufos. These studies are required because of the observance of neuropathological lesions in the subchronic study with hens and the combined chronic toxicity/carcinogenicity study in rats.

Exposure and Risk Assessments Conducted

Exposure and risk assessments were conducted for tribufos as follows: acute and chronic dietary assessments to capture exposure estimates for the general public; and, dermal and inhalation exposure assessments to capture estimates for occupational exposures. Nonoccupational (residential/institutional) exposure and risk assessments are not applicable since there are no registered nonoccupational (residential/institutional) uses at this time.

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Dietary Exposure and Risk

Acute

For the acute dietary risk assessment, the acute Reference Dose (RfD) of 0.01 mg/kg/day was derived by the use of the NOAEL of 1 mg/kg/day and an uncertainty factor (UF) of 100 which includes 10X for interspecies extrapolation and 10X for intraspecies variation. The NOAEL was based on inhibition of plasma and red blood cell (RBC) ChE activity at 7 mg/kg/day (LOAEL) observed in the developmental toxicity study in rats.

Chronic

For the chronic dietary risk assessment, the chronic RfD of 0.001 mg/kg/day was derived by the use of a NOAEL of 0.1 mg/kg/day and an uncertainty factor of 100 which includes 10X for interspecies extrapolation and 10X for intraspecies variation. The NOAEL was based on plasma ChE inhibition at 0.4 mg/kg/day (LOAEL) observed in a chronic toxicity study in dogs.

As per current OPP policy, an RfD modified by an FQPA Safety Factor is referred to as a Population Adjusted Dose (PAD). For tribufos the FQPA 10X safety factor was retained. Therefore, the acute PAD (aPAD) is 0.001 mg/kg/day and the chronic PAD (cPAD) is 0.0001 mg/kg/day.

Short- and Intermediate-Term

For short- and intermediate-term dermal risk assessments, the dermal LOAEL of 2 mg/kg/day was selected; a NOAEL was not established. The LOAEL was based on dose-dependent inhibitions of plasma; and RBC, and brain ChE activity observed in the 21-day dermal toxicity study in rabbits. This dose and endpoint was supported by the LOAEL of 2.6 mg/kg/day established in the 90-day dermal toxicity study in hens. A NOAEL for whole blood ChE was also not established in the hen study.

The Hazard Identification Assessment Review Committee (HIARC) determined that a Margin of Exposure (MOE) of 1000 is required for occupational exposure dermal risk assessments. The MOE of 1000 includes the conventional 100X and an additional 10X for the use of a LOAEL (i.e., lack of a NOAEL in the critical study). Note that the additional uncertainty factor of 10 is applied based on FIFRA considerations (i.e., use of a LOAEL) and not for FQPA since there are no residential/institutional uses at this time.

An MOE greater than 1000 does not exceed HED's level of concern for occupational dermal exposure risk assessments

For short- and intermediate-term inhalation risk assessments the inhalation NOAEL of 2.43 mg/L (0.9 mg/kg/day) was selected for inhalation risk assessments. The LOAEL of 12.2 mg/L (4.5 mg/kg/day) was based on RBC and plasma ChE inhibition seen in a subchronic study in rats.

An MOE greater than 100 (since a NOAEL was used) does not exceed HED's level of concern for occupational inhalation exposure risk assessments.

Dietary (Food) Exposure

The main route of exposure to tribufos for the general public (nonoccupational) is through food. Dietary (food) exposure to tribufos can occur via residues present in cottonseed oil or meal or as a result of transfer of residues from livestock feed items (cotton gin-byproducts, cottonseed hulls and cottonseed meal) to meat and milk.

The existing tolerances for meat, meat byproducts (mbyp), and fat are all 0.02 ppm; the existing milk tolerance is 0.002 ppm. Based on the maximum theoretical dietary burden for livestock, the existing tolerance is adequate to cover residues of tribufos expected in meat and mbyp. However, the existing tolerance for fat should be increased to 0.15 ppm and the tolerance for milk should be raised to 0.01 ppm.

Acute

Acute dietary (food) exposure and risk estimates do not exceed HED's level of concern. At the 99.9th percentile exposure, the most highly exposed population subgroup is children 1-6 years (8.5% of the aPAD). The acute exposure analysis was conducted using the DEEM™ software and using probabilistic (Monte Carlo techniques). For cottonseed oil and meal (the only cotton food items included in DEEM™), anticipated residues (ARs) were calculated using field trial data, reduction factors from processing studies, and percent of crop treated data. Residues in meat and milk were estimated using data from livestock metabolism and feeding studies. No further refinements can currently be made to these ARs as the USDA Pesticide Data Program (PDP) and the FDA monitoring program do not analyze for tribufos. Thus this exposure analysis has been refined to greatest extent currently possible.

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Chronic

Chronic dietary (food) exposure and risk estimates do not exceed HED's level of concern. The percent of the cPAD occupied ranged from 3% for non-nursing infants to 6% for children 1-6 years old. This exposure estimate has been extensively refined. The chronic dietary exposure analysis (from food sources) was conducted using ARs from field trials and adjustment for percent of crop treated for cottonseed oil and cottonseed meal. Residues in meat and milk were estimated using data from livestock metabolism and feeding studies. As discussed above, no further refinements can currently be made to these ARs as the USDA PDP and the FDA monitoring program do not analyze for tribufos.

Cancer

A dietary cancer risk assessment using a low-dose linear extrapolation (i.e., q_1^* approach) was not conducted because tribufos is classified as an "unlikely human carcinogen" at low doses. HED's CPRC recommended a non-quantitative approach (i.e., non-linear, Margin-of-Exposure) since evidence of carcinogenicity was seen only at the highest dose tested accompanied by severe toxicity indicative of ChE inhibition. The use of the MOE approach for cancer risk assessment is currently under review by OPP; thus, a quantitative assessment was not conducted. Also, the Agency is currently revising the 1996 Cancer Risk Assessment Guidelines.

In the case of tribufos, cancer risk from dietary exposure is less of a concern because: (1) while the chronic NOAEL was 0.1 mg/kg/day for plasma ChE inhibition, tumors were seen in mice only at the highest dose tested (48 mg/kg/day); (2) the dose of 0.1 mg/kg/day used for deriving the chronic RfD is approximately 500-fold lower than the dose that caused tumors (i.e., 48 mg/kg/day); (3) the primary concern is the non-cancer risk which manifests as ChE inhibition at a very low dose; and (4) the application of the 10X FQPA Safety Factor to the chronic RfD yields a cPAD that provides even more protection than for non-cancer dietary risk (i.e., the cPAD of 0.0001mg/kg/day is 500,000 times lower than the dose at which tumors were seen). For all these reasons and because tribufos is classified as an "unlikely human carcinogen" at low doses, HED determined that a quantitative dietary cancer risk assessment was not necessary for tribufos.

Dietary (Water) Exposure

Estimated Environmental Concentrations

Estimated environmental concentrations (EECs) from surface water sources were provided by the Environmental Fate and Effects Division (EFED). Because environmental fate testing indicates that tribufos binds to the soil and appears to be

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immobile, EFED was not concerned about residues of tribufos in groundwater. Based on the results of a Tier 2 analysis (PRIZM/EXAM II), tribufos residues can potentially be present in surface waters. The environmental EECs were 14 ppb for day 0 (maximum concentration) and the annual chronic average was 1.66 ppb based on the chronic (60-day average) EEC of 5 ppb.

Drinking Water Levels of Comparison

Currently, HED uses drinking water levels of comparison (DWLOCs) as a surrogate to capture risk associated with exposure to pesticides in drinking water. A DWLOC is the concentration of a pesticide in drinking water that would be acceptable as an upper limit in light of total aggregate exposure to that pesticide from food, water, and residential/institutional uses (if any). A DWLOC may vary with drinking water consumption patterns and body weights for specific subpopulations.

Based on the acute and chronic dietary (food) exposure estimates summarized above, DWLOCs were calculated using the Agency's default body weights and consumption values (70 kg/2L (adult male); 60 kg/2L (adult females) and 10 kg/1L (child)). Acute DWLOCs range from 10 ppb for children to 33 ppb for adult males. Chronic DWLOCs range from 1 ppb for children to 3 ppb for females and males.

Aggregate Exposures and Risk Estimates

Acute

Acute aggregate exposure and risk estimates do not exceed HED's level of concern. Acute dietary (food) exposure and risk estimates do not exceed HED's level of concern. At the 99.9th percentile exposure, the most highly exposed population subgroup is children 1-6 years at 8.5% of the aPAD. This exposure analysis has been highly refined, as described above, and cannot be further refined with data currently available. HED has no concern for acute effects through exposure to tribufos in drinking water.

Short- and Intermediate-Term

Aggregate Risks for Short- and Intermediate-Term exposure were not estimated as there are no residential/institutional exposures expected with registered uses.

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Chronic

Chronic aggregate exposure and risk estimates do not exceed HED's level of concern. For all population subgroups examined, chronic dietary exposure to tribufos residues do not exceed HED's level of concern. The percent of the cPAD occupied ranged from 3% for non-nursing infants to 6% for children 1-6 years old. Residential/institutional exposure is not expected. HED has no concern for chronic effects through exposure to tribufos in drinking water.

Occupational Exposure and Risk

Occupational chemical-specific exposure data along with data obtained from the Pesticide Handlers Exposure Database, (PHED) Version 1.1, were used to calculate short- and intermediate-term dermal and inhalation exposure to tribufos. Based on the tribufos use patterns, HED has identified four scenarios for short- and intermediate-term occupational dermal and inhalation exposure to tribufos residues: (1a) mixing/loading for aerial application; (1b) mixing/loading liquids for groundboom application; (2) applying sprays with fixed-wing aircraft; (3) applying sprays with a groundboom sprayer and (4) flagging liquid aerial applications. Long-term occupational exposures are not expected to occur for the registered uses of tribufos. The PHED data used to estimate occupational exposure are all rated "Best Available," high or medium confidence. "Best Available" is defined by HED as meeting OPP Subdivision U Guidelines.

HED identified four exposure scenarios for post-application exposure to tribufos: (1) picker operator, (2) module builder operator, (3) raker, and (4) tramper. A chemical specific study was used to determine dermal and inhalation exposures for these scenarios. Worker exposures were calculated using dosimetry data obtained from this study. Exposure estimates for post-application activities are therefore highly refined.

Occupational Risk Estimates

Short- and Intermediate-Term

Applicator Risk Estimates - Handler/Mixer/Loader/Applicator/Flagger scenarios exceed HED's level of concern for dermal risk. Risk estimates, expressed as MOEs for dermal exposure are less than 1000 despite maximum mitigation measures for the four identified exposure scenarios listed above.

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Cancer (chronic)

A quantitative cancer (chronic) risk assessment for occupational exposure was not conducted since a non-quantitative approach (i.e., non-linear, Margin-of-Exposure) was recommended for human risk characterization. The use of the MOE approach for cancer risk assessment is currently under review by OPP. Also, to apply the MOE approach for occupational exposure, a chronic exposure scenario must exist (>180 days of continuous exposure in a year). The current use pattern does not present long term dermal or inhalation exposure scenarios. Therefore, this risk assessment was not conducted.

Occupational Aggregate Risk Indexes

The Aggregate Risk Index Approach Method (ARI; reciprocal equation = $dermal_{MOE}$ + $inhalation_{MOE}$) must be used for aggregating dermal and inhalation risk estimates because the dermal exposure is being compared to an MOE with an uncertainty factor of 1000, while the inhalation exposure is being compared to an MOE with an uncertainty factor of 100.

All dermal MOEs (baseline, personal protective equipment, and engineering) exceed HED's level of concern. Some baseline, all personal protective equipment (PPE), and engineering inhalation MOEs do not exceed HED's level of concern. All ARI's for dermal and inhalation occupational exposures to tribufos however are below one, and therefore exceed HED's level of concern (see Table 12).

Post-Application Risk Estimates

Short- and Intermediate-Term

The short- and intermediate-term post-application dermal MOEs are greater than 1000 only after the following reentry intervals:

- Picker Operator: 26 days
- Module Builder Operator: 20 days
- Raker: 28 days
- Tramper: 30 days

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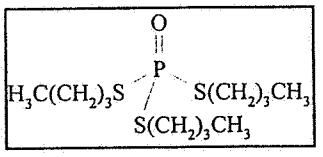
II. Product Chemistry and Use Profile

A. Physical and Chemical Properties

Tribufos (also named DEF and DEF6; chemical name, *S,S,S*-tributyl phosphorotrithioate) is an emulsifiable concentrate (EC) cotton defoliant registered for use as a total defoliant and as a bottom defoliant to reduce or prevent losses from boll rot organisms, and also as a mix with the last insecticide application to accelerate the aging of cotton leaves.



Empirical Formula: $C_{12}H_{27}OPS_3$
Molecular Weight: 314.5 g/mole
CAS Registry No.: 78-48-8
Shaughnessy No.: 074801

Tribufos is a colorless to yellow liquid with a mercaptan-like odor and a boiling point of ~150°C. Tribufos is practically insoluble in water (2.3×10^{-4} g/100 ml), but is completely miscible in dichloromethane, n-hexane, 2-propanol, and toluene. Tribufos is relatively stable to heat and under acidic conditions, but slowly hydrolyzes under alkaline conditions.

A search of the Reference Files System (REFS) conducted in July, 1999 identified a single manufacturing-use product (MP) registered to Bayer Corporation (formerly Mobay Corporation then Miles, Inc.) under Shaughnessy No. 074801, the 98% technical (T; EPA Reg. No. 3125-96). Only the Bayer tribufos T/TGAI (Technical Grade Active Ingredient) is subject to a reregistration eligibility decision.

B. Use Profile

There is one technical product of tribufos (98.0%) presently registered to Bayer Corporation (EPA Reg. No. 3125-96). There are three end-use products, one registered to Bayer (EPA Reg. No. 3125-282) and one each to Rhône-Poulenc Ag Company and Crystal Chemical Inter-America – EPA Reg. Nos. 264-498 and 67801-3, respectively. There is also one Special Local Need (SLN) product registered in Texas, (SLN #TX810045). The end-use and SLN formulations are 70.5%. The conclusions regarding the reregistration eligibility of tribufos are based on the use patterns registered by the basic producer, Bayer Corporation.

Table 1. Product Chemistry Data Summary on the Technical

Guideline Number	Requirement	Are Data Requirements Fulfilled? [1]	MRID Number [2]
61-1	Product Identity and Disclosure of Ingredients	Y	41618801
61-2	Starting Materials and Manufacturing Process	Y	41618801
61-3	Discussion of Formation of Impurities	Y	41618801
62-1	Preliminary Analysis	Y	41618802
62-2	Certification of Ingredient Limits	Y	41618802
62-3	Analytical Methods to Verify the Certified Limits	Y	41618802
63-2	Color	Y	41618803
63-3	Physical State	Y	41618803, **42382701**
63-4	Odor	Y	41618803
63-5	Melting Point	N/A [3]	
63-6	Boiling Point	Y	41618803
63-7	Density, Bulk Density or Specific Gravity	Y	41618803
63-8	Solubility	Y	41618803
63-9	Vapor Pressure	Y	41618803
63-10	Dissociation Constant	N/A [4]	
63-11	Octanol/Water Partition Coefficient	Y	41618803
63-12	pH	Y	**42382701**
63-13	Stability	Y	41618803

[1] Y = Yes; N = No; N/A = Not Applicable.

[2] All citations were reviewed under CBRS No. 8291, D166323, 12/9/91, K. Dockter, except for those **bolded** citations which were reviewed under CBRS No. 10286, D180879, 9/8/92, F. Toghrol.

[3] Data are not required because the TGAI is a liquid at room temperature.

[4] Data are not required because the TGAI/PAI does not dissociate.

All of the pertinent data concerning the tribufos TGAI are satisfied for the purposes of reregistration.

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III. Hazard Assessment

A. Toxicity Assessment

1. Acute Toxicity

Provided in Table 2 is a summary of the acute toxicity of tribufos.

Table 2. Acute Toxicity of Tribufos

Guideline Number	Study Type	MRID	Results	Toxicity Category
81-1	Acute Oral - Rat	41954903	LD_{50} =192-235 mg/kg	II
81-2	Acute Dermal - Rabbit	41954902	LD_{50} =>1000 mg/kg (m) <2000 mg/kg (f)	II
81-3	Acute Inhalation - Rat	41782301	LC_{50} =4650 mg/m^3 (m) 2460 mg/m^3 (f)	III
81-4	Primary Eye Irritation -Rat	none	Data required (irritation likely)	NA
81-5	Primary Skin Irritation - Rat	41896203	Mild to moderate erythema, dry cracked skin, edema	IV
81-6	Dermal Sensitization	41618812	negative	NA
81-7	Acute Neurotoxicity hen	none	data not required[1]	none

[1]Literature references and an acceptable 90-day dermal study in the hen show that tribufos produces organophosphate induced delayed neurotoxicity. Therefore, an acute study in the hen is not required.

2. Subchronic Toxicity

Subchronic oral toxicity studies are not available. Oral studies, however, are not required in the rodent and non-rodent species because acceptable chronic studies are available in the rat and dog.

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21-Day Dermal Toxicity Study - Rabbits

In a 21-day dermal toxicity study, groups of New Zealand White rabbits (10/sex/dose) received repeated dermal applications of tribufos at doses of 0, 2, 10 or 25 mg/kg/day nominal (0, 2, 11 or 29 mg/kg/day actual), 6 hours/day, 5 days/week over a period of 21-day. No mortality occurred at 2 or 11 mg/kg/day where as one male and four females died or were sacrificed *in extremis* at 29 mg/kg/day. Mild to moderate dermal irritation was observed at 11 and 29 mg/kg/day in both sexes. Signs of dose-related toxicity were observed in both sexes at 11 and 29 mg/kg/day, with a greater effect at the higher dose. At termination, dose-related inhibition of plasma, erythrocyte (RBC) and brain ChE activity was observed in both sexes at all dose levels. Statistically-significant ($p<0.05$) inhibition was observed in plasma (males) and erythrocytes (females) at 2 mg/kg/day and in all compartments (plasma, RBC and brain) at 11 and 29 mg/kg/day in both sexes. No recovery was observed in erythrocyte and brain ChE activity at 33-34 days (14 days post-dose). The LOAEL was 2 mg/kg/day based on plasma and brain ChE inhibition in males and females, respectively; a NOAEL was not established (MRID 42007201).

Subchronic Inhalation Toxicity Study - Rats

In a subchronic toxicity study, groups of rats (10/sex/concentration) were exposed via inhalation to tribufos at concentrations of 0, 0.93, 2.43, 12.2 or 59.5 mg/m^3 actual (0, 0.3, 0.9, 4.5, 22 mg/kg/day), 6 hours/day, 5 days/week for 90 days. No ChE inhibition was observed in either sex at 0.93 or 2.43 mg/m^3. Plasma ChE inhibition was observed in males at 12 and 60 mg/m^3 and in females at 60 mg/m^3. RBC ChE inhibition was observed at 12 and 60 mg/m^3 in both sexes. Brain ChE inhibition was seen at 60 mg/m^3 both sexes. The adrenals showed cortical fat deposition at 60 mg/m^3 in both sexes. Electro Retiniogram (ERG) was depressed (a- and b- waves) at 60 mg/m^3 in both sexes indicative of a toxic effect on the rods and cones of the retina (MRID 42399801).

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3. Chronic Toxicity

Chronic Toxicity Study - Dogs

In a chronic toxicity study, groups of four male and four female Beagle dogs were fed diets containing tribufos at doses of 0, 4, 16 or 64 ppm (equivalent to 0, 0.1, 0.4, or 1.7 mg/mg/day in males and 0, 0.1, 0.4, or 2.0 mg/kg/day in females, respectively) for 52 weeks. Inhibition of plasma ChE activity was observed in both sexes at 16 ppm. Inhibition of erythrocyte ChE activity was observed in both sexes at 64 ppm. A possible decrease in the number of erythrocytes at 64 ppm was observed in both sexes (1.7 mg/kg males, 2.0 mg/kg females). No other toxic effects were observed. The LOAEL for plasma ChE is 16 ppm (0.4 mg/kg) and the NOAEL is 4 ppm (0.1 mg/kg). The LOAEL for erythrocyte ChE is 64 ppm (1.7 mg/kg) and the NOAEL is 16 ppm. The NOAEL for brain ChE inhibition is 64 ppm (HDT) (MRID 42007203).

4. Carcinogenicity

Combined Chronic Toxicity/Carcinogenicity Study - Rats

In a combined chronic toxicity/carcinogenicity study, Fischer rats (50/sex/dose) received diets containing tribufos at doses of 0, 4, 40 or 320 ppm (equivalent to 0.0, 0.2, 1.8 and 16.8 mg/kg/day in males and 0.0, 0.2, 2.3 and 21.1 mg/kg/day in females, respectively). Complete bilateral retinal atrophy (obliteration) was observed at 12 months at the high dose, 16.8 mg/kg (320 ppm). At 24 months statistically-significant ocular damage at the high dose included cataract, lens opacity, corneal opacity, corneal neovascularization and bilateral retinal atrophy (obliteration). At doses of 0, 0.2 and 1.8 mg/kg/day ppm terminal retinal atrophy was generally unilateral and histopathologically different from that seen at the high dose.

Treatment-related effects observed included: at 0.2 mg/kg/day decreased plasma ChE was observed in both sexes; at 1.8 mg/kg/day decreased weight gain, cholesterol and calcium were observed in males; and decreased RBC ChE, RBC count, hemoglobin, and hematocrit were observed in both sexes; and at 16.8 mg/kg/day decreased weight gain in the females. In addition, both sexes of rats at 16.8 mg/kg/day exhibited the following effects: increased food consumption, cataract, lens opacity, corneal opacity, corneal neovascularization, iritis/uveitis; decreased total protein, globulin, cholesterol, calcium; increased blood urea nitrogen (BUN); decreased

brain ChE adrenals; vacuolar degeneration (12 month); retinal atrophy (12 month); autolysis, vacuolar degeneration in the small intestines (12 and 24 months); retinal atrophy, uveitis, cataract, neovascularization (24 month); atrophy of the optic nerve (24 month); vacuolar degeneration, hyperplasia of the small intestines (24 months). There was no evidence of carcinogenicity in rats. For plasma ChE inhibition, the LOAEL was 0.2 mg/kg/day LDT; a NOAEL was not achieved. For RBC ChE inhibition the LOAEL was 1.8 mg/kg/day and the NOAEL was 0.2 mg/kg/day. For brain ChE inhibition the LOAEL was 16.8 mg/kg/day and the NOAEL was 1.8 mg/kg/day (MRID 42553601).

Retinal toxicity was also observed following oral dosing in rats in the chronic/carcinogenicity study at the highest dose tested (16.8 mg/kg/day). Retinal toxicity in rats was observed at comparable doses following oral (16.8 mg/kg/day) and inhalation (22 mg/kg/day) exposure and, as such, the effect on the ERG in the inhalation study can be considered predictive of the retinal damage observed in the chronic/carcinogenicity study.

Carcinogenicity Study - Mice

In a carcinogenicity study CD-1 mice (50/sex/dose) were fed diets containing tribufos at doses of 0, 10, 50 or 250 ppm for 90 weeks. These doses were equivalent to 0, 1.64, 8.28 or 48.02 mg/kg/day in males and 0, 2.08, 11.14 or 63.4 mg/kg/day in females. At 10 ppm, decreased plasma and RBC ChE was observed in both sexes and decreased brain ChE in males. At 78 weeks, males showed decreased mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) and, at week 90 females showed decreased hematocrit. At 50 ppm, an increased number of males showed paleness and hunched backs. At 78 weeks males showed decreased MCV and MCH and at week 90 decreased MCH. At week 90 females showed decreased RBC count, hemoglobin and hematocrit.

Statistically-significant decreases in plasma, RBC and brain ChE activity was observed in both sexes at all dose levels. Pla Histopathology of the males showed: adrenals amyloid, epididymis hyperspermatogenensis, small intestine amyloid and vacuolar degeneration epithelium, and spleen hematopoiesis. At 250 ppm loose stools were observed in females, enlarged abdomen in both sexes, increased mortality/decreased life span in both sexes, and increased food consumption and body weight in both sexes. Decreased RBC count, hemoglobin, hematocrit, MCV and MCH was observed in males and

decreased RBC count, hemoglobin and hematocrit in females. Histopathology in males showed: adrenals degeneration, liver hemangiosarcoma, rectum acute inflammation, necrosis aid ulcer, small intestine adenocarcinoma, dilated/distended and mucosal hyperplasia. In females, histopathology showed: adrenals calcification and degeneration/pigmentation, caecum edema, liver hypertrophy, lung alveolar/bronchiolar adenoma, mesenteric lymph node congestion, rectum acute inflammation, necrosis and ulcer, and small intestine adenocarcinoma dilated/distended, mucosal hyperplasia). There was evidence of carcinogenicity in mice only at the highest dose tested (48.02 mg/kg/day in males and 63.4 mg/kg/day in females); males exhibited statistically-significant increase in hemangiosarcomas and adenocarcinomas of the small intestines and females exhibited statistically-significant increase in alveolar/bronchiolar adenomas (MRID 41171001).

5. Developmental Toxicity

Developmental Toxicity Study - Rats

In a developmental toxicity study pregnant Crl:COBS-CD(SD) rats received oral doses of tribufos in corn oil at 0, 0.05, 0.1 or 0.2 mg/kg/day during gestation days six through 15. For maternal toxicity, the NOAEL was 0.2 mg/kg/day (HDT); a LOAEL was not established. For developmental toxicity, the NOAEL was 0.1 mg/kg/day and the LOAEL was 0.2 mg/kg/day based on increases in early fetal resorptions, the number of litters with two or more resorptions, and post-implantation losses. There was no evidence of teratogenicity (MRID 00147533).

Developmental Toxicity Study - Rabbits

In a developmental toxicity study, pregnant New Zealand White rabbits were given a single oral dose of tribufos 0, 0.05, 0.10, 0.25 or 0.50 mg/kg/day during gestation days seven through 19. For maternal toxicity, the NOAEL was 0.1 mg/kg/day and the LOAEL was 0.25 mg/kg/day based on decreased body weight gain and increased incidence of soft stools. For developmental toxicity, the NOAEL was 0.25 mg/kg/day and the LOAEL was 0.5 mg/kg/day based on a slight reduction in fetal body weight and an increase in resorptions. There was no evidence of teratogenicity (MRID 40886301).

6. Reproductive Toxicity

Two-Generation Reproduction Study - Rats

In a two-generation reproduction study, Sprague-Dawley rats were fed diets containing tribufos at 0, 0.5, 1 or 2.5 ppm for nine weeks prior to mating (males and females) as well as during both gestation and lactation. There was no increased sensitivity to pups over the adults. The maternal/offspring NOAEL was 1 ppm (0.08 - 0.09 mg/kg/day) and the LOAEL was 2.5 ppm (0.22-0.24 mg/kg/day) based on a decreased body weight gain in females during lactation and lower pup weights during lactation days 14 and 21. For reproductive toxicity, the NOAEL was 1 ppm (0.07 mg/kg/day) and the LOAEL was 2.5 ppm (0.17 mg/kg/day) based on a decrease in pregnancy rate and male fertility. For ChE inhibition (measured only in adults), the NOAEL was 0.5 ppm (0.04 mg/kg/day) and the LOAEL was 1 ppm (0.08 mg/kg/day) based on >50% inhibition of plasma ChE activity (MRID 43649402).

A cross-fostering study to determine if pup loss in the 2-generation reproduction study (discussed above) was due to treatment of dams, pups *in utero* or both. Male and female Sprague-Dawley rats, were assigned to each of four test groups of 15 males and 30 females each. (Group 1: treated with pups with untreated dams; Group 2: untreated dams and pups; Group 3: untreated pups, treated dams; Group 4: treated pups and dams.) Groups 1 and 2 received 0 ppm and groups 3 and 4 received 260 ppm (15 mg/kg/day) tribufos in the diet. After 10 weeks on the test diet these animals were bred within their test groups. After birth, pups from groups 1 and 3 were cross-fostered so that the 0 ppm dams reared pups from 260 ppm fed dams and the 260 ppm dams reared from 0 ppm dams. Pups from groups 2 and 4 were cross-fostered within the test groups. That is, pups from 0 ppm dams were raised by 0 ppm dams that were not their birth dams and the same with pups from 260 ppm dams. Mean pup loss was 0.00, 0.47, 1.50 or 2.85 per litter for groups 1 through 4, respectively. Cannibalism was observed in treated dam groups (3 and 4). Evidence for both mechanisms plus a synergistic effect was observed in group 4. (MRID 42040103)

7. Mutagenicity

Gene Mutation Assay

In a gene mutation assay with Salmonella typhimurium strain TA98, TA1000, TA1537 and TA1538, tribufos was non-mutagenic without and with microsomal activation at concentrations up to 10,000 µg/plate (MRID 41459101).

Unscheduled DNA Synthesis Assay

In an *in vitro* unscheduled DNA synthesis assay with rat primary hepatocytes, tribufos was negative at concentrations of 0.0001 to 0.006 µg/ml. Higher concentrations were cytotoxic (MRID 41459102).

Chromosomal Aberrations Assay

In an *in vitro* chromosomal aberrations assay in Chinese hamster ovary cells, tribufos was negative without and with microsomal activation. Doses tested without activation, 0.004, 0.007, 0.013, 0.025 and 0.05 µl/ml, showed toxicity at 0.025 and 0.05 µl/ml. Doses tested with activation, 0.007, 0.013, 0.025, 0.05 and 0.1 µl/ml, showed toxicity at 0.05 and 0.1 µl/ml (MRID 41459103).

8. Metabolism

The metabolism study using [1-C^{14}] tribufos was performed in five male and five female rats given a single oral dose, 5mg/kg or 100 mg/kg or 5 mg/kg/day X 14 days cold tribufos followed by 5 mg/kg [1-C^{14}] tribufos. 55 to 80% was absorbed of which 90+% was excreted in 72 hours. There was no significant tissue residue. Absorbed material was extensively and completely metabolized (MRID 42034501).

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9. Neurotoxicity

Sufficient data are available on the subchronic neurotoxicity of tribufos by the dermal route in hens to detect organophosphate induced delayed neurotoxicity (OPIDN).

Subchronic Neurotoxicity - Hens

Tribufos was applied to the comb of 12 hens at doses of 0, 2.6, 11, or 42 mg/kg/day for 90 days. Triortho-cresolphosphate (TOCP) was utilized as a positive control at 18 mg/kg/day. Doses were applied to the comb of the hen. Effects observed in the tribufos-treated hens were failure to gain weight, ataxia in seven of twelve hens, and whole blood ChE inhibition. Histopathology indicative of neurotoxicity was observed primarily in the brain and spinal cord of hens at the highest dose tested (42 mg/kg/day). Whole blood ChE inhibition was observed at the lowest dose tested (2.6 mg/kg/day). For systemic toxicity, the LOAEL was 11 mg/kg/day based on decreased weight gain and the NOAEL was 2.6 mg/kg/day. For ChE inhibition, the LOAEL was 2.6 mg/kg/day; a NOAEL was not achieved (MRID 42007202).

In addition to its' neurotoxicity secondary to irreversible ChE inhibition, tribufos displayed organophosphate type delayed neurotoxicity in the hen and toxicity of the visual system in the rat. The visual system toxicity is manifested histopathologically by bilateral retinal atrophy (obliteration) at 12 months and atrophy of the optic nerves at 24 months in a lifetime feeding study in the rat. These effects were also observed in the rat subchronic inhalation study

Effect and no effect levels for ChE inhibition have been demonstrated in the rat, rabbit, and dog by the full battery of toxicity tests (oral, dermal and inhalation) that monitor this parameter.

Effect and no effect levels for organophosphate type delayed neurotoxicity have been demonstrated by clinical observation and by histopathology in a 90-day dermal study in the hen. Histopathological examination of the nervous system followed *in situ* perfusion and fixation. This method minimizes artifacts induced by removal of the tissue and allows for highly sensitive detection of chemical induced lesions. Also, the hen is sensitive to this unique human toxicity.

Effect and no effect levels for the visual system toxicity have been demonstrated in the rat lifetime feeding study. However, the unique toxicity (bilateral retinal atrophy (obliteration) at the high dose at 12 months) is manifest as a completed process at the first scheduled sacrifice. The retina and its unique cells are gone. Sometime during the 12-month dosing period the cells of the retina were killed by the treatment and removed. It is necessary, for risk assessment, to determine when this irreversible process started. The subsequent optic nerve atrophy also indicated the possibility of additional CNS toxicity. Although the brain and spinal cord were examined histopathologically in the lifetime study at 12 and 24 months they were not perfused *in situ*.

Data Requirement

Because of the neurotoxicity demonstrated via the oral and dermal routes, HIARC determined that a 90-day neurotoxicity study in the rat is required. This study must include ChE determinations (before, during and at termination), electroretinograms (before, during and at termination) and histopathology of the nervous system after *in situ* fixation. Tissues examined must include the eye, brain, spinal cord, and representative peripheral nerves. The functional observation battery is not necessary. The high dose must be at least as high as that in the chronic rat feeding study (16.8 mg/kg/day). A higher dose may be considered to hasten the onset of neurotoxicity. A study protocol should be submitted to HED before commencing the study.

10. Dermal Absorption

A dermal absorption study was performed in the rat at doses of 2.8, 14.0 or 140 µg/cm^2 and exposures of 1, 4 and 10 hours plus a 10-hour wash with 168-hour exposure (158 hours after exposure, the animals were sacrificed). Significant skin residue remained after the soap and water wash at 1, 4, and 10 hours (30-40%). The 10-hour residue was mostly absorbed at 168 hours. Maximum absorption was 34-44 % after the 168-hour exposure (MRID 42350003).

B. Dose Response Assessment

1. Special Sensitivity to Infants and Children

On August 8, 1998 the HED FQPA Safety Factor Committee evaluated both the hazard and exposure data for tribufos. Although no increased sensitivity of fetuses as compared to maternal animals was observed following *in utero* exposure in developmental toxicity studies in rats and rabbits and no increased sensitivity of pups as compared to adults was observed in a multigeneration reproduction study in rats, the Committee recommend that the FQPA 10X Safety Factor should be retained for tribufos because:

(a) A data gap exists for acute and subchronic neurotoxicity studies in rats. Thus, data on ChE inhibition, functional observation battery, as well as histopathology of the central and peripheral nervous systems are not available for evaluation after single or repeated exposures to tribufos.

(b) A developmental neurotoxicity study is *required,* based on OPIDN. The concern for the developmental neurotoxic potential of tribufos was elicited by neuropathological lesions in the subchronic study with hens (MRID 42007202) and in the combined chronic toxicity/carcinogenicity study in rats (MRID 42335101), as well as data gaps for acute and subchronic neurotoxicity studies in rats.

2. Toxicity Endpoint Selection

On January 28, 1997, the HED's Toxicology Endpoint Selection Committee (TESC) selected the doses and endpoints for acute dietary as well as occupational exposure risk assessments. On May 14, 1998, during the comprehensive review of the organophosphates, HED's HIARC confirmed the doses and endpoints selected by the TESC.

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a. Acute Dietary (Acute Reference Dose)

An acute RfD of 0.01 mg/kg/day was derived from the NOAEL of 1 mg/kg/day based on decreases in plasma and RBC ChE activity at 7 mg/kg/day (LOAEL) in the prenatal developmental toxicity study in rats (MRID 40190601) and an uncertainty factor of 100 which includes the 10X interspecies extrapolation and 10X for intraspecies variation.

The TESC selected the dose and endpoint from the developmental toxicity study as: (1) an acute neurotoxicity study (single exposure) is not available in the database; (2) it was presumed that the plasma and RBC inhibition seen on Gestation Day 16 can occur after a single dose; and (3) this dose and endpoint is supported by the results of the prenatal developmental toxicity study in rabbits (MRID 40190602). In that study following oral dosing at 0, 1, 3 or 9 mg/kg/day, significant decreases in ChE activity was seen at all doses tested; plasma and RBC ChE inhibition was seen on Gestation Day 20 and RBC inhibition was seen on Gestation Day 28. The LOAEL was 1 mg/kg/day; a NOAEL was not established for ChE inhibition.

$$\textbf{Acute RfD} = \frac{\text{1 mg/kg/day (NOAEL)}}{\text{100 (UF)}} = \textbf{0.01 mg/kg}$$

As per current OPP policy, an acute RfD modified by an FQPA Safety Factor is referred to as an acute Population Adjusted Dose (aPAD). Thus, with the FQPA 10X Safety Factor, the aPAD is 0.001 mg/kg/day.

$$\textbf{Acute PAD} = \frac{\text{0.01 mg/kg (acute RfD)}}{\text{10 (FQPA safety factor UF)}} = \textbf{0.001 mg/kg}$$

b. Chronic Dietary (Chronic Reference Dose)

A chronic RfD of 0.001 mg/kg/day was derived by using the NOAEL of 0.01 mg/kg/day and an uncertainty factor of 100 which includes the 10X for interspecies extrapolation and 10X for intraspecies variation. The NOAEL was based on plasma ChE inhibition seen at 0.4 mg/kg/day in a chronic toxicity study (MRID 42007203) in the dog.

$$\textbf{Chronic RfD} = \frac{0.1 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}} = \textbf{0.001 mg/kg}$$

As per current OPP policy, a chronic RfD modified by an FQPA Safety Factor is referred to as a chronic Population Adjusted Dose (cPAD). Thus, with the FQPA 10X Safety Factor, the cPAD is 0.001 mg/kg/day.

$$\textbf{Chronic PAD} = \frac{0.001 \text{ mg/kg (acute RfD)}}{10 \text{ (FQPA Safety Factor UF)}} = \textbf{0.0001 mg/kg}$$

c. Carcinogenicity Classification

In accordance with the Proposed Guidelines for Carcinogen Risk Assessment (April 23, 1996), the HED Cancer Peer Review Committee (CPRC) has classified tribufos as an "unlikely human carcinogen" since all tumor increases occurred only at the highest dose tested (48.02 mg/kg/day in males and 63.4 mg/kg/day in females) and were accompanied by severe toxicity indicative of ChE inhibition. The CPRC concluded that the overall evidence indicated that tribufos is a "likely human carcinogen" at high doses, based on increases in tumors in both sexes of CD-1 mouse, the liver of male mice, in the lung of female mice, and in the small intestine in both sexes of mice. The CPRC recommended a non-quantitative approach (i.e., non-linear, Margin-of-Exposure) for the purpose of risk characterization utilizing the most sensitive toxic endpoint. The CPRC did not recommend a low-dose linear approach (i.e., q_1^*) because of the severe accompanying toxicity, typical of orangophosphate chemicals, which occurred at all doses in the mouse. It was determined that the most sensitive endpoint for chronic toxicity was plasma ChE inhibition in the one-year dog study, for which the NOAEL was 0.1 mg/kg/day. In addition, there was no apparent concern for mutagenicity and no structural analogs of concern were identified.

d. Occupational Exposure

(i). Short-Term Dermal

The dermal LOAEL of 2 mg/kg/day (the lowest dose tested) based on dose-dependent inhibitions of plasma, RBC and brain ChE activity from a 21-day dermal toxicity study in rabbits (MRID 42007201) was selected for this exposure scenario. This dose and endpoint was supported by the LOAEL of 2.6 mg/kg/day in the 90-day dermal toxicity study in hens; a NOAEL was not established (MRID 42007202).

An MOE greater than 1000 does not exceed HED's level of concern for this risk assessment. The MOE of 1000 includes the conventional 100X and an additional 10X due the observance of severe neurotoxic effects seen in the hen study (thus indicating that tribufos is a potent neurotoxicant) and for the use of a LOAEL. The additional 10X is applied based on FIFRA, not FQPA, considerations (i.e., for the use of a LOAEL).

(ii). Intermediate-Term Dermal

The dermal LOAEL of 2 mg/kg/day was also selected for this exposure scenario; an MOE greater than 1000 does not exceed HED's level of concern for this risk assessment.

(iii). Long-Term Dermal

A risk assessment for this exposure scenario is not required because based on the current use pattern (cotton), chronic exposure is not anticipated.

(iv). Inhalation Exposure (Short- and Intermediate-Term)

An inhalation NOAEL of 2.43 mg/L (0.9 mg/kg/day) established in the 90-day inhalation study (MRID 42399801) in rats was selected for this exposure scenario. The NOAEL is based on the inhibition of plasma and erythrocyte ChE activity observed at 12 mg/mL (LOAEL). An MOE greater than 100 (use of a NOAEL) does not exceed HED's level of concern for this risk assessment.

e. Summary of Toxicological Endpoints

Provided in Table 3 is a summary of the toxicological endpoints that will be used in the tribufos risk assessments, along with their respective NOAELs, Uncertainty Factors, and PADs.

Table 3. Summary of Toxicological Endpoints for Tribufos

Exposure Period	Endpoint, etc.
Acute Dietary	**Endpoint and Effect Level:** plasma and RBC ChE inhibition; NOAEL of 1 mg/kg/day **Acute RfD:** 0.01 mg/kg/day **UF:** 100 **FQPA SF:** 10 **Acute PAD:** 0.001 mg/kg/day.
Chronic Dietary	**Endpoint and Effect Level:** plasma ChE inhibition; NOAEL of 0.1 mg/kg/day **Chronic RfD:** 0.001 mg/kg/day **UF:** 100 **FQPA SF:** 10 **Chronic PAD**: 0.0001 mg/kg/day
Short-Term Dermal	**Endpoint and Effect Level:** plasma, erythrocyte and brain ChE inhibition; dermal LOAEL of 2 mg/kg/day **MOE Threshold**: MOE greater than 1000 does not exceed HED's level of concern

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Table 3. Summary of Toxicological Endpoints for Tribufos

Exposure Period	Endpoint, etc.
Intermediate-Term Dermal	**Endpoint and Effect Level:** plasma, erythrocyte and brain ChE inhibition; dermal LOAEL of 2 mg/kg/day **MOE Threshold**: MOE greater than 1000 does not exceed HED's level of concern
Short and Intermediate-Term Inhalation	**Endpoint and Effect Level:** plasma and RBC ChE inhibition; inhalation NOAEL of 2.43 mg/L (0.9 mg/kg/day) **MOE Threshold**: MOE greater than 100 does not exceed HED's level of concern
Long-Term Dermal and Inhalation	Long-term dermal or inhalation occupational exposure are not expected to occur for the registered uses of tribufos.

IV. Exposure Assessment

A. Dietary (food/drinking water) Exposure and Risk Characterization

1. Dietary Exposure - Food Sources

a. Plant Metabolism

The reregistration requirements for plant metabolism are fulfilled. An acceptable study, depicting the qualitative nature of the residue in cotton plants, has been submitted and evaluated. Parent tribufos was the principal residue identified, and accounted for >80% of TRR in/on cotton forage and 50% of TRR in/on cottonseed. Based on this study, the HED Metabolism Committee has determined that the residue of concern in/on plant commodities is tribufos *per se*, which is the residue that is currently regulated. (40 CFR §180.272)

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b. Animal Metabolism

The reregistration requirements for animal metabolism are fulfilled. Acceptable studies, depicting the qualitative nature of the residue in ruminant and poultry, have been submitted and evaluated. The HED Metabolism Committee (June 7, 1995) has concluded that the residue of concern in animal commodities is tribufos *per se*, which is the residue that is currently regulated. The metabolism of tribufos in ruminants and poultry is proposed to occur by hydrolysis of the parent butyl mercaptan, which is further metabolized and incorporated into natural products such as fatty acids, glycerides, and phospholipids. Butyl mercaptan may also be incorporated into proteins or converted 3-hydroxybutyl-methyl sulfone. 3-Hydroxybutylmethyl sulfone can form sulfate and glucuronic conjugates.

Based on the results of the poultry metabolism study, the Agency has concluded that a poultry feeding study is not required; there is no reasonable expectation of finite residues of tribufos in eggs and poultry tissues (Category 3 of 40 CFR §180.6 (a)). Because the ruminant metabolism study indicated a potential for residue accumulation and the residue of concern, tribufos, was identified in milk and fat, a ruminant feeding study was required.

c. Residue Analytical Method - Plants and Animals

The requirements for residue analytical methods are fulfilled for the purposes of reregistration. Acceptable methods are available for enforcement and data collection purposes for cottonseed commodities and milk. A method for the determination of tribufos in animal tissues and milk that is a modification of PAM Vol. II, Method II has been submitted and is adequate for enforcement purposes.

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d. Storage Stability

Adequate storage stability data are available to support the storage intervals and conditions of samples of cottonseed, processed commodities of cottonseed (meal, hulls, and refined oil) and ruminant commodities used for tolerance reassessment. Storage stability data were submitted to support the confined rotational crop study. All pertinent rotational crop samples used to characterize/identify tribufos residues in rotational crops were stored for less than 30 days prior to analysis, negating the need for storage stability data. No additional storage stability data are required.

e. Magnitude of the Residue - Meat, Milk, Poultry & Eggs

There are no registered direct animal treatments for tribufos on cattle, goats, hogs, horses, sheep, or poultry. Reregistration requirements for magnitude of the residue in meat, milk, poultry, and eggs are partially fulfilled and can be upgraded. An animal feeding study has been conducted on dairy cows fed tribufos at 9 ppm, 33 ppm, and 121 ppm in their feed.

The existing tolerances for meat, meat byproducts (mbyp), and fat are all 0.02 ppm. The existing tolerance is adequate to cover residues of tribufos expected from meat and mbyp. However, the existing tolerance for fat (0.02) appears to be too low. The existing tolerance for fat should be revoked and a tolerance of 0.15 ppm is recommended for tribufos residues in fat.

Additional data concerning the tribufos residues in milk from cows fed at the 6X feeding level should be submitted; until such data are available, the existing milk tolerance is reassessed at 0.01 ppm (from 0.002 ppm).

Tolerances for fat of cattle, goats, and sheep should be raised to 0.15 ppm.

Tolerances for residues of tribufos in the fat, meat, and meat byproducts of hogs and horses at 0.02 ppm must be proposed.

Based on the results of the poultry metabolism study, the Agency has concluded that a poultry feeding study is not required; there is no reasonable expectation of finite residues of tribufos in eggs and poultry tissues (Category 3 of 40 CFR §180.6 (a)).

f. Magnitude of the Residue - Crop Field Trials/Processed Food/Feed

Adequate field trial data, reflecting use of the registered EC formulation at the maximum registered use pattern, have been submitted for the raw agricultural commodities (RACs) cottonseed and cotton gin byproducts. The field trial data for cottonseed support the established 4 ppm tolerance. The data for cotton gin byproducts indicate that a 40 ppm tolerance should be established for this RAC. The feed additive tolerance of 6 ppm for cottonseed hulls is not required and should be revoked.

The reregistration requirements for magnitude of the residue in processed cottonseed commodities are fulfilled. An acceptable cottonseed processing study has been submitted; residues of tribufos *per se* were not observed to concentrate in cottonseed meal, hulls, and refined oil. Reduction factors for these processed commodities are summarized below in Table 4.

Table 4. Residues of Tribufos in Cottonseed and its Processed Commodities

Commodity	Residue (ppm)[1]	Average Residues (ppm)	Reduction Factor
Cottonseed	7.144, 7.451, 7.204	7.266	N/A
Meal	0.073, 0.059, 0.063	0.065	0.0089
Hulls	0.957, 1.098, 1.073	1.043	0.143
Crude Oil	0.576, 0.656, 0.510	0.581	0.0799
Refined Oil	0.227, 0.146, 0.266	0.213	0.029

[1]Samples analyzed in triplicate and averaged.

Based on the submitted processing study, HED concluded that a tolerance for cottonseed hulls is not warranted. Therefore, the established feed additive tolerance of 6 ppm for cottonseed hulls should be revoked.

g. Anticipated Residues

Table 5 summarizes the calculated ARs for acute and chronic exposures.

Table 5. Anticipated Residues to Be Used in Dietary Exposure (DEEM™) Analysis

Commodity	Tolerance in 40 CFR §180.272 (ppm)	Reassessed Tolerance (ppm)	ARs for Use in Risk Assessment	
			Chronic	Acute
Cottonseed oil	Not Required	--	0.010	0.029[1]
Cottonseed meal	Not Required	--	0.003	0.009[1]
Milk	0.002	0.01	0.0009[2]	0.002[2]
Fat	0.02	0.03	0.006	0.0249
Meat	0.02	0.02	0.0005	0.0018
Meat byproducts	0.02	0.02	0.0001	0.0249

[1]Acute AR = HAFT (2.82 ppm) x processing factor (0.029 for oil and 0.009 for meal) x percent crop treated (35%)

[2]All of the residue will be found in milk fat. No residues are expected in milk based water, milk non-fat solids, or milk sugar (lactose) - these milk fractions were not included in either the acute or chronic exposure analysis.

2. Dietary Risk Characterization - Food Sources

The 1989 to 1992 consumption data and the Dietary Exposure Evaluation Model (DEEM™), was used to estimate acute and chronic dietary risk for tribufos. HED uses DEEM™ to combine the pesticide residue data with food consumption data. Thus, dietary (food source) exposure is equal to pesticide residues present in food multiplied by consumption data for the food item.

a. Acute Dietary Exposure and Risk Estimates

Acute dietary (food) exposure and risk estimates do not exceed HED's level of concern. At the 99.9th percentile exposure, the most highly exposed population subgroup is children 1-6 years, at 8.5% of the aPAD.

The acute dietary analysis (from food sources) estimates the distribution of single-day exposures for the overall U.S. population and certain population subgroups. The analysis evaluates individual one-day food consumption as reported by the respondents in the USDA 1989-1992 Continuing Survey of Food Consumption by Individuals and accumulates exposure to the chemical for each commodity.

The acute exposure analysis was also conducted using the DEEM™ software and using probabilistic (Monte Carlo techniques). For cottonseed oil and meal (the only cotton food items included in DEEM™), ARs were calculated using field trial data, reduction factors from processing studies, and percent of crop treated data. Residues in meat and milk were estimated using data from livestock metabolism and feeding studies. No further refinements can currently be made to these ARs as the USDA PDP and the FDA monitoring program do not analyze for tribufos. Thus, this exposure analysis has been highly refined. Results are summarized below in Table 6.

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Table 6. Acute Dietary (Food) Exposure and Risk Estimates at Various Percentiles of Exposure

Population	95th Percentile		99th Percentile		99.9th Percentile	
	Exposure	% aPAD	Exposure	% aPAD	Exposure	% aPAD
U.S. Population	0.000012	1.2	0.000025	2.5	0.000050	5.0
Non-nursing Infants (<1 year)	0.000008	0.8	0.000023	2.3	0.000060	6.0
Children (1-6 years)	0.000026	2.6	0.000046	4.6	0.000085	8.5
Females (13+ years)	0.000009	0.9	0.000016	1.6	0.000026	2.6
Males (13+years)	0.000010	1.0	0.000019	1.9	0.000033	3.3

b. Chronic Dietary Exposure and Risk Estimate

Chronic dietary (food) exposure and risk estimates do not exceed HED's level of concern. The most highly exposed population subgroup is children 1-6 years old at 6% of the cPAD.

This exposure estimate has been extensively refined. The chronic dietary exposure analysis (from food sources) was conducted using ARs from field trials and correction for 35% crop treated for cottonseed oil and cottonseed meal. Residues in meat and milk were estimated using data from livestock metabolism and feeding studies. No further refinements can currently be made to these ARs as the USDA PDP and the FDA monitoring program do not analyze for tribufos.

The anticipated residue contribution (ARC) from food was estimated for the general population and 22 population subgroups. The results for the general population and the most sensitive subpopulations are summarized below in Table 7.

Table 7. Chronic Dietary Exposure and Risk from Food Sources

Population	Reassessed Tolerances	
	ARC (mg/kg/day)	%PAD
U.S. population	0.000003	3
Non-nursing infants <1 yr	0.000001	1
Children (ages 1-6 years)	0.000006	6
Children (ages 7-12 years)	0.000004	4
Females (13-19)	0.000003	3
Males (13-19)	0.000003	3

c. Cancer Risk Assessment

A dietary cancer risk assessment using a low-dose linear extrapolation (i.e., q_1^* approach) was not conducted since tribufos is classified as an "unlikely human carcinogen" at low doses. HED's CPRC recommended a non-quantitative approach (i.e., non-linear, Margin-of-Exposure), since evidence of carcinogenicity was seen only at the highest dose tested accompanied by severe toxicity indicative of ChE inhibition. The use of the MOE approach for cancer risk assessment is currently under review by OPP; thus, a non-quantitative assessment was not conducted. Also, the Agency is currently revising the 1996 Cancer Risk Assessment Guidelines.

In the case of tribufos, cancer risk from dietary exposure is less of a concern because: (1) while the chronic NOAEL was 0.1 mg/kg/day for plasma ChE inhibition, tumors were seen in mice only at the highest dose tested (48 mg/kg/day); (2) the dose of 0.1 mg/kg/day used for deriving the chronic RfD is approximately 500-fold lower than the dose (48 mg/kg/day) that caused tumors; (3) the primary concern is the non-cancer risk which manifests as ChE inhibition at a very low dose; and (4) the application of the 10X FQPA Safety Factor to the chronic RfD yields a cPAD that provides

even more protection for non-cancer dietary risk (i.e., the cPAD of 0.0001mg/kg/day is 500,000 times lower than the dose at which tumors were seen). For all these reasons and because tribufos is classified as an "unlikely human carcinogen" at low doses, HED determined that a quantitative dietary cancer risk assessment was not necessary for tribufos.

3. Dietary Exposure - Drinking Water Source

The available drinking water information is inadequate to fully assess exposure to tribufos and its metabolites on a national level. However, information is available on local detections in California and Texas of tribufos that can be used to extrapolate the following conclusions and generalizations.

a. Groundwater

A drinking water health advisory level for tribufos has not been established; however, some groundwater data are available for tribufos. According to *EPA Pesticide in Groundwater Data Base: A compilation of Monitoring Studies, 1971-1991 A National Summary* (EPA 734-12-92-001 September,1992) between 1984 and 1988, 569 wells were tested for tribufos in the states of CA and TX, and tribufos was not detected in any of these samples. Although an absence of detections of tribufos residues does not necessarily mean there is no exposure, environmental fate data indicate that tribufos should not be a concern in groundwater because it binds to the soil and appears to be immobile.

b. Surface Water

Tribufos can potentially contaminate surface water at application by spray drift. Substantial fractions of applied tribufos may remain available for runoff for many months postapplication (aerobic soil metabolism half-life of 745 days). The relatively high soil/water partitioning of tribufos indicates that runoff will generally occur primarily via adsorption eroding soil as opposed to dissolution in runoff water.

Tribufos is stable to abiotic hydrolysis at pHs 5 and 7, stable to direct aqueous photolysis, has a relatively low volatilization potential, undergoes slow abiotic hydrolysis at pH 9, and appears to undergo extremely slow biodegradation under aerobic conditions. Consequently, tribufos will probably be persistent in the water column of most surface waters except those with short hydrologic residence times for which flow out of the system may be the major dissipation pathway. The results of the anaerobic soil metabolism study and the anaerobic aquatic metabolism study indicate that tribufos may be a little less persistent under the anaerobic conditions found in most sediments, but that it will still be relatively persistent.

OPP does not have any monitoring data from tribufos in surface waters, but did conduct Tier 1 (GENEEC) and Tier 2 (PRZM2/EXAMS II) modeling to provide EECs of tribufos in surface water. The refined EECs are for an edge of the field pond and represent upper bound estimates of concentrations that may occur in such systems. The EECs represent conservative screens for other types of surface waters, including flowing water and lakes and ponds not located at the edge of the field.

The estimated maximum concentrations of tribufos in surface water is 14 ppb, and the estimated range of average concentrations of tribufos in surface water over a sixty (60) day period is 5 ppb. To estimate chronic exposure in drinking water, HED uses annual mean concentrations of pesticides in water. Because the concentration estimate provided represents a 60-day average, and not an annual mean, HED divided 5 ppb by a factor of three (as per the Interim Guidance for Conducting Drinking Water Exposure and Risk Assessments, October 16, 1998). The concentration estimate to use in chronic drinking water assessments is approximately 1 to 2 ppb.

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c. Drinking Water Levels of Comparison

A human health DWLOC is the concentration of a pesticide in drinking water that would result in unacceptable aggregate risk, after having already factored in all food exposures and other nonoccupational exposures for which OPP has reliable data. DWLOCs were calculated and compared to model estimates of tribufos concentrations in ground and surface water. Based on the acute and chronic dietary exposure estimates presented in Tables 6 and 7, DWLOCs were calculated using the formulas presented below.

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

where:

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

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

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 (adult male), 60 kg/2L (adult female) and 10 kg/1L (child).

(i). Acute DWLOC

The acute DWLOC for children is 10 ppb, for females it is 29 ppb, and for males it is 33 ppb:

(ii). Chronic DWLOC

The chronic DWLOC for children is 1 ppb, and 3 ppb for adult females and males.

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(iii). Comparison of DWLOCs to Model Estimated EECs

Groundwater

Concentrations of tribufos in groundwater were not estimated; however, based on the available groundwater monitoring data and the physical/chemical characteristics of tribufos, EFED determined that residues of tribufos are not expected to reach groundwater (EFED Reregistration Eligibility Determination chapter, 11/8/96 and memo from D. Spatz to R. Keigwin, 12/17/97). Therefore, HED has no concern for acute or chronic effects from tribufos in groundwater-sourced drinking water.

Surface Water

Based on the proximity of the model estimates to DWLOC values, HED has no concern for acute or chronic effects through exposure to tribufos in surface water-sourced drinking water. The model estimates represent upper-bound concentrations of tribufos residues in surface water (a small pond), and HED does not expect these concentrations to occur in finished drinking water for the following reasons: the estimates are based on a worst-case scenario (i.e., high rainfall and spray drift, soils with maximum runoff potential, and the entire simulated field is assumed to be cropped with cotton and treated with tribufos at the maximum labeled use rate). Additionally, the small pond receiving the field runoff is a closed system (i.e., it does not allow for inflow or outflow) and is of insufficient size to support a drinking water facility. Furthermore, for the chronic exposure scenarios, the model only provided 60-day mean concentrations instead of potential values for long term exposures (true chronic, i.e., lifetime) values.

B. Occupational & Residential Exposure and Risk Characterization

1. Occupational and Residential Exposure

Residential Exposure

HED has not identified any tribufos products that are intended for home use, or uses in/around schools, parks, or other public areas. Therefore, residential assessments are not appropriate.

Occupational Exposure

Tribufos is a defoliant used commercially for cotton crops. It is specifically used to defoliate cotton in preparation for machine harvesting. Tribufos accelerates the defoliation process by stimulating the formation of the abscission layer where the stem joins the stalk, causing the leaves and stems to drop cleanly to allow mechanical harvesting of the crop without staining the lint. Tribufos is formulated as a liquid technical grade, 97% active ingredient (ai), and as a liquid in EC (70.5% ai). Tribufos can be applied with aerial equipment and groundboom sprayers. Application rates vary from 1.5 -1.875 lb ai/A depending upon the application scenario. Tribufos is applied only to cotton crops. Therefore only short- and intermediate-term (no long-term) occupational exposures are expected.

a. Handler Exposure and Risk Estimate

HED has determined that there are potential exposures to mixers, loaders, applicators, and other handlers engaged in activities associated with the use-patterns associated with tribufos. Based on these use patterns, four major exposure scenarios were identified:

(1a) mixing/loading liquids for aerial application;
(1b) mixing/loading liquids for groundboom application;
(2) applying sprays with a fixed-wing aircraft;
(3) applying sprays with groundboom equipment; and,
(4) flagging for aerial spray applications.

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Occupational exposure data are available reflecting short- and intermediate-term dermal and inhalation exposures. The available chemical-specific data are included in the Pesticide Handlers Exposure Database (PHED) Version 1.1. Therefore, a separate assessment of the chemical-specific data are not necessary.

Table 8, which is located at the end of this section, "Handler Exposure and Risk Estimate," describes and summarizes the caveats and parameters specific to each exposure scenario and corresponding risk assessment.

Table 9 (see end of this section) presents the estimated short- and intermediate-term baseline dermal and inhalation exposures.

Table 10 (see end of this section) presents inhalation risk estimates for both the short- and intermediate-term exposures.

Table 11 (see end of this section) presents dermal risk estimates for both short- and intermediate term exposures.

Table 12 (see end of this section) presents the dermal and inhalation aggregate risk indices for occupational exposure. The aggregate risk index (ARI) is necessary because of the differences in the MOEs for dermal (MOE=1000) and inhalation (MOE=100) exposure risk assessments.

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Chemical-Specific Handler Study

The registrant's chemical-specific handler exposure study (MRID 42685901) was designed to determine the dermal and inhalation exposures to the workers and to monitor their blood ChE activity. The study was conducted in California and Mississippi. The worker exposures in this study, and subsequent MOEs, were determined from dosimetry data. Although ChE was also evaluated as a biological endpoint, this was not a biomonitoring study *per se* because it did not determine a quantifiable absorbed dose. The California Department of Pesticide Regulation requires that workers be removed from pesticide handling in the event of significant ChE depression which did not occur in this study. Group mean percentages of post-exposure baseline values for all job activities ranged from 95.8-06.9 for erythrocyte ChE and 95.9 - 107.5 for plasma ChE.

Application rates in the study ranged from 1.127 lb ai/acre to the maximum labeled rate of 1.877 lb ai/acre. Six groups of workers were evaluated: (1) aerial crew mixer/loaders - closed system (eight replicates); (2) ground crew mixer/loaders - closed system (eight replicates); (3) aerial crew mixer/loaders - open system (eight replicates); (4) aerial applicator/pilot (eight replicates); (5) groundboom applicator (eight replicates); and (6) aerial flaggers (16 replicates).

In California, four commercial applicator crews were monitored (two aerial and two ground crews). The mixer/loaders for the aerial applications used closed-system mixing equipment to mix tribufos from commercially-available 500-gallon bulk containers with water in the mix tank and transfer the spray mixture to the aircraft. Ayers Corporation S2R-600 aircraft were used to apply tribufos. Flaggers assisted the pilots by directing their spraying patterns. Ground spray applications, also conducted in California, used closed-system mixing equipment. For the groundboom tractors, tribufos was open mixed in commercially available containers (30 gallon drums and 5 gallon cans) with water and then the diluted spray was transferred to the sprayer. The applicators used John-Deere Hi-Cycle boom sprayers equipped with air conditioned closed cabs to treat 531 acres of cotton.

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In Mississippi, the mixer/loaders mixed tribufos with water in open mix systems and then transferred the spray mixture to the aircraft. Aerial applications were not monitored in Mississippi. Applicator replicates ranged from 3.95 - 5.05 hours in duration. The mixer/loader replicates ranged in duration from 1.55 - 4.8 hours.

The test subjects wore a long-sleeved, white, cotton or cotton synthetic blend tee-shirt and a pair of white cotton or cotton/synthetic blend tights (footless) as the whole body dosimeter. Cotton/polyester coveralls were worn over dosimeter garments. The mixer/loaders wore chemical-resistant gloves, aerial and groundboom applicators wore chemical-resistant gloves when exiting the cockpit/tractor cab. Workers also wore a baseball-type hat (or a helmet in the case of the pilots). Gauze patches were attached the outside of the worker's clothing at the chest, back, cap or helmet, and both forearms. Ethanol hand washes were used to monitor hand exposure. Personal air-sampling pumps and OVS-2 tubes were used to monitor potential inhalation exposure.

The quality assurance/quality control data (e.g., method validation, field recoveries, and storage stability) were collected and found be in the acceptable range. However, concurrent laboratory recovery data were not generated.

Calculations and Assumptions

The following assumptions are made:

- The average of the median body weights for males and females is 70 kg;
- Area treated in each scenario: a range of 350 to 1,200 acres for aerial applications (including flaggers and mixer/loaders supporting aerial applications), and 80 acres for groundboom applications; and
- Use of a dust/mist respirator assumes a five-fold protection factor.

Potential daily dermal exposure is calculated using the following formula:

Daily dermal exposure (mg ai/ay) = Unit exposure (mg ai/lb ai) x Use Rate (lb ai/A) x Daily Acres Treated (A/day).

No dermal absorption adjustment is necessary since a dermal dose was used for risk assessments.

The daily dermal and inhalation dose is calculated using a 70 kg body weight for short and intermediate-term exposures.

$$\text{Daily Dose}\left(\frac{\text{mg ai}}{\text{Kg/Day}}\right) = \text{Daily Exposure}\left(\frac{\text{mg ai}}{\text{Day}}\right) x \left(\frac{1}{\text{Body Weight (Kg)}}\right)$$

These calculations of daily dermal and inhalation doses of tribufos received by handlers are used to assess the risk to those handlers. The short-term MOEs were calculated using a dermal LOAEL of 2 mg/kg/day and an inhalation NOAEL of 0.9 mg/kg/day. The short- and intermediate-term MOEs were calculated using the following formula:

$$MOE = \frac{NOAEL\ (mg/kg/day)}{Daily\ Dose\ (mg/kg/day)}$$

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Table 8. Exposure Scenario Descriptions for the Use of Tribufos

Exposure Scenario (Scenario No.)	Data Source	Standard Assumptions[1]	Comments[2]
Mixer/Loader Descriptors			
Mixing/Loading Liquid Formulations (1a and 1b)	PHED V1.1 and MRID 426859-01	range of 350 to 1,200 acres for aerial; 80 acres for groundboom	**Baseline:** "Best Available" grades: Hands, dermal, and inhalation acceptable grades. Hands = 53 replicates; Dermal = 72 to 122 replicates; and Inhalation 85 replicates. High confidence in dermal and inhalation data. **PPE:** "Best Available" grades: Hands and dermal acceptable grades. Hands = 59 replicates and Dermal = 72 to 122 replicates. High confidence in dermal data. **Engineering Controls:** "Best Available" grades: Hands and dermal acceptable grades. Hands = 31 replicates and Dermal = 16 to 22 replicates. High confidence in dermal data. PHED data used for baseline, no protection factors (PFs) were necessary. A 50 percent PF was used for PPE represent double layer of clothing. Gloves were worn during use of engineering controls.
Applicator Descriptors			
Applying Sprays with a Fixed-Wing Aircraft (2)	PHED V1.1 and MRID 426859-01	range of 350 to 1,200 acres	**Engineering Controls:** "Best Available" grades: Hands = acceptable grades, and dermal and inhalation ABC grades. Hands = 34 replicates; Dermal = 24 to 48 replicates; Inhalation = 23 replicates. Medium confidence in dermal and inhalation data. PHED data used no PFs were necessary.

Exposure Scenario (Scenario No.)	Data Source	Standard Assumptions[1]	Comments[2]
Applying Sprays with a Groundboom Sprayer (3)	PHED V1.1 and MRID 426859-01	80 acres	**Baseline:** "Best Available" grades: Hands, dermal, and inhalation acceptable grades. Hands = 29 replicates; Dermal = 23 to 42 replicates; and Inhalation = 22 replicates. High confidence in dermal and inhalation data. **PPE:** "Best Available" grade: Dermal grades acceptable; hand grades A,B,C. Hands = 21 replicates; Dermal= 23 to 42 replicates. Medium confidence in dermal data. **Engineering Controls:** "Best Available" grade: Dermal of hands grades A,B,C. Hands= 16 replicates; Dermal= 20 to 31 replicates. Medium confidence in dermal data. PHED data used for baseline and engineering controls, no PFs were necessary. A 50 percent PF was used for PPE represent double layer of clothing.
Flagger Descriptors			
Flagging Aerial Spray Applications (4)	PHED V1.1 and MRID 426859-01	range of 350 to 1,200 acres	**Baseline, PPE, and Engineering Controls:** "Best Available" grades: Hands, dermal, and inhalation acceptable grades. Hands = 16 replicates; Dermal = 16 to 18 replicates; and Inhalation = 28 replicates. High confidence in dermal and inhalation data. PHED data were used for baseline, no PFs were necessary. A 50 percent PF was added for PPE represent coveralls. A 98% PF was added for Engineering Controls represent flagging from an enclosed truck.

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

[2]"Best Available" grades are defined by HED SOP for meeting Subdivision U Guidelines. Best available grades are assigned as follows: matrices with grades A and B data and a minimum of 15 replicates; if not available, then grades A, B and C data and a minimum of 15 replicates; if not available, then all data regardless of the quality and number of replicates. Data confidence are assigned as follows:

High = grades A and B and 15 or more replicates per body part
Medium= grades A, B, and C and 15 or more replicates per body part
Low= grades A, B, C, D and E or any combination of grades with less than 15 replicates

Table 9. Short- and Intermediate-Term Baseline Dermal and Inhalation Exposures to Tribufos

Exposure Scenario (Scenario Number)	Baseline Dermal Unit Exposure (mg/lb ai)[1]	Baseline Inhalation Unit Exposure (μg/lb ai)[2]	Application Rate (lb ai/acre)[3]	Daily Acres Treated[4]	Daily Inhalation Exposure (mg/day)[5]	Daily Dermal Exposure (mg/day)[6]
Mixer/Loader Exposure						
Mixing/Loading Liquids for Aerial Application (1a)	2.9	1.2	1.875	(1) 350	(1) 0.79	(1) 1,900
				(2)1,200	(2) 2.7	(2) 6,500
Mixing/Loading Liquids for Groundboom Application (1b)			1.875	80	0.18	440.00
Applicator Exposure						
Applying Sprays with a Fixed-Wing Aircraft (2)	See Engineering Controls	See Engineering Controls	1.875	(1) 350 (2) 1,200	See Engineering Controls	See Engineering Controls
Applying Sprays with a Groundboom Sprayer (3)	0.014	0.74	1.875	80	0.11	2.10
Flagger Exposure						
Flagging Aerial Spray Applications (4)	0.011	0.35	1.875	(1) 350	(1) 0.23	(1) 7.2
				(2) 1,200	(2) 0.79	(2) 25

[1]Baseline dermal unit exposure represents long pants, long sleeved shirt, no gloves, open mixing/loading, open cab tractor. Baseline data are not available for aerial application

[2]Baseline inhalation exposure represents no respirator

[3]Application rates are maximum values found in the tribufos labels

[4]Daily acres treated values are from EPA estimates of acreage that could be treated in a single day for each exposure scenario of concern. A range of acres treated is reported for aerial applications to cotton

[5]Daily Inhalation Dose (mg/day) = Inhalation Unit Exposure (μg/lb ai) * (1 mg/1,000 μg conversion) * Appl. rate (lb ai/acre) * Acres treated

[6]Daily Dermal Dose (mg/day) = Dermal Unit Exposure (mg/lb ai) * Appl. rate (lb ai/acre) * Acres treated

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Table 10. Short- and Intermediate-Term Inhalation Risk Estimates to Tribufos

Exposure Scenario (Scenario Number)	Baseline		Risk Mitigation Measures					
			Additional PPE -- Dust/Mist Respirator (5 - fold protection factor)			Engineering Controls		
	Dose (mg/kg/day)[1]	MOE[2]	Unit Exposure (μg/lb ai)[3]	Daily Dose (mg/kg/day)[4]	MOE[2]	Unit Exposure (μg/lb ai)[4]	Daily Dose (mg/kg/day)[1]	MOE[2]
Mixer/Loader Risk Estimate								
Mixing/Loading Liquids for Aerial Application (1a)	(1) 1.1×10^{-2}	(1) 82	0.24	(1) 2.3×10^{-3}	(1) 390	0.083	1) 7.8×10^{-4}	1) 1154
	(2) 3.9×10^{-2}	(2) 23		(2) 7.7×10^{-3}	(2) 120		2) 2.7×10^{-3}	2) 333
Mixing/Loading Liquids for Groundboom Application (1b)	2.6×10^{-3}	350		5.2×10^{-4}	1700		1.8×10^{-4}	5000
Applicator Risk Estimate								
Applying Sprays with a Fixed-Wing Aircraft (2)	See Engineering Controls	See Engineering Controls	See Engineering Controls	See Engineering Controls	See Engineering Controls	0.068	(1) 6.4×10^{-4}	(1) 1,400
							(2) 2.2×10^{-3}	(2) 410
Applying Sprays with a Groundboom Sprayer (3)	1.6×10^{-3}	560	0.15	3.2×10^{-4}	2800	0.043	9.2×10^{-5}	9800
Flagger Risk Estimate								
Flagging Aerial Spray Applications (4)	(1) 3.3×10^{-3}	(1) 270	0.07	(1) 6.6×10^{-4}	(1) 1400	0.024	1) 2.2×10^{-4}	1) 4090
	(2) 1.1×10^{-2}	(2) 82		(2) 2.3×10^{-3}	(2) 390		2) 7.7×10^{-4}	2) 1200

[1]Inhalation Dose (mg/kg/day) = Inhalation Exposure (mg/day)/Body weight (70 kg); the baseline inhalation exposure, application rates, and acres treated are listed in Table 8. A range of application rates are reported for aerial applications to cotton: (1) 350 acres, and (2) 1,200 acres

[2]Inhalation MOE = NOAEL of 0.9 (mg/kg/day)/Daily Inhalation Dose (mg/kg/day)

[3]Additional PPE: Dust/Mist respirator (Decreases the baseline unit exposure by 80%, if and only if, the worker has achieved a protective seal. This is accomplished by the worker being medically qualified to wear the specific respirator, fit tested to ensure a protective seal was achieved, and he/she has had the appropriate training to maintain the respirator in good condition in accordance with the American National Standards Institute (ANSI) and or OSHA 29CFR 1910.34)

[4]Engineering Controls: Scenarios(1a) and (1b) applies to a closed mixing system, (2) applies to an enclosed cockpit, (3) and (4) applies to an enclosed cab/truck

Table 11. Short- and Intermediate-Term Dermal Risk Estimates to Tribufos

Exposure Scenario (Scenario Number)	Baseline		Risk Mitigation Measures			
			Additional PPE[2]		Engineering Controls [3]	
	Potential Dermal Dose (mg/kg/day)[1]	Dermal MOE	Potential Dermal Dose (mg/kg/day)[1]	MOE	Potential Dermal Dose (mg/kg/day)[1]	MOE
Mixer/Loader Risk Estimate						
Mixing/Loading Liquids for Aerial Application (1a)	(1) 27	(1) < 1	(1) 0.16	(1) 13	(1) 0.081	1) 25
	(2) 93	(2) < 1	(2) 0.55	(2) 4	(2) 0.28	2) 7
Mixing/Loading Liquids for Groundboom Application (1b)	6.2	< 1	0.036	56	0.018	110
Applicator Risk Estimate						
Applying Sprays with a Fixed-Wing Aircraft (2)	See Engineering Controls	See Engineering Controls	See Engineering Controls	See Engineering Controls	(1) 0.047	(1) 43
					(2) 0.16	(2) 13
Applying Sprays with a Groundboom Sprayer (3)	0.03	67	0.024	83	0.011	180
Flagger Risk Estimate						
Flagging Aerial Spray Applications (4)	(1) 0.1	(1) 20	(1) 0.094	(1) 21	(1) 0.0021	1) 950
	(2) 0.36	(2) 6	(2) 0.32	(2) 6	(2) 0.0071	2) 280

[1]Daily Dermal Dose (mg/kg/day) = Dermal Exposure (mg/day)/Body weight (70 kg). The baseline dermal exposure, application rates, and acres treated are listed in Table 8; baseline daily dermal dose, PPE daily dermal dose, and engineering daily dermal dose are from Table 9. A range of application rates are reported for aerial applications to cotton: (1) 350 acres, and (2) 1,200 acres.

[2] Additional PPE:
Scenario 1a, 1b, & 3: Double layer of clothing and chemical resistant gloves.
Scenario 4: Double layer of clothing and no gloves.

[3] Engineering Controls:
Scenario 1a and 1b: Closed mixing/loading, single layer of clothing, chemical resistant gloves.
Scenario 2, & 3: Enclosed cockpit or cab, single layer of clothing, no gloves.
Scenario 4: Enclosed truck, single layer of clothing, no gloves

MOE = LOAEL (2 mg/kg/day)/Dermal dose (mg/kg/day); MOE = 1000

Table 12. Occupational Aggregate Risk Indexes *(ARI Approach Method* = (Reciprocal Equation =Dermal ARI + Inhalation ARI))*

Exposure Scenario (Scenario Number)	Baseline			PPE			Engineering Controls		
	Dermal MOE [1]	Inhalation MOE[2]	Aggregate ARI [3]	Dermal MOE	Inhalation MOE	Aggregate ARI	Dermal MOE	Inhalation MOE	Aggregate ARI
Mixer/Loader Risk Estimate									
Mixing/Loading Liquids for Aerial Application (1a)	(1) <1 (2) <1	(1) (2)	(1) 7.0×10^{-5} (2) 2.0×10^{-5}	(1) 13 (2) 4	(1) 390 (2) 120	(1) 1.3×10^{-2} (2) 3.6×10^{-3}	(1) 25 (2) 7	(1) 1154 (2) 333	(1) 2.5×10^{-2} (2) 7.0×10^{-3}
Mixing/Loading Liquids for Groundboom Application (1b)	<1	350	3.0×10^{-4}	56	1700	5.6×10^{-2}	110	5000	1.1×10^{-1}
Applicator Risk Estimate									
Applying Sprays with a Fixed-Wing Aircraft (2)	See Engineering Controls	See Engineering Controls	See Engineering Controls	See Engineering Controls	See Engineering Controls	See Engineering Controls	(1) 43 (2) 13	(1) 1400 (2) 410	(1) 4.3×10^{-2} (2) 1.3×10^{-3}
Applying Sprays with a Groundboom Sprayer (3)	6.7×10^{-2}	5.6	6.6×10^{-2}	8.3×10^{-2}	28	8.3×10^{-2}	180	9800	1.8×10^{-1}
Flagger Risk Estimate									
Flagging Aerial Spray Applications (4)	(1) 20 (2) 6	(1) 270 (2) 82	(1) 2.0×10^{-2} (2) 6.0×10^{-3}	(1) 21 (2) 6	(1) 1400 (2) 390	(1) 2.1×10^{-2} (2) 6.3×10^{-3}	(1) 950 (2) 280	(1) 4090 (2) 1200	(1) 9.5×10^{-1} (2) 2.8×10^{-1}

***Note:** The ARI Approach Method (ARI) must be utilized due to the Dermal Exposure being compared to an acceptable MOE of greater than 1000, and the Inhalation being compared to an acceptable MOE of greater than 100. All ARIs below 1 are considered to be of concern*

[1]Dermal MOE = LOAEL 2.0 (mg/kg/day)/Daily Dermal Dose (mg/kg/day)

[2] Inhalation MOE = NOAEL 0.9 (mg/kg/day)/Daily Inhalation Dose (mg/kg/day)

[3] $$ARI = \frac{1}{\frac{1}{MOE_{dermal}} + \frac{1}{MOE_{inhalation}}}$$

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b. Postapplication Exposure and Risk Estimates

Chemical-Specific Study

A chemical-specific study was conducted to determine the dermal and inhalation exposures (and to monitor the blood ChE) of workers engaged in postapplication activities. Ten replicates for picker operators, six replicates for module builder operators, 10 replicates for rakers, and four replicates for trampers were done as these workers conducted their activities in tribufos treated cotton fields (MRID 42701601). In addition, this study was used to compare dermal exposure and dislodgeable residue (DR) data to calculate a dermal transfer coefficient for each job category. The worker exposures in this study, and subsequent MOEs, were determined from dosimetry data. Although ChE was also evaluated as a biological endpoint, this was not a biomonitoring study *per se* because absorbed dose was not quantified. Review of the individual and group mean ChE monitoring results for workers in each job category indicates that all post-exposure ChE values were within acceptable limits. None of the workers had to be removed from exposure due to a significant ChE depression as required by the study protocol and CDPR regulations.

Tribufos was applied to cotton fields at a maximum proposed label rate of 2.5 pints/acre (equal 1.9 lb ai/acre). For the reentry exposure portion of the study, two sites in the San Joaquin Valley of California were used. For the dislodgeable residue portion of the study, two residue trials were conducted in Mississippi and two were conducted in California. Tribufos was applied using either aerial equipment or power-operated groundboom spray equipment.

In the reentry portion of the exposure study conducted in California, workers were monitored for dermal and inhalation exposure, as well as for blood ChE activity after 15 and 17 days after treatment (DAT) from the aerially treated field, and 20 DAT from the ground-treated field. Dermal exposures were monitored using gauze patch dosimeters on different parts of the worker's body, whole body dosimetry, and solvent hand rinses. Inhalation exposures were monitored using personal air sampling within the breathing zone. Air sampling pumps were attached to an OVSD-2 tube with a glass fiber filter with XAD-2 resin. The erythrocyte and plasma ChE activity of workers was also monitored on a weekly basis for a five-six week period. The passive dosimetry results of these studies were used develop transfer coefficients for picker operators, module builder operators, rakers, and trampers.

Dislodgeable residues were measured by collecting cotton bolls (tribufos is a defoliant). Cotton boll samples were collected 0, 1, 2, 4, 7 through 13, 15, and 17 DAT in California for the aerially treated field. For the field in California sprayed by ground equipment, samples were taken on 0, 1, 2, 4, 7 through 13, 15, 16, 17, 18 and 20 DAT. In Mississippi, samples were taken on 0, 1, 2, 4, 7 through 17 DAT for trial one. For trial two in Mississippi, samples were taken prior to initial application and on 0, 1, 2, 4, and 7 through 14 DAT. For the dislodgeable residue sample collection, each treated plot was divided into three subplots. At each sampling interval, one sample was collected from each subplot totaling three sample/interval/site. Cotton bolls were randomly selected, alternating from upper, middle, and lower parts of the plant to obtain a 50g sample. The cotton bolls were then immersed in 200 ml of Nekal/water solution, shaken, squeezed and decanted in a sample container.

Field, laboratory, and storage stability data were generated for each matrix. Average recoveries were found to be in acceptable ranges. The calculated dermal exposures, doses, and MOEs for the picker operators, module builders, rakers, and trampers are presented in Tables 13, 14, 15, and 16, respectively.

The transfer coefficients used for these tables were calculated using predicted dislodgeable residue data. The following transfer coefficients (expressed as a worker contacting "x" number of 50g weight cotton bolls per hours) were used for each category: picker operator 92.36 (50 g bolls/hour), module builder operator 26.13 (50 bolls/hour), rakers 15.9 (50 bolls/hour), and trampers 212.76 (50 g bolls/hour). All of the transfer coefficients represent the arithmetic means of both the aerial and ground applications. For the tramper, data were only provided for the aerial exposure.

Potential average daily exposure (ADE) is calculated as follows:

Potential ADE =

$$\frac{DR\ (\mu g/50g\ ball) \times Transfer\ Coefficient\ (50g\ bolls/hr) \times Work\ Day\ (8\ hr)}{Unit\ Adjustment\ from\ \mu g\ mg\ (1000\ \mu g)}$$

Postapplication dermal MOEs are calculated using the following formula:

MOE = LOAEL (mg/kg/day)/Dermal Dose (mg/kg/day)

For tribufos, the short- and intermediate-term LOAEL for dermal toxicity is 2 mg/kg/day. A dermal absorption adjustment was not included since the toxicity endpoint is from a study using the dermal route of exposure. MOEs of greater than 1,000 do not indicate a dermal risk estimate of concern.

The postapplication inhalation exposure data collected on days 15, 17, or 20 after treatment do not indicate a risk estimate concern. The highest individual sample collected (day 15) was 14 μg/hr. Assuming an 8-hour work day and a body weight of 70 kg, the inhalation dose at 15 DAT would be 0.0016 mg/kg/day corresponding to a MOE of 560. An inhalation MOE greater than 100 does not indicate an inhalation risk estimate of concern. The risks prior to day 15 were not estimated.

Table 13. Picker Operator Reentry Exposure to Tribufos Residues Following Application to Cotton Bolls

Days After Treatment (DAT)	Best Fit Dislodgeable Residue (μg/50g)[1]	Tc (50g/hr)[2]	Dermal Exposure (mg/day)[3]	Potential Dermal Dose (mg/kg/day)[4]	Dermal MOE[5]
0	75.55	92.36	55.82	0.80	3
5	21.00	92.36	15.52	0.22	9
10	6.32	92.36	4.67	0.067	30
15	2.02	92.36	1.49	0.021	95
20	0.67	92.36	0.50	0.0071	282
25	0.23	92.36	0.17	0.0024	833
26	0.19	92.36	0.14	0.0020	1,000

[1]The average dislodgeable residues (i.e., cotton boll) from study MRID 427016-01, were derived by converting the measured dislodgeable residue data (μg/50 gram sample) into the natural log and then running a linear regression equation to estimate the dissipation over time.

[2]Transfer coefficients calculated using: exposure (μg/hr)/dislodgeable residue (μg/50g cotton).

[3]Exposure (mg/day) = ((Best Fit Dislodgeable Residue (μg/50g) x Transfer Coefficient (50g/hr) x 0.001 mg/μg) x 8 hrs/day

[4]Dose (mg/kg/day) = Exposure (mg/day)/70 kg.

[5]MOE = LOAEL (2 mg/kg/day)/Dose (mg/kg/day). MOEs of greater than 1000 do not indicate a risk estimate of concern.

Table 14. Module Builder Operator Reentry Exposure to Tribufos Residues Following Application to Cotton Bolls

Days After Treatment	Best Fit Dislodgeable Residue (μg/50g)[1]	Tc (50g/hr)[2]	Dermal Exposure (mg/day)[3]	Potential Dermal Dose (mg/kg/day)[4]	Dermal MOE[5]
0	75.55	26.13	15.79	0.23	9
5	21.00	26.13	4.39	0.063	32
10	6.32	26.13	1.32	0.019	105
15	2.02	26.13	0.42	0.0060	333
20	0.67	26.13	0.14	0.0020	1,000

[1]The average dislodgeable residues (i.e., cotton boll) from study MRID 427016-01, were derived by converting the measured Dislodgeable Foliar Residue (DFR) data (μg/50 gram sample) into the natural log and then running a linear regression equation to estimate the dissipation over time.

[2]Transfer coefficients calculated using: exposure (μg/hr)/dislodgeable residue (μg/50g cotton).

[3]Exposure (mg/day) = ((Best Fit Dislodgeable Residue (μg/50g) x Transfer Coefficient (50g/hr) x 0.001 mg/µg) x 8 hrs/day

[4]Dose (mg/kg/day) = Exposure (mg/day)/70 kg.

[5]MOE = LOAEL (2 mg/kg/day)/Dose (mg/kg/day). MOEs of greater than 1000 do not indicate a risk estimate of concern.

Table 15. Raker Reentry Exposure to Tribufos Residues Following Application to Cotton Bolls

Days After Treatment	Best Fit Dislodgeable Residue (μg/50g)[1]	Tc (50g/hr)[2]	Dermal Exposure (mg/day)[3]	Potential Dermal Dose (mg/kg/day)[4]	Dermal MOE[5]
0	75.55	150.98	91.25	1.3	2
5	21	150.98	25.36	0.36	6
10	6.32	150.98	7.64	0.11	18
15	2.02	150.98	2.44	0.035	57
20	0.67	150.98	0.81	0.012	167
25	0.23	150.98	0.12	0.004	500
26	0.19	150.98	0.23	0.0033	606
27	0.15	150.98	0.18	0.0026	769
28	0.12	150.98	0.14	0.002	1000

[1]The average dislodgeable residues (i.e., cotton boll) from study MRID 427016-01, were derived by converting the measured dislodgeable residue data (μg/50 gram sample) into the natural log and then running a linear regression equation to estimate the dissipation over time

[2]Transfer coefficients calculated using: exposure (μg/hr)/dislodgeable residues (μg/50g cotton)

[3]Exposure (mg/day) = [(Best Fit Dislodgeable Residues (μg/50g) x Transfer Coefficient (50g/hr)/0.001 mg/μg/] x 8 hrs/day

[4]Dose (mg/kg/day) = Exposure (mg/day)/70 kg

[5]MOE = LOAEL (2 mg/kg/day)/Dose (mg/kg/day). MOEs of greater than 1000 do not indicate a risk estimate of concern

Table 16. Tramper Reentry Exposure to Tribufos Residues Following Application to Cotton Bolls

Days After Treatment	Best Fit Dislodgeable Residues (μg/50g)[1]	Tc (50g/hr)[2]	Dermal Exposure (mg/day)[3]	Potential Dermal Dose (mg/kg/day)[4]	MOE[5]
0	75.55	212.76	128.51	1.84	1
5	21	212.76	35.74	0.51	4
10	6.32	212.76	10.76	0.15	13
15	2.02	212.76	3.44	0.049	41
20	0.67	212.76	1.14	0.016	125
25	0.23	212.76	0.39	0.0056	357
30	0.082	212.76	0.14	0.002	1000

[1]The average dislodgeable residues (i.e., cotton boll) from study MRID 427016-01, were derived by converting the measured dislodgeable residue data (μg/50 gram sample) into the natural log and then running a linear regression equation to estimate the dissipation over time

[2]Transfer coefficients calculated using: exposure (μg/hr)/dislodgeable residues (μg/50g cotton)

[3]Exposure (mg/day) = [(Best Fit Dislodgeable Residues (μg/50g) x Transfer Coefficient (50g/hr) 0.01 mg/μg/mg] x 8 hrs/day

[4]Dose (mg/kg/day) = Exposure (mg/day)/70 kg

[5]MOE = LOAEL (2 mg/kg/day)/Dose (mg/kg/day). MOE's of greater than 1000 do not indicate a risk estimate concern

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2. Occupational Risk Summary and Characterization

a. Dermal and Inhalation Exposure Risk

The short- and intermediate-term dermal and inhalation risk from hand exposures are summarized below:

The calculations of short- and intermediate-term dermal risk estimates indicate that the MOEs are more than 1,000 at baseline, additional PPE, or engineering controls for the following scenarios:

- None

The calculations of short- and intermediate-term dermal risk estimates indicate that the MOEs are not more than 1,000 despite the maximum mitigation measure for the following scenarios:

(1a) mixing/loading liquids for aerial application;

(1b) mixing/loading liquids for groundboom application;

(2) applying sprays with a fixed-wing aircraft;

(3) applying sprays with a groundboom sprayer; and

(4) flagging liquid aerial operations.

The calculations of short- and intermediate-term inhalation risk estimates indicate that the MOEs are more than 100 at engineering controls for the following scenarios:

(1a) mixing/loading liquids for aerial application at PPE;

(1b) mixing/loading liquids for groundboom application at baseline;

(2) applying sprays with a fixed-wing aircraft; and

(3) applying sprays with a groundboom sprayer; and

(4) flagging liquid aerial applications at baseline (350 acres treated) and at PPE (1,200 acres treated).

b. Occupational Aggregate Risk Indices

The Aggregate Risk Index (ARI) approach was utilized due to the differences in the MOEs for dermal (1000) and inhalation (100). As shown in Table 12, all ARI's are below 1; therefore the risk is of concern. Chronic dermal or inhalation exposure is not expected for use of tribufos in agricultural areas, hence a chronic risk assessment were not conducted.

c. Postapplication Exposure Risk Estimates

As shown in Tables 13 -16, the short- and intermediate-term postapplication dermal MOEs are greater than 1000 only after the following reentry intervals:

- Picker Operator: 26 days
- Module Builder Operator: 20 days
- Raker: 28 days
- Tramper: 30 days

3. Incidence Reports

The OPP Incident Data System (IDS), Poison Control Centers database, California Department of Food and Agriculture database and the National Pesticide Telecommunications Network (NPTN) have been consulted for poisoning incident data on the tribufos. From the review of the IDS and reports from California, it appears that a significant number of spray drift cases result from the use of tribufos. It is not clear from the information collected how many of these cases are due to anticholinergic effects versus the obnoxious odor of the pesticide. Some cases result in flu-like symptoms as a result of spraying tribufos near residential areas. There were too few incidents involving mixer/loader workers that applied tribufos for HED to make any conclusions.

The Minnesota Department of Agriculture surveyed 32 states about spray drift and found a total of 2,681 complaints from 1993 through 1995. Tribufos was involved in 27 which is only 1% but it ranked 10th out 38 pesticides reported on. The second main reason was a survey by the California Department of Health Services in 1987. A total of 232 exposed residents were interviewed and 175 controls. Those with high likelihood of exposure to tribufos complained of fatigue, eye irritation, rhinitis, throat irritation, difficulty in breathing, wheezing, nausea and diarrhea. California (reportedly) no longer allows tribufos to be used within one-half mile of residential areas.

Since HED's 1997 review, there have been two drift complaints: one from Georgia in 1996 with flu-like symptoms (did not see a doctor) and one from North Carolina in 1998 where a women was outdoors when a crop duster flew over. She reported mist on skin and had inhaled the mist. She also reported nausea, headache, and developed hypertension. Her physician felt tribufos was likely the cause of her symptoms.

V. Aggregate Risk Estimates

A. Acute Aggregate Risk Estimate

Acute aggregate exposure and risk estimates do not exceed HED's level of concern. The acute aggregate risk estimate takes into consideration acute dietary food and water exposure. Based on a highly-refined probabilistic (Monte Carlo) exposure assessment, acute dietary food exposure estimates did not exceed HED's level of concern. For the most highly exposed population, children 1-6 years old, 8.5% of the aPAD was occupied at the 99.9th percentile exposure.

For acute water exposure, the maximum EEC for tribufos residues in surface water, based on Tier 2 modeling (PRZM-EXAMS) is 14 ppb. This value is higher than the DWLOC for children (10 ppb), but less than that for males and females (29 and 33 ppb respectively). However, based on the proximity of the model estimates to the DWLOC values, HED has no concern for acute effects through exposure to tribufos in drinking water. The model estimate represents an upper-bound concentration of tribufos residues in surface water (a small pond), and HED does not expect these concentrations to occur in finished drinking water (see previous discussion on drinking water risk).

B. Short- and Intermediate-Term Aggregate Risk Estimate

Tribufos does not have any registered residential/institutional uses. Because there are no residential exposures expected for tribufos, short- and intermediate-term aggregate risk assessments are not required.

C. Chronic Aggregate Risk Estimate

Chronic aggregate exposure and risk estimates do not exceed HED's level of concern. The chronic aggregate risk estimate takes into consideration chronic dietary food and water exposure. Based on a slightly refined exposure assessment, chronic dietary food exposure estimates did not exceed HED's level of concern. For the most highly exposed population, children 1-6 years old, 6% of the cPAD was occupied.

For chronic water exposure, the 60-day average EEC for tribufos residues in surface water, based on Tier 2 modeling (PRZM-EXAMS) is 5 ppb. To estimate chronic exposure in drinking water, HED uses annual mean concentrations of pesticides in water. Because the concentration estimate provided represents a 60-day average, and not an annual mean, HED divided 5 ppb by a factor of three (as per the Interim Guidance for Conducting Drinking Water Exposure and Risk Assessments, October 16, 1998). The concentration estimate to use in chronic drinking water assessments is approximately 1 to 2 ppb.

Based on the proximity of the model estimates to DWLOC values, HED has no concern for chronic effects through exposure to tribufos in drinking water. The model estimates represent upper-bound concentrations of tribufos residues in surface water (a small pond), and HED does not expect these concentrations to occur in finished drinking water (see previous discussion on drinking water risk).

VI. Tolerance Reassessment

Provided in Table 17 is a summary of the tribufos tolerance reassessment.

A. Tolerances Listed Under 40 CFR §180.272:

The tolerances listed in 40 CFR §180.272 are expressed in terms of tribufos. The HED Metabolism Committee has concluded that tribufos *per se* is the compound to be regulated. The tolerance expression is adequate.

Sufficient field trial data reflecting the maximum registered use patterns are available to ascertain the adequacy of the established tolerance for cottonseed; these data support the existing cottonseed tolerance.

Ruminant metabolism and feeding studies indicate that the established tolerances for the meat, and meat byproducts of cattle, goats, and sheep are adequate. Additional data concerning tribufos residues in milk are required before the adequacy of the established tolerance for milk can be assessed. Based on the data currently available, milk and fat tolerances have been reassessed at 0.01 and 0.15 ppm respectively. The term "negligible residues" should be removed from the tolerance expressions for fat, meat, and meat byproducts of cattle, goats, and sheep, and milk.

B. Tolerances To Be Proposed Under 40 CFR §180.272:

Tolerances for residues of tribufos in the meat, and meat byproducts of hogs and horses at 0.02 ppm must be proposed. Once adequate data concerning tribufos residues in cotton gin byproducts from cotton harvested at the established PHI are submitted, a tolerance for cotton gin byproducts must be proposed.

C. Tolerances Listed Under 40 CFR §186.5800:

Based on FQPA and the results of an acceptable cottonseed processing study, the established feed additive tolerance for cottonseed hulls should be revoked.

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Table 17. Tolerance Reassessment Summary for Tribufos

Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	Comment/ *(Correct Commodity Definition)*
Tolerances Listed Under 40 CFR §180.272:			
Cattle, fat	0.02[1]	0.15	
Cattle, meat	0.02[1]	0.02	
Cattle, meat byproducts	0.02[1]	0.02	
Cottonseed	4	4	*(Cotton, undelinted seed)*
Cotton Gin byproducts	none	40	*(Cotton, gin byproducts)*
Goats, fat	0.02[1]	0.15	
Goats, meat	0.02[1]	0.02	
Goats, meat byproducts	0.02[1]	0.02	
Milk	0.002[1]	0.01	
Sheep, fat	0.02[1]	0.15	
Sheep, meat	0.02[1]	0.02	
Sheep, meat byproducts	0.02[1]	0.02	
Tolerances to Be Proposed Under 40 CFR §180.272:			
Hogs, fat	None	0.15	
Hogs, meat	None	0.02	
Hogs, meat byproducts	None	0.02	
Horses, fat	None	0.15	
Horses, meat	None	0.02	
Horses, meat byproducts	None	0.02	
Tolerances Listed Under 40 CFR §186.5800:			
Cottonseed hulls	6	Revoke	Not warranted based on the results of an acceptable cottonseed processing study.

[1]Negligible residues

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VII. Data Requirements

A. Toxicology

- ❖ Acute Neurotoxicity - Rat (§81-8)
- ❖ Subchronic Neurotoxicity - Rat (§82-5)
- ❖ Developmental Neurotoxicity - Rat (§83-6)

B. Residue Chemistry

Magnitude of the Residues - Crop Field Trials (§171-4; k)

C. Occupational Exposure

Handler studies may be required pending the outcome of discussions on handler risk estimates and risk mitigation.

There is a data gap for the following scenario, for which HED is unable to estimate risk: (2) baseline and PPE data for applying liquids with a fixed-wing aircraft. NOTE: Only enclosed cockpit data are available.

Postapplication studies may be required pending the outcome of discussions on postapplication risk estimates and risk mitigation.

APPENDIX I

Residue Chemistry Science Assessments for Reregistration of Tribufos

GLN: Data Requirements	Current Tolerances, ppm (40 CFR)	Must Additional Data Be Submitted?	References [1]
171-3: Directions for Use	N/A = Not Applicable	Yes [2]	
171-4 (a): Plant Metabolism	N/A	No	**42350009**
171-4 (b): Animal Metabolism	N/A	No	**42034502, 42034503, 42350010, 42350011**
171-4 (c/d): Residue Analytical Methods			
- Plant commodities	N/A	No	42799001 [3], 42848001 [3], 42848002 [3], 42848003 [3]
- Animal commodities	N/A	Yes [4]	43837802 [5]
171-4 (e): Storage Stability	N/A	No[6]	42184701[7], 42350009, 43821601[8], 43837801 [5]
171-4 (k): Magnitude of the Residue in Plants			
- Cottonseed and gin byproducts	4 (seed) (§180.272)	No[2]	43837801[5], 4443901 [9]
171-4 (l): Magnitude of the Residues in Processed Food/Feed			
- Cottonseed processed commodities	6 (hulls) (§186.5800)	No	43783701 [10]
171-4 (j): Magnitude of the Residue in Meat, Milk, Poultry, and Eggs			
- Milk and the Fat, Meat, and Meat Byproducts of Cattle, Goats, Hogs, Horses, and Sheep	0.002 (milk); 0.02 (fat, meat, meat byproducts of cattle, goats, and sheep) (§180.272)	No	43821601 [8]
- Eggs and the Fat, Meat, and Meat Byproducts of Poultry	N/A	No	
171-4 (f): Nature and Magnitude of the Residue in Water	N/A	N/A	

GLN: Data Requirements	Current Tolerances, ppm (40 CFR)	Must Additional Data Be Submitted?	References [1]
171-4 (g): Nature and Magnitude of the Residue in Fish	N/A	N/A	
171-4 (h): Nature and Magnitude of the Residue in Irrigated Crops	N/A	N/A	
171-4 (l): Magnitude of the Residue in Food-Handling Establishments	N/A	N/A	
165-1: Rotational Crops (Confined)	--	No	42184701 [7]
165-2: Rotational Crops (Field)	--	No	

1. **Bolded** references were evaluated in an Agency Memorandum, CRBS Nos. 8763 and 10031, DP Barcodes D169854 and D179581, 11/23/93; S. Funk; all references were reviewed as noted.

2. No field residue data are available to support LV/ULV application of tribufos or aerial application of tribufos using oil as a diluent. Unless the registrants wish to submit field trial data to support these applications, LV/ULV Applications and aerial applications in which diesel fuel may be used a diluent should be deleted from product labels. The label should be amended to clearly state the maximum seasonal use rate of 1.9 lb ai/A.

No field residue data are available to support the registered SLN use of tribufos. Unless the registrant wishes to Submit data to support the use if tribufos on cotton at 2.25 lb ai/A, this SLN should be canceled.

3. CRBS No. 12460, DP Barcode D194656, 12/8/95, C. Eiden.

4. The submitted method for the determination of tribufos in animal tissues and milk is a modification of PAM Vol. II, Method II; independent laboratory and Agency validation is required before the method can be deemed adequate for use as an enforcement method.

5. CRBS No. 16554, DP Barcode D221143, 1/14/96, C. Eiden.

6. No further data on the storage stability requirements for tribufos are required. CRBS No. 16989, DP Barcode 223962, 4/4/96, C. Eiden.

7. CRBS Nos. 14759 and 16457, DP Barcodes D209511 and D174442, 211/15/95, C. Eiden.

8. CRBS No. 16437, DP Barcode D220694, 12/18/95, C. Eiden.

9. DP Barcode 244658, 6/16/98, J. Garbus.

10. CRBS No. 16315, DP Barcode D219920, 11/14/95, C. Eiden.

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References and/or Agency Memoranda Cited In This Document

Tribufos labels, 264-498, 3125-96, 3125-282, 67801-3, TX 81004500.

U.S. EPA 1996. Tribufos LUIS Report dated 6/10/96.

U.S. EPA 1997. Tribufos Toxicology Endpoint Selection Document.

U.S. EPA 1997. Tribufos Report of the Hazard Identification Assessment Review Committee.

U.S. EPA 1998. Tribufos Dietary Exposure Analysis (DRES) Report dated 4/24/98 (D 254069).

U.S. EPA 1998. Tribufos Dietary Exposure Analysis (DRES) Report dated 2/4/98 (D 242598).

U.S. EPA 1997. Tribufos Dietary Exposure Analysis (DRES) Report dated 3/24/97.

U.S. EPA 1996. Tribufos Usage (BEAD Memo) A. Grubbe. Memo dated 3/22/96.

U.S. EPA 1998. Report of the Hazard Identification Assessment Review Committee: A Comprehensive Review Of the Organophosphates. 7/7/98.

U.S. EPA 1998. FQPA Safety Factor Recommendations for the Organophosphates: A Combined Report of the Hazard identification Assessment Review Committee and the FQPA Safety Factor Committee. 8/6/98.

Eberhart DC. 1993. Evaluation of Worker Exposures to Tribufos During Aerial and Ground Applications of DEF 6 to Cotton. Miles, Inc. Report Number 103889 (MRID 426859-01).

Eberhart DC. and Ellisor GK. 1993. Evaluation of Worker Exposure to Tribufos During Harvesting of Cotton Treated with DEF 6. MRID 427016-01.

41618801 Talbott, T. 1990. Product Chemistry of DEF Technical: Lab Project Number: VAP0007:JDMOO66: 2172. Unpublished study prepared by Mobay Corp. 65 p.

41618802 Talbott, T. 1990. Product Chemistry of DEF Technical: Lab Project Number: 91978: 99857: 99856. Unpublished study prepared by Mobay Corp. 115 p.

41618803 Talbott, T. 1990. Product Chemistry of DEF Technical: Lab Project Number 90606: 94500: 94682. Unpublished study prepared by Mobay Corp. 29 p.

68875

42382701 Fontaine, L. 1992. Supplement to MRID 41618803: Product Chemistry of DEF Technical: Lab Project Number: BR 1804. Unpublished study prepared by Miles, Inc. 6 p.

42034502 Hall, L. 1991. The Metabolism of [Carbon 14] and [S 35]-Tribufos in Hens: Lab Project Number: DE040501: 101329. Unpublished Study prepared by Mobay Corp. 123 p.

42034503 Sahali, Y. 1991. Metabolism of [Carbon 14]-Tribufos in Lactating Goats: Lab Project Number: DE041001:. 101330. Unpublished study prepared by Mobay Corp. 83 p.

42184701 Leimkuehier, W.; Moore, K. 1991. [Carbon 14] Tribufos Residues in Confined Rotational Crops: Lab Project Number: DE051601. Unpublished study prepared by Mobay Corp. 37 p.

42350009 Chopade, H. 1992. Metabolism of [n-Butylthio-l-carbon 14] Tribufos in Cotton: Lab Project Number: DE41601: 102639. Unpublished study prepared by Miles, Inc. 87 p.

42350010 Hall, L. 1992. The Metabolism of [carbon 14] and [sulfur 35] Tribufos in Laying Hens: Lab Project Number: DE040501: 101329-1. Unpublished study prepared by Miles, Inc. 158 p.

42350011 Sahali, Y.; Jett, C. 1992. Metabolism of [1-carbon 14] Tribufos in Lactating Goats: Lab Project Number: DE041001: 101330-1. Unpublished study prepared by Miles, Inc. 114 p.

42799001 Bajzik, M. 1992. The Independent Laboratory Method Validation for the Analysis of Tribufos in Cottonseed and Soapstock: Lab Project Number: DE1 1 1601: 105003. Unpublished study prepared by Huntingdon Analytical Services. 90 p.

42848001 Gronberg, R.; Sanders, D. 1993. An Improved Analytical Residue Method for the Determination of Tribufos in Cottonseed and Cottonseed Processed Products: Lab Project Number: AO 1 2.004: DE II 1603: 105026. Unpublished study prepared by Huntingdon Analytical Services and Miles Inc. 126 p.

42848002 Gronberg, R.; Sanders, D. 1993. A Registered Product Interference Study for the Analytical Residue Method for Tribufos in Cottonseed and Cottonseed Processed Products: Lab Project Number: DE141601: 105178. Unpublished study prepared by Miles Inc. 131 p.

69875

42848003 Gronberg, R.; Sanders, D. 1993. Extraction Efficiency of the Analytical Residue Method for Tribufos in Cottonseed: Lab Project Number: DEI 1 1602: 105179. Unpublished study prepared by Miles, Inc. 21 p.

43783701 Grace, T. 1995. DEF 6EC--Magnitude of Residue in Cotton Processed Products: Lab Project Number: DE19CT01: 106988. Unpublished study prepared by Miles Research Park and Bayer Corp. 405 p.

43821601 Mathew, A.; Nguyen, T. 1995. Tribufos--A 28-Day Dairy Cattle Feeding Study: Lab Project Number: 107104: DE060401: DE130401. Unpublished study prepared by Bayer Corp. 508 p.

43837801 Krolski, M. 1995. DEF 6EC--Magnitude of the Residue on Cotton: Lab Project Number: 106993: DE19CT02: 351-DE001-94D. Unpublished study prepared by Bayer Corp. 542 p.

43837802 Gronberg, R.; Sanders, D. 1995. An Analytical Residue Method for the Determination of Tribufos Residue in Animal Tissues and Milk: Lab Project Number: 107068:DE120201. Unpublished study prepared by Bayer Corp. 32 p.

MRID 401906-01 A teratology study with DEF technical in the rat. R.L. Kowalski, Miles Laboratories Inc. Laboratory Report No. 87320, Aug 8, 1986.

MRID 401906-02 A teratogy study with DEF technical in the rabbit. G.R. Clemens, J.J. Bare and R.E. Hartnagel Jr. Miles Laboratories Inc. Laboratory Report No. MTDO003, #94468, Jan 22, 1987.

MRID 411710-01 Oncogenicity study of technical tribufos (DEFO) with mice. R.H. Hayes, Mobay, Corp. Toxicology Depart. Study No. 86-27101, Report No. 99175, Jun 29, 1989.

MRID 414591-01 Salmonella/Mammalian-microsome p late incorporation mutagenicity assay (Ames test), R.D. Curren, P.E. Gentry, Microbiological Associates, T8299.501, 1/26/89.

MRID 414591--02 Unscheduled DNA synthesis in rat primary hepa-to-cytes R.D. Curren, Microbiological Associates, T8299.3801, 3/3/89.

MRID 414591-03 Chromosome aberrations in Chinese hamster ovary (CHO) cells, D.L. Putman & M.J. Morris, Microbiological Associates, T82)R9.337, 3/21/89.

MRID 416188-12 Dermal sensitization study with technical grade tribufos (DEFO) in guinea pigs, L.P. Sheets, Mobay Corp Toxicology Dept., Study No. 90-324-GK, Aug 17, 1990.

70875

MRID 417823-01 Acute four-hour inhalation toxicity study with technical grade DEF in rats, D.L. Warren, Mobay.

Toxicology Department. Study number 90-042-HQ, Report # 100593, Dec 26, 1990.

MRID 418963-03 Primary dermal irritation study with technical grade tribufos (DEF'81) in rabbits, L.P. Sheets, M.K. Fuss.

Mobay Corp Toxicology Dept., Study No. 90-325-FS, Apr 30, 1991.

MRID 419549-02 Acute Dermal Toxicity study with Technical grade tribufos (DEFO) in rabbits, L.P. Sheets, S.D. Phillips Mobay, Study No 90-025-FE, Report # 100698, May 31, 1991.

MRID 419549-03 Acute Oral Toxicity with Technical grade tribufos (DEF@9) in rats, L.P. Sheets, Mobay, Study No 90012-ES, Report # 100697, May 20, 1991.

MRID 420072-01 21-day dermal toxicity study with technical grade Tribufos (DEFO) in rabbits, L.P. Sheets & S.D. Phillips, Mobay, Study Number 90-125-FR, Report # 101279 Aug 21, 1991.

MRID 420072-02 Subchronic delayed neurotoxicity study with technical grade tribufos (DEFO) in hens, L.P. Sheets, Mobay, Corporate Toxicology Department, Study number 89-428-CS, Feb 26, 1991.

MRID 420072-03 Chronic feeding toxicity study of technical grade tribufos (DEFO) with dogs, W.R. Christenson, Mobay Corporate Toxicology Department, Study Number 88-274-AB, Feb 26, 1991.

MRID 420345-01 Disposition and metabolism of [1-14C] Tribufos in rats. L-R. M. Kao, R.N. Midden, L.L. Bosnal and M.E. Krolski; Mobay, Ag Chem Div, Research and Development Department, Study Number DE041801, Report Number 101331, Aug 28, 1991.

MRID 420401-01 A two-generation dietary reproduction study in rats using Tribufos (DEFO), D.A. Eigenberg; Mobay, Corporate Toxicology Department, Study Number 88-671-AK; Sept 10, 1991.

MRID 420401-02 A dietary reproductive toxicity study investigation the fertility of FI rats using Tribufos (DEFI&), D.A. Eigenberg; Mobay, Corporate Toxicology Department, Study Number 88-971-DC; Aug 27, 1991.

7127

MRID 420401-03-A Cross-Fostering study in rats using Tribufos (DEFO) administered in the diet, D.A. Eigenberg; Mobay, Corporate Toxicology Department, Study Number 88-971-BZ; Aug 29, 1991.

MRID 423351-01 Technical grade tribufos (DEFO): A chronic Tee@din@g study in the Fischer 344 rat, W.R. Christenson, Miles Inc. Study No 88271-AA, Report # 102675, May 1,.1992.

MRID 423500-02 Addendum 1, Additional characterization of metabolites from the disposition and metabolism of (-IC) Tribufos in rats (miles report 101331), ME Krolski & LL Bosnak, Miles Stilwell KS, Study No DE041801, Report No 101331-1, 6/2/92.

MRID 423500-03 Dermal absorption of tribufos by rats from DEF6 emulsifiable formulation using 14C-tribufos, R.S. Schroeder, Miles Inc. Ag Div, Tox, South Metcalf KA, Study No. 91-722-KW, May 19, 1992.

MRID 423998-01 Study of the subchronic inhalation toxicity to rats in accordance with OECD Guideline No. 413; J. Pauluhn; BAYER AG, FRG; Report No: 102697; June 2, 1992.

MRID 419549-03 Experimental Acute Oral Toxicity with HBM sulfone (a metabolite of Tribufos, DEFO) in female rats. A.B. Astroff & S.D. Phillips, Miles, Study No 92-.912-OD' Report 102684, June 18,.1992.

CBRS No.: 8763 and 10031
DP Barcode: D169854 and D179581
Subject: Reregistration of Tribufos (List B, Case 2145, Chemical 74801). Nature of the Residue in Cotton. Nature of the Residue in Poultry and in Ruminants. Storage Stability in Soil. Waiver Requests for Feeding Study and Animal Commodity Analytical Methods.
From: S. Funk
To: B. Sidwell/M. Wilhite
Dated: 11/23/93
MRID(s): 42034502, 42034503, 42350008-42350012

CBRS No.: None
DP Barcode: None
Subject: Tribufos. Issues to be Presented to the HED Metabolism Committee on 05/09/95. Reregistration Case No. 2145. Chemical No. 74801.
From: C. Eiden
To: HED Metabolism Committee
Dated: 4/28/95
MRID(s): None

72275

CBRS No.: None
DP Barcode: None
Subject: Tribufos. Outcome of the 5/9/95 Meeting of the HED Metabolism Committee. Reregistration Case No. 2145. Chemical No. 74801.
From: C. Eiden
To: Files and HED Metabolism Committee
Dated 7/95
MRID(s): None

CBRS No.: 16315
DP Barcode: D219920
Subject: Tribufos. Reregistration List B. Chemical No. 074801. Case No. 2145. Cotton Processing Study. GLN: (171-4(l)).
From: C. Eiden
To: M. Wilhite/B. Sidwell
Dated: 11/14/95
MRID(s): 43783701

CBRS No.: 4759 and 16457
DP Barcode: D209511 and D174442
Subject: Tribufos. Reregistration List B. Chemical No. 074801. Case No. 2145. Rotational Crop Study. GLN: (165-1).
From: C. Eiden
To: M. Wilhite/B. Sidwell
Dated: 11/15/95
MRID(s): 42184701

CBRS No.: 12460
DP Barcode: D194656
Subject: Tribufos. Reregistration List B. Chemical No. 074801. Case No. 2145. Residue Analytical Method(s). GLN: 171-4(c).
From: C. Eiden
To: M. Wilhite/B. Sidwell
Dated: 12/8/95
MRID(s): 42799001, 42848001-42848003

CBRS No.: 16437
DP Barcode: D220694
Subject: Tribufos. Reregistration List B. Chemical No. 074801. Case No. 2145. Animal Feeding Study. GLN: 171-4(o).
From: C. Eiden
To: M. Wilhite/B. Sidwell
Dated: 12/18/95
MRID(s): 438216001

3875

CBRS No.: 16554
DP Barcode: D221143
Subject: Tribufos., Reregistration List B. Magnitude of the Residue Data-Crop Field Trials. GLN 171-4(k) and Residue Analytical Method: Animals GLN 171 4(d). Chemical No. 074801. Case No. 2145.
From: C. Eiden
To: Wilhite/B. Sidwell
Dated: 4/96
MRID(s): 43837801 and 43837802

DP Barcode: D227007
Subject: Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document for Tribufos.
From: B.Tarplee
To: Risk Characterization and Analysis Branch
Dated: 3/12/97
MRID(s): 426859-01 and 427016-01

DP Barcode: D234253
Subject: Review of DEF Incident Reports, Chemical #074801
From: J. Blondell
To: B. Tarplee
Dated: 4/1/97

DP Barcode: D244658
Subject: Tribufos: Magnitude of the Residue on Cottonseed and Cotton Gin Trash.
From: J. Garbus
To: T. Luminello
Dated: 6/16/98
MRID: 444391-01

DP Barcode: 248995
Subject: Amendment: The HED Chapter of the Reregistration Eligibility Decision Document forTribufos
From: S. Law, C. Eiden
To: S. Knizner
Dated: 9/1/98

DP Barcode: 250061
Subject: Revised Anticipated Residues for Tribufos
From: S. Knizner
To: T. Luminello
Dated: 10/6/98

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DP Barcode: 251691
Subject: Monte Carlo Acute Dietary Exposure Estimate for Tribufos
From: S. Piper
To: Jess Rowland
Dated: 2/16/99

DP Barcode: D253352
Subject: Revised Chronic Anticipated Residues of Tribufos.
From: S. Knizner
To: A. Overstreet
Dated: 2/18/99

DP Barcode: D253404
Subject: Chronic DEEM™ Analysis for Tribufos.
From: S. Law
To: A. Overstreet
Dated: 2/18/99