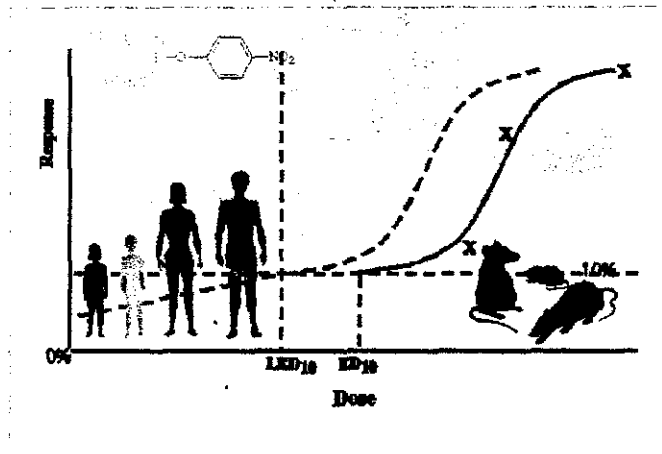


OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

HUMAN HEALTH RISK ASSESSMENT

Tribufos



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

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June 26, 2000

HUMAN HEALTH RISK ASSESSMENT

Tribufos

Final

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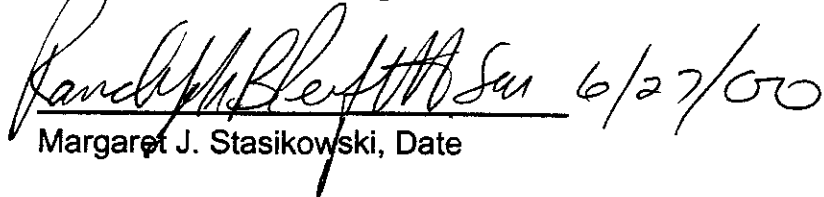

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1 Executive Summary

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, at a high dose, displayed organophosphate-type delayed neuropathology in the hen. Tribufos also displayed ocular toxicity in the rat following either oral or inhalation exposure. The ocular 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 offspring following pre-/postnatal 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 organophosphate 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 should be retained to account for increased susceptibility of infants and children (as required by FQPA). The rationale for this determination is: although no increased susceptibility was seen following *in utero* exposure and pre-/postnatal 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.

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. 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.

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. 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, and the chronic PAD (cPAD) is 0.0001 mg/kg/day.

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 to 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.

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 to 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 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 to 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.

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 to 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

Short- and Intermediate-Term

The Hazard Identification Assessment Review Committee (HIARC) selected endpoints for short-and intermediate-term dermal risk assessments from a 21-day rabbit dermal toxicity study. A LOAEL of 2 mg/kg/day was established; it was based on statistically-significant inhibitions of plasma and red blood cell (RBC) cholinesterase activities in males and females, respectively. A NOAEL was not established. This dose and endpoint was supported by the LOAEL of 2.6 mg/kg/day established in a 90-day dermal toxicity study in hens. The LOAEL was based on whole blood cholinesterase inhibition; a NOAEL was also not established in the hen study. The HIARC determined that a conversion factor of seven should be used with the LOAEL for risk assessment to account for species differences in dermal absorption. Based on cholinesterase inhibition data, HED's level of concern for dermal occupational exposure is 300, expressed as a Margin of Exposure (MOE). The MOE of 300 includes the conventional 100x and an additional 3x for the use of a LOAEL (*i.e.*, lack of a NOAEL in the critical study). Note that the additional uncertainty factor of three 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.

The HIARC selected the inhalation NOAEL of 2.43 mg/L (0.9 mg/kg/day) for short and intermediate-term inhalation exposure 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. Since a NOAEL was used, an MOE greater than 100-fold does not exceed HED's level of concern for occupational inhalation exposure risk assessments.

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 postapplication 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 postapplication activities are therefore highly refined.

Occupational Risk Estimates

Handlers (Mixers/Loaders/Applicators)

The results of the short- and intermediate-term handler assessments indicate that at the reduced application rate of 1.125 lb ai/acre the aggregate risk index (ARI) is of concern (*i.e.*, below one) for the aerial mixer/loader and pilot at the high acreage (1200 acres). Dermal exposure is contributing more to the risk estimate than inhalation exposure. The dermal MOE for the aerial mixer/loader supporting 1200 acres is 82 and the pilot MOE is 150 (level of concern is a MOE greater than 300). The dermal MOEs for the other scenarios range from 290 to 12,000. All inhalation MOEs are above the level of concern (*i.e.*, MOEs are greater than 100 and range from 560 to 23,000). At the current application rate of 1.875 lb ai/acre, mixer/loader exposure is also of concern at the lower estimate of acreage treated (*i.e.*, dermal MOE of 170). The dermal MOE at 1200 acres is 49 for the mixer/loader and 90 for the pilot. All inhalation MOEs exceed the level of concern (*i.e.*, MOEs are greater than 100).

Postapplication

The results of the short- and intermediate-term postapplication assessments indicate that at the reduced application rate of 1.125 lb ai/acre the dermal MOEs do not exceed the level of concern (*i.e.*, all MOEs are greater than 300) at seven days after treatment for all four activities (*i.e.*, pickers, module builders, rakers, and trampers). At the current application rate of 1.875 lb ai/acre, the MOEs at seven days after treatment are 210 for the pickers, 480 for the module builder, 200 for the rakers, and 230 for the trampers.

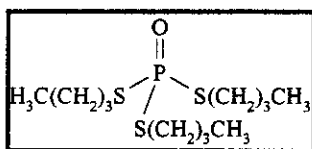
Cancer (chronic)

A quantitative cancer (chronic) risk assessment for occupational exposure was not conducted since the current use pattern does not present long term dermal or inhalation exposure scenarios. Also, 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), and this scenario is not anticipated based on the current use pattern. Therefore, a cancer risk assessment was not conducted.

2 Product Chemistry and Use Profile

2.1 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 $\sim 150^\circ\text{C}$. 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.

2.2 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 and supported 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

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

²All 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.

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

⁴Data 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.

3 Hazard Assessment

3.1 Toxicity Assessment

3.1.1 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

¹Literature 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.

3.1.2 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.

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), six hours per day, five days per 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 RBC (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 to 34 days (14 days post-dose). The LOAEL was 2 mg/kg/day based on plasma (males) and RBC (females) ChE inhibition; a NOAEL was not established for cholinesterase inhibition (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/m³ actual (0, 0.3, 0.9, 4.5, 22 mg/kg/day), six hours per day, five days per week for 90 days. No ChE inhibition was observed in either sex at 0.93 or 2.43 mg/m³. Plasma ChE inhibition was observed in males at 12 and 60 mg/m³ and in females at 60 mg/m³. RBC ChE inhibition was observed at 12 and 60 mg/m³ in both sexes. Brain ChE inhibition was seen at 60 mg/m³ both sexes. The adrenals showed cortical fat deposition at 60 mg/m³ in both sexes. Electro Retiniogram (ERG) was depressed (a- and b- waves) at 60 mg/m³ in both sexes indicative of a toxic effect on the rods and cones of the retina. The NOAEL was 2.43 mg/m³ (0.9 mg/kg/day) and the LOAEL was 12 mg/m³ (4.5 mg/kg/day) based on RBC cholinesterase inhibition (MRID 42399801).

3.1.3 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. For plasma cholinesterase inhibition, the NOAEL was 0.1 mg/kg/day and the LOAEL was 0.4 mg/kg/day. For red blood cell cholinesterase inhibition, the NOAEL was 0.4 mg/kg/day and the LOAEL was 1.7 mg/kg. For brain cholinesterase inhibition, the NOAEL was 1.7 mg/kg/day (HDT); a LOAEL was not established for this compartment.) (MRID 42007203).

3.1.4 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 hyperspermatogenesis, 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 and 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).

3.1.5 Developmental Toxicity

Developmental Toxicity Study -- Rats

In a developmental toxicity study pregnant CrI:COBS-CD (SD) rats received oral doses of tribufos at 0, 1, 7 or 28 mg/kg/day during gestation days six through 16. For maternal toxicity, the NOAEL was 1 mg/kg/day and the LOAEL was 7 mg/kg/day, based on inhibition of plasma and red blood cell cholinesterase activity. No developmental toxicity was observed. For developmental toxicity, the NOAEL was \geq 28 mg/kg/day (MRID 40190601).

Developmental Toxicity Study -- Rabbits

In a developmental toxicity study, pregnant American Dutch rabbits were given a oral administration of tribufos at 1, 3, or 9 mg/kg/day during gestation days seven through 19. For cholinesterase inhibition, the LOAEL was 1 mg/kg/day based on inhibition of plasma and red blood cell cholinesterase activity; a NOAEL was not established for this marker. For maternal toxicity, the NOAEL was 3 mg/kg/day and the LOAEL was 9 mg/kg/day based on statistically-significant decreases in mean body weight gain. No developmental toxicity was seen. For developmental toxicity, the NOAEL was \geq 9 mg/kg/day; a LOAEL was not established (MRID 40190602).

3.1.6 Reproductive Toxicity

Two-Generation Reproduction Study -- Rats

In a two-generation reproduction study, Sprague-Dawley rats were fed diets containing tribufos at 0, 4, 32 or 260 ppm (0, 0.2, 1.7, or 15 mg/kg/day) for two successive generations. There was no evidence of increased susceptibility of pups over the adults. The parental systemic toxicity the LOAEL was 4 ppm (0.2 mg/kg/day), the lowest dose tested, based on inhibition of plasma cholinesterase activity; a parental/systemic toxicity NOAEL was not established. For reproductive toxicity, the NOAEL was 32 ppm (1.7 mg/kg/day) and the LOAEL was 260 ppm (15 mg/kg/day) based on significant increase in the number of litters with still born pups and pup death (including cannibalism) through lactation; decrease in F1 and F2 pup body weights; and significant increase in F1 gestation period (MRID 42040101).

A cross fostering study was conducted to determine if pup loss in the two-generation reproduction study (discussed above; MRID 42040101) 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).

3.1.7 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).

3.1.8 Metabolism

The metabolism study using [1- C¹⁴] 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-C¹⁴] tribufos. Fifty-five 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).

3.1.9 Neurotoxicity

Neurotoxicity data are limited to exposure via the dermal route. Datagap exists for acute and subchronic neurotoxicity studies via the oral route. In addition, a developmental neurotoxicity study in rats is also required.

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 organophosphate induced neuropathy (OPIDN) 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, NOAEL was 2.6 mg/kg/day and the LOAEL was 11 mg/kg/day based on decreased weight gain. For OPIDN the NOAEL was 11 mg/kg/day and the LOAEL was 42 mg/kg/day based on histopathological lesions. For Cholinesterase 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 an acute and subchronic neurotoxicity studies in the rat are required. The subchronic 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. The HIARC also determined that 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 and in the combined chronic toxicity/carcinogenicity study in rats.

3.1.10 Dermal Absorption

A dermal absorption study was performed in the rat at doses of 2.8, 14.0 or 140 $\mu\text{g}/\text{cm}^2$ and exposures of one, four, 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 one, four, and 10 hours (30 to 40%). The 10-hour residue was mostly absorbed at 168 hours. The mean dermal absorption rates were determined to be 47.5%, 47.9% and 33.9% at dose levels of 2.8, 14 and 140 $\mu\text{g}/\text{cm}^2$ (MRID 42350003).

In a dermal absorption study conducted with rhesus monkeys, five young adult males received a single dermal dose of 3.5 $\mu\text{g}/\text{cm}^2$ [^{14}C]-tribufos. The application site was washed with soap and water eight hours after dosing and this site was tape stripped after 48 hours. Blood samples were collected to 48 hours post-dose. Total urine and feces were collected for 120 hours post-dose. Thereafter total urine was collected until radioactivity was below twice background. There was no evidence of toxicity after treatment. Radioactivity in plasma and whole blood was at or below twice background in all samples. Mean (percent of administered dose) total dose recovery is as follows: urine (6.24%), feces (0.72%), biscuits (0.48%), dermal dome (1.25%), duodenum (2.73%), dermal swabs (93.8%), and tape strips (0.08%). Mean absorbed dose was 6.96% of the dose (the sum of urine and fecal excretion) (MRID 45019901).

3.2 Dose Response Assessment

3.2.1 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. There was no evidence of increased susceptibility of young rat or rabbit fetuses following *in utero* exposure in the developmental toxicity studies in rats and rabbits and there was also no evidence of increased susceptibility of offspring as compared to adults following pre-/postnatal exposure in the two generation reproduction study in rats. However, 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.

3.2.2 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 Hazard Identification Assessment Review Committee (HIARC) confirmed the doses and endpoints selected by the TESC. The previous risk assessment (September 14, 1999) was conducted using the doses and endpoints selected by the TESC and the HIARC.

Since then the Registrant has submitted a new dermal absorption study in monkeys with tribufos. On May 9, 2000, the HIARC evaluated this study and its impact on the doses and endpoints previously selected for dermal risk assessments.

3.2.2.1 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.

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

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.

$$\text{Acute PAD} = \frac{0.01 \text{ mg / kg / day (acute RfD)}}{10 \text{ (FQPA Safety Factor)}} = 0.001 \text{ mg / kg}$$

3.2.2.2 Chronic Dietary (Chronic Reference Dose)

A chronic RfD of 0.001 mg/kg/day was derived by using the NOAEL of 0.1 mg/kg/day and an uncertainty factor of 100 which includes the 10X for intraspecies extrapolation and 10X for interspecies 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.

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

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.

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

3.2.2.3 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 organophosphate 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.

3.2.2.4 Occupational Exposure

3.2.2.4.1 Adjustment for Species Differences in Dermal Absorption

For occupational exposure risk assessments a NOAEL or a LOAEL (when a NOAEL is not established) derived by the same route as the human exposure is used to calculate the Margin of Exposures (MOEs). In this process, unless proven otherwise, it is presumed that human and animal absorption of the chemical is identical for the same route of exposure.

The previous dermal risk assessments (September 14, 1999), were conducted using a LOAEL of 2 mg/kg/day established in the 21-day dermal toxicity study in rabbits. The MOEs were calculated using the assumption that dermal penetration of tribufos through rabbit and human skin is equivalent. Since then, the Registrant has submitted a dermal absorption study in monkeys. This study demonstrated that tribufos is poorly absorbed through the skin of monkeys. After eight hours of dermal exposure, only 7% of the applied dose had been absorbed through the skin into the systemic circulation.

With the availability of this new monkey dermal absorption data, HIARC re-evaluated the dermal toxicity in rabbits relative to the poor dermal absorption shown in monkeys because: (1) in general, the skin of rabbit is more permeable to chemicals than skin of humans, and (2) the penetration of a chemical through the skin of primate (monkeys) can be used as a better surrogate for penetration through human skin.

A dermal absorption study in rats is also available. This study showed that absorption is greater than in the monkey. At a comparable dose, in which the application site is washed after 10 hours of exposure, 48% of the dose is absorbed.

As per HED's policy, when an oral dose is selected for dermal risk assessments, a dermal absorption factor would be applied for route-to-route extrapolation. Therefore, had an oral dose been selected for tribufos, then the 7% dermal absorption rate (from the monkey study) would have been directly applied to the oral dose. For tribufos, however, a LOAEL from a dermal study was selected. Therefore, it was necessary to adjust the rabbit dermal absorption to reflect the differences in absorptions in human skin vs. rabbit skin.

The HIARC accepted that the dermal absorption data in monkeys can be used as a surrogate for penetration through human skin. Because it is presumed that rat and rabbit dermal absorption are comparable, an adjustment can be made to the dose (LOAEL) used for risk assessment to account for species differences in dermal absorption. Consequently, using the dermal absorption rates of 48% in rats and 7% in monkeys, a 6.9 conversion factor was obtained, to account for species differences in dermal absorption:

$$\frac{\text{Dermal absorption in rats (48\%)}}{\text{Dermal absorption in monkeys (7\%)}} = 6.9$$

The HIARC determined that the conversion factor of seven (rounded up from 6.9) should be applied to the LOAEL of 2 mg/kg/day from the rabbit dermal toxicity study that was selected for short and intermediate-term dermal risk assessments.

3.2.2.4.2 Short- and Intermediate-Term Dermal

The HIARC concurred with the dose and endpoint selected previously by the Toxicology Endpoint Selection. The LOAEL of 2 mg/kg/day (the lowest dose tested) established in the 21-day dermal toxicity study was selected for this exposure scenario. The LOAEL is based on plasma cholinesterase inhibitions in males and red blood cell cholinesterase inhibition in females. This dose and endpoint is supported by the LOAEL of 2.6 mg/kg/day in the 90-day dermal toxicity study in hens based on whole blood cholinesterase inhibition also at the lowest dose tested; a NOAEL was not established.

The HIARC determined that a conversion factor of seven should be used with the LOAEL of 2 mg/kg/day to compensate for the species difference in dermal absorption. Use of this factor results in a dose of 14 mg/kg/day ($2 \times 7 = 14$) which should then be compared to occupational exposure data to calculate the MOEs.

3.2.2.4.3 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.

3.2.2.4.4 Margins of Exposure for Dermal Risk Assessments

The previous risk assessment (September 14, 1999), specified that a MOE of 1000 was required (which included the conventional 100x and additional 10x) as recommended by the TESC. The additional 10x factor encompassed the use of the LOAEL and the concern for the severe neurotoxic effects seen in the 90-day neurotoxicity study in hens.

At the May 9, 2000 HIARC meeting it was determined that an MOE of 300 is appropriate (*i.e.*, for the use of a LOAEL) without requiring additional uncertainty factors, as previously determined, for the neurotoxic effects seen in the hen study. This determination was made based on the following factors: (1) in the hen study, organophosphate induced neuropathy (OPIDN) occurred only at the highest dose tested (42 mg/kg/day) and a NOAEL (11 mg/kg/day) was established for this effect; and (2) Application of the 3x factor to the 2 mg/kg/day LOAEL yields a dose of 0.7 mg/kg/day which is 60 times higher than the dose (42 mg/kg/day) that induced OPIDN in the hens and therefore 3x is sufficient to protect against OPIDN. Additionally, the ocular lesions seen at 17 mg/kg/day in the chronic study in rats and the retinal toxicity seen at 22 mg/kg/day in the 28-day inhalation study in rats were also seen at the highest doses tested in those studies and NOAELs were established for these effects.

For short and intermediate-term dermal exposure risk assessments, a MOE greater than 300 does not exceed HED's level of concern. The MOE of 300 includes the conventional 100 and an additional factor of three for the use of a LOAEL (*i.e.*, lack of a NOAEL in the critical study).

3.2.2.4.5 Inhalation Exposure (Short- and Intermediate-Term)

The NOAEL of 2.43 mg/L (converted to 0.9 mg/kg/day) established in the 90-day inhalation study in rats was selected for this exposure scenario. The NOAEL is based on the inhibition of plasma and erythrocyte cholinesterase 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.

3.2.3 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	Dose and Endpoints for Risk Assessments
Acute Dietary	<p>Dose and Endpoint: NOAEL = 1 mg/kg; plasma and RBC ChE inhibition</p> <p>Acute RfD: 0.01 mg/kg</p> <p>Uncertainty Factor: 100 FQPA Safety Factor: 10</p> <p>Acute PAD: 0.001 mg/kg</p>
Chronic Dietary	<p>Dose and Endpoint: NOAEL = 0.1 mg/kg/day; plasma ChE inhibition</p> <p>Chronic RfD: 0.001 mg/kg/day</p> <p>Uncertainty Factor: 100 FQPA Safety Factor: 10</p> <p>Chronic PAD: 0.0001 mg/kg/day</p>
Short-and Intermediate Term Dermal	<p>Dose and Endpoint: LOAEL = 2 mg/kg/day; inhibition of plasma (males) and red blood cell (females) cholinesterase activity. Use of a 7% conversion factor to account for species differences in dermal absorption results in a dose of 14 mg/kg/day for calculating the Margins of Exposures (MOEs).</p> <p>Level of Concern: MOE greater than 300 does not exceed HED's level of concern</p>
Short and Intermediate-Term Inhalation	<p>Dose and Endpoint: NOAEL = 2.43 mg/L (0.9 mg/kg/day); plasma and RBC ChE inhibition</p> <p>Level of Concern: MOE greater than 100 does not exceed HED's level of concern</p>
Long-Term Dermal and Inhalation	<p>Long-term dermal or inhalation occupational exposure are not expected to occur for the registered uses of tribufos.</p>

4 Exposure Assessment

4.1 Dietary (food/drinking water) Exposure and Risk Characterization

4.1.1 Dietary Exposure -- Food Sources

4.1.1.1 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)

4.1.1.2 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.

4.1.1.3 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. Independent laboratory validation (ILV) data are required for this method. Following receipt of ILV data, the Agency will conduct a Tolerance Method validation (TMV).

4.1.1.4 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.

4.1.1.5 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.

If the registrant desires a tolerance less than 0.01 ppm, then, 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)).

4.1.1.6 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

¹Samples 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.

4.1.1.7 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

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

²All 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.

4.1.2 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.

4.1.2.1 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 to 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.

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

Population	95 th Percentile		99 th Percentile		99.9 th 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

4.1.2.2 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 to 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

4.1.2.3 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.

4.1.3 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.

4.1.3.1 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.

4.1.3.2 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 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.

4.1.3.3 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.

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

where:

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

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

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).

4.1.3.3.1 Acute DWLOC

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

4.1.3.3.2 Chronic DWLOC

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

4.1.3.3.3 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.

4.2 Occupational & Residential Exposure and Risk Characterization

4.2.1 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.

The previous risk assessment was based on a range of the application rates on the label (from 1.5 to 1.875 lb ai/A). Tribufos is applied only to cotton. Since then, the registrant has proposed to reduce the application rate to 1.5 pts/A (*i.e.*, 1.25 lb ai/A). This document includes HED's reassessment of the occupational exposure/risk based on the reduced application rate and the use of a conversion factor (with the LOAEL) to account for species differences in dermal absorption. Based on the use pattern, only short- and intermediate-term (no long-term) occupational exposures are expected.

4.2.1.1 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.

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.

The registrant submitted a chemical-specific study (using passive dosimetry methodologies). The data from the registrant's study were combined with similar data from Pesticide Handlers Exposure Database (PHED V1.1) to assess the uses with a more robust data set. The chemical-specific data were combined with PHED, as per HED's policy, to increase the sample size and number of studies. HED's policy of combining chemical-specific data with available surrogate data to increase the sample size is in effect because individual chemical-specific studies do not necessarily encompass the variety of equipment in use throughout the country and the large variability of exposures among handlers.

This risk assessment also includes the registrant's data as monitored in the field without extrapolation. The data were not extrapolated down to the proposed application rate because they are *only partial day* replicates. Furthermore, even though the mixer/loader is only represented by 16 replicates, the groundboom by eight replicates, and the pilots by eight replicates, the geometric mean values are reported. *As shown in Table 9, these data are included only for illustrative purposes only.* The regulatory assessment would be based on a full day's work and because this is a short-term endpoint, a high end estimate would be used.

Table 8, titled "*Handler Exposure and Risk Estimate*," describes and summarizes the caveats and parameters specific to each exposure scenario and corresponding risk assessment.

Table 9 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 (Level of Concern: MOE=300) and inhalation (Level of Concern: MOE=100) exposure risk assessments. An ARI of less than one is the level of concern.

Table 10 presents the dermal, inhalation and aggregate risk indices at the application rate of 1.875 lb ai/Acre.

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 to 106.9 for erythrocyte ChE and 95.9 to 107.5 for plasma ChE.

Application rates in the study ranged from 1.127 lb ai/acre to the maximum labeled rate of 1.875 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 five 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.

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 to 5.05 hours in duration. The mixer/loader replicates ranged in duration from 1.55 to 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 to 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:

$$\text{Daily dermal exposure (mg ai/day)} = \text{Unit exposure (mg ai/lb ai)} \times \text{Use Rate (lb ai/A)} \times \text{Daily Acres Treated (A/day)}.$$

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.

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

These calculations of daily dermal and inhalation doses of tribufos received by handlers are used to assess the risk to those handlers. The MOEs for short- and intermediate-term dermal exposures MOEs were calculated using a dose of 14 mg/kg/day which represents the dermal LOAEL of 2 mg/kg/day x a conversion factor of seven to account for species differences in dermal absorption. The MOEs for short- and intermediate-term inhalation exposures were calculated using an inhalation NOAEL of 0.9 mg/kg/day. The MOEs were calculated using the following formula:

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

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	<p>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.</p> <p>PPE: "Best Available" grades: Hands and dermal acceptable grades. Hands = 59 replicates and Dermal = 72 to 122 replicates. High confidence in dermal data.</p> <p>Engineering Controls: "Best Available" grades: Hands and dermal acceptable grades. Hands = 31 replicates and Dermal = 16 to 22 replicates. High confidence in dermal data.</p> <p>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.</p>
Applicator Descriptors			
Applying Sprays with a Fixed-Wing Aircraft (2)	PHED V1.1 and MRID 426859-01	range of 350 to 1,200 acres	<p>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.</p> <p>PHED data used no PFs were necessary.</p>
Applying Sprays with a Groundboom Sprayer (3)	PHED V1.1 and MRID 426859-01	80 acres	<p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p>

Exposure Scenario (Scenario No.)	Data Source	Standard Assumptions ¹	Comments ²
Flagger Descriptors			
Flagging Aerial Spray Applications (4)	PHED V1.1 and MRID 426859-01	range of 350 to 1,200 acres	<p>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.</p> <p>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.</p>

¹Standard Assumptions based on an eight-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 Dermal, Inhalation, and Total MOEs for Tribufos at 1.125 lb ai/A

Exposure Scenario (Scenario #)	Dermal Unit Exposure (mg/lb ai)	Inhalation Unit Exposure (µg/lb ai) ^b	Application Rate (lb ai/A)	Acres Treated	Dermal - Eng. Controls ^{b,*}		Inhalation - Eng. Controls ^{c,*}		ARI Target ≥1	
					Daily Dose (mg/kg/day)	MOE	Daily Dose (mg/kg/day)	MOE		
Mixer/Loader Exposure										
Mixing/loading liquids for aerial applications -- PHED V1.1 combined with MRID 426859-01 (1a)	0.0086	0.083	1.125	350	0.048	290	0.00047	1900	0.92	
				1200	0.17	82	0.0016	560	0.26	
Mixing/loading liquids for aerial applications -- Registrant data only, as monitored in MRID 426859-01, no extrapolation to a full day's work (1a) ILLUSTRATIVE PURPOSE ONLY*	Dermal = 3.6 mg/day; Inhalation = 0.080 mg/day (geo. means) 96 to 1,569 lb ai handled (avg. 686 lb ai); 4 to 4.8 hours sampled; total of 16 replicates				0.051	270	0.0011	820	0.81	
Mixing/loading liquids for groundboom application -- PHED V1.1 (1b)	0.0086	0.083	1.125	80	0.011	1300	0.00011	8400	4.12	
Applicator Exposure										
Aerial (Liquids) -- Enclosed Cockpit -- PHED V1.1 (2)	0.005	0.068	1.125	350	0.028	500	0.00038	2400	1.56	
				1200	0.096	150	0.0013	690	0.47	
Aerial Enclosed Cockpit -- Registrant data only, as monitored in MRID 426859-01, no extrapolation to a full day's work (2) ILLUSTRATIVE PURPOSE ONLY*	Dermal = 3.2 mg/day; Inhalation = 0.048 mg/day (geo. means) Application rate ranged from 1.127 to 1.879 lb ai/acre; 605 to 1061 acres treated (average 838 acres); 681 to 1568 lb ai handled; 4.22 to 5.05 hours sampled; total of 8 replicates				0.046	300	0.00069	1300	0.93	
Groundboom Tractor -- PHED V1.1 (3)	0.005	0.043	1.125	80	0.0064	2100	5.5E-5	16,000	6.67	
Groundboom Tractor -- Registrant data only, as monitored in MRID 426859-01, no extrapolation to a full day's work (3) ILLUSTRATIVE PURPOSE ONLY*	Dermal = 0.35 mg/day; Inhalation = 0.012 mg/day (geo. means) Application rate of 1.879 lb ai/acre; 51 to 80 acres treated; 96 to 150 lb ai handled; 3.95 to 4.77 hours sampled; total of 8 replicates				0.0050	2800	0.00017	5300	7.94	

Exposure Scenario (Scenario #)	Dermal Unit Exposure (mg/lb ai)	Inhalation Unit Exposure (µg/lb ai) ^b	Application Rate (lb ai/A)	Acres Treated	Dermal - Eng. Controls ^{b, e}		Inhalation - Eng. Controls ^{c, e}		ARI Target ≥1
					Daily Dose (mg/kg/day)	MOE	Daily Dose (mg/kg/day)	MOE	
Flagger Exposure									
Flagging Spray Applications -- PHED V1.1 (4)	0.00022	0.007	1.125	350	0.0012	12,000	0.000039	23,000	34.07
				1200	0.0042	3300	0.00014	6700	9.45

Note: Proposed reduction in application rate reduces the maximum-rate from 2.5 pts/acre formulated product to 1.5 pts/acre formulated product (DEF6 is 6 lb ai/gal or 1.125 lb ai per 1.5 pts product). Memo from J. Thornton, Bayer Corp., to A. Overstreet, EPA/OPP/SRRD, dated January 5, 2000. The results of the registrant's study for scenarios 1a, 2, and 3 are included as monitored in the study without extrapolation to a full day's work or reduced to 1.125 lb ai/A for comparison to the full day extrapolation using the same data combined with PHED data. See PHED Surrogate Exposure Guide (August 1998) for details on the PHED unit exposure values. The results in this table does not include data for the current application rate of 1.875 lb ai/A.

^aEngineering control unit exposures represent the use of closed systems (e.g., closed loading and enclosed cab tractors/cockpit) long pants, long sleeved shirt, and no gloves (except for closed loading which is based on the use of chemical-resistant gloves).

^bPotential dermal daily dose (mg/kg/day) = [dermal unit exposure (mg/lb ai) * Appl. rate (lb ai/acre) * Acres treated * 1 dermal absorption]/Body weight (70 kg). Dermal absorption is not factored into the dose because it is compared to the 21-day dermal study, and therefore, it is a "potential" dose.

^cPotential inhalation daily dose (mg/kg/day) = [inhalation unit exposure (mg/lb ai) * 0.001 µg/mg unit conversion * max appl rate (lb ai/A or lb ai/gal) * area treated (acres or gal) * 1 inhalation absorption]/Body weight (70 kg).

^eMOE = NOAEL or LOAEL (mg/kg/day)/Daily Dose [Where for Dermal LOAEL 2 mg/kg/day with a conversion factor of seven to account for species difference in dermal absorption = 14 mg/kg/day and for Inhalation = NOAEL = 0.9 mg/kg/day]. MOEs greater than 300 for the dermal route and 100 for the inhalation route does not exceed HED' level of concern.

^dTotal MOE uses the Aggregate Risk Index (ARI) because the target MOEs for dermal and inhalation are not equivalent = $1/((1/(\text{Dermal MOE}/300\text{UF})) + (1/(\text{Inhalation MOE}/100\text{ UF}))$. An ARI of greater than one does not exceed HED's level of concern.

^e These scenarios are identified as "illustrative" because they are based on the chemical-specific study that monitored partial day replicates (e.g., groundboom applicators working for 4 to 4.8 hours). The regulatory assessment is based on these data combined with surrogate data from PHED and extrapolated to a full days work.

Table 10. Dermal, Inhalation and Aggregate MOEs at Current Application Rate (1.875 lb ai/A)

Exposure Scenario (Scenario #)	Acres Treated	Dermal MOE	Inhalation MOE	ARI
Mixer/Loader Exposure				
Mixing/loading liquids for aerial applications -- PHED V1.1 combined with MRID 426859-01 (1a)	350	170	1140	0.54
	1200	49	330	0.16
Mixing/loading liquids for groundboom application -- PHED V1.1 (1b)	80	780	5040	2.47
Applicator Exposure				
Aerial (Liquids) -- Enclosed Cockpit -- PHED V1.1 (2)	350	300	1440	0.94
	1200	90	414	0.28
Groundboom Tractor -- PHED V1.1 (3)	80	1260	9600	4.02
Flagger Exposure				
Flagging Spray Applications -- PHED V1.1 (4)	350	7200	1380	8.76
	1200	1980	4020	5.67

4.2.1.2 Postapplication Exposure and Risk Estimates

The previous risk assessment (September 14, 1999) was based on exposures to pickers, module builders, rakers and trampers. The exposure assessment was based solely on the data submitted by the Registrant. Since then, the Registrant has proposed to reduce the maximum application rate from 2.5pts/acre of tribufos to 1.5 pts/acre (i.e., 1.125 lb ai/A) and also a proposed seven day restricted-entry interval (REI).

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 to 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 to six week period. The passive dosimetry results of these studies were used to develop transfer coefficients for picker operators, module builder operators, rakers, and tramps.

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 Nekaal/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 transfer coefficients 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:

$$\text{Potential ADE} = \frac{\text{DR (ug / 50g boll)} \times \text{Transfer Coefficient (50g bolls / hr)} \times \text{Work Day (8hr)}}{\text{Unit Adjustment from ug mg (1000 ug)}}$$

Postapplication dermal MOEs are calculated using the following formula:

$$\text{MOE} = \frac{\text{LOAEL (mg / kg / day)} \times \text{conversion factor}}{\text{Dermal Dose (mg / kg / day)}}$$

The short- and intermediate-term dermal MOEs are calculated by comparing the exposure (*i.e.*, dermal dose) to the dose of 14 mg/kg/day which represents the LOAEL of 2 mg/kg/day and a conversion factor of seven to account for species differences in dermal absorption. Since a LOAEL was used, MOEs of greater than 300 do not exceed HED's level 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 $\mu\text{g/hr}$. Assuming an eight-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 to avoid any uncertainties that are introduced into the assessment by extrapolating the data monitored on one day to another.

Table 11 presents the data monitored by the registrant on 15, 17, and 20 days after treatment (DAT). The data were monitored at the maximum application rate of 1.875 lb ai/acre. The only other extrapolation was to use a linear extrapolation of the exposure to an eight hour work day. Moreover, the average exposure of the three or four replicates were used, not the highest one monitored (the highest exposure has merit because only three or four replicates were monitored on each day).

Table 11. Tribufos Dermal Exposures for Picker Operators, Module Builder Operators, Rakers, and Trampers^a

Replicate ^b	Days After Treatment (DAT)	Dermal Exposure ($\mu\text{g/hr}$) ^c			
		Pickers	Module	Rakers	Trampers
1	15	118	72	123	NA
2	15	89	120	184	NA
3	15	49	46	83	NA
Average dermal exposure ($\mu\text{g/hr}$)		85	79	390	NA
Daily Dermal Dose (mg/kg/day) ^d		0.0097	0.0090	0.0445	NA
MOE ^e		1400	1600	300	NA
4	17	165	20	80	NA
5	17	154	22	54	NA
6	17	92	20	26	NA
Average dermal exposure ($\mu\text{g/hr}$)		137	21	53	NA

Replicate ^b	Days After Treatment (DAT)	Dermal Exposure ($\mu\text{g/hr}$) ^c			
		Pickers	Module	Rakers	Trampers
Daily Dermal Dose (mg/kg/day) ^d		0.0156	0.0024	0.0060	NA
MOE ^e		890	580	2300	NA
1	20	169	NA	65	61
3	20	243	NA	59	83
2	20	205	NA	156	440
4	20	234	NA	133	401
Average dermal exposure ($\mu\text{g/hr}$)		213	NA	103	246
Daily Dermal Dose (mg/kg/day) ^d		0.0243	NA	0.0117	0.0281
MOE ^e		570	NA	1100	490

NA. Data not available.

^aPassive dosimetry monitoring data were collected at the California sites (DAT 15 and 17 are from the aerially treated field and DAT 20 is from the ground-treated field).

^bReplicate refers to the study defined replicates for reviewers to match these results to the original study. Five different individuals were used for the pickers, three for the module builder operators, six for the rakers, and two for the trampers.

^cThe dermal exposure represents workers wearing cotton/polyester coveralls over the whole body dosimeters. Individual data points reported as monitored in MRID 427016-01 at an application rate of 1.875 lb ai/acre. No extrapolations were made to the data.

^dDaily Dermal Dose (mg/kg/day) = (corr. Avg. Dermal exposure ($\mu\text{g/hr}$) x 8 hrs/day x 0.001 mg/ μg unit conversion)/70 kg BW.

^eMOE = 14 mg/kg/day (LOAEL of 2 mg/kg/day x a conversion factor of 7)/Dermal Dose mg/kg/day. Level of Concern = MOE of 300

In addition to presenting the MOEs on the day that the data were collected, a transfer coefficient approach was used to estimate the dermal MOEs on 24 hours after application (current REI) and on 7 DAT (registrant proposed REI) as shown below:

Table 12. Tribufos Dermal Exposures for Picker Operators, Module Builder Operators, Rakers, and Trampers

	Worker Categories *			
	Pickers	Module	Rakers	Trampers
Results at 24 hours after treatment				
Average dermal dose @ 1.875 lb ai/acre (mg/kg/day) ^b	0.30	0.13	0.31	0.27
MOEs for AZ and CA	47	110	45	52
Average dermal dose (mg/kg/day) corrected for the lower (1.125 lb ai A) application rate ^c	0.18	0.078	0.19	0.16
MOE^f @ 1.125 lb ai/acre^d	78	180	74	88
Results at Seven Days After Treatment (DAT)				
Average dermal dose @ 1.875 (mg/kg/day) ^b	0.066	0.029	0.069	0.060
MOEs for AZ and CA	210	480	200	230
Average dermal dose (mg/kg/day) corrected for the lower (1.125 lb ai A) application rate ^c	0.040	0.017	0.041	0.036
MOE^f @ 1.125 lb ai/acre^d	350	820	340	390

^aPassive dosimetry monitoring data were collected at the California sites (DAT 15 and 17 are from the aerially treated field and DAT 20 is from the ground-treated field).

^bThe dermal exposure represents workers wearing cotton/polyester coveralls over the whole body dosimeters. The average dermal dose is calculated from the data reported in MRID 427016-01 at an application rate of 1.875 lb ai/acre. The dermal exposure data were collected on 15, 17, and 20 DAT and corresponding cotton boll residues were also collected. Based on these data, transfer coefficients (Tc) were calculated to extrapolate the dose from 15, 17, and 20 DAT down to 24 hours and 7 DAT. The Tc are 45, 20, 47, and 41 50g/hour for the pickers, module builders, rakers, and trampers, respectively. The dose (mg/kg/day) = (residue (ug/50g boll) x Tc X 0.001 mg/ug unit conversion x 8 hours worked)/70 kg BW.

^cCorrected Average dermal exposure (mg/kg/day) = Avg dermal exposure@1.875 lb ai/A (mg/kg/day) x 0.6 correction factor for new application rate (i.e., 1.125 lb ai/A/1.875 lb ai/A). Where the Avg. Daily Dermal Dose (mg/kg/day) = (Avg. Dermal exposure(ug/hr) x 8 hrs/day x 0.001 mg/ug unit conversion)/70 kg BW.

^dMOE = 14 mg/kg/day (LOAEL of 2 mg/kg/day x a conversion factor of 7)/Dermal Dose mg/kg/day. Level of Concern = MOE of 300

4.2.2 Occupational Risk Summary and Characterization

4.2.2.1 Dermal and Inhalation Exposure Risk

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

As shown in **Table 9**, the short- and intermediate-term **dermal risk estimates** indicate that the MOEs for the two scenarios listed below exceed HED's level of concern (*i.e.*, MOEs are less than the target MOE of 300) despite the maximum mitigation measure (reduced application rate and engineering controls):

(1a) mixing/loading liquids for aerial applicators

(2) aerial applicators (*i.e.*, pilots)

The Registrant study showed that the mixer/loaders using closed system for mixing/loading handled an average of 686 lb ai per replicate which resulted in a MOE of 270. When these data were combined with the PHED data and extrapolated to a full days work using the reduced application rate of 1.125 lb ai/A, the resulting MOEs were 290 at 350 acres treated and 82 at 1200 acres treated.

Aerial application of liquids in an enclosed cockpit (*i.e.*, pilots) attain a MOE of 500 (does not exceed HED's level of concern) when 350 acres are treated, whereas when 1200 acres are treated, the MOE correspond to 150 (exceed HED's level of concern). The registrant study showed that the pilot in an enclosed cockpit applying tribufos to an average of 838 acres over a 4.2 to 5.1 hour period had exposures that correspond to a MOE of 300 using application rates of 1.127 to 1.879 lb ai/Acre.

The MOES for the scenarios listed below do not exceed HED's level of concern (*i.e.*, dermal MOEs are greater than 300 and range from 300 to 12,000) at engineering controls:

- (1b) mixing/loading liquids for groundboom applications;
- (2) aerial applicators (*i.e.*, pilots) (350 acres treated)
- (3) groundboom tractor
- (4) flagging spray applications

As shown in **Table 9**, the short- and intermediate-term **inhalation risk estimates** indicate that the MOEs for the following scenarios do not exceed HED's level of concerns (*i.e.*, MOEs are greater than the target MOE of 100 and range from 560 to 23,000) at engineering controls:

- (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 applications.

As shown in **Table 10**, at the current application rate (1.875 lb ai/A) in Arizona and California, the MOEs for dermal exposure for the following scenarios exceed HED's level of concern

- (1a) mixing/loading liquids for aerial applicators;
- (2) aerial applicators (*i.e.*, pilots) (1200 acres treated)

Even at a higher application rates, the MOEs for inhalation exposure do not exceed HED's level of concern (*i.e.*, MOEs are greater than 100 and range from 330 to 5040) at engineering controls.

4.2.2.2 Occupational Aggregate Risk Indices

The Aggregate Risk Index (ARI) approach was utilized due to the differences in the MOEs for dermal (300) and inhalation (100). An ARI less than one indicates a level of concern. As shown in **Table 9**, all ARI's are below one for mixing/loading liquid for aerial applications (1a) and aerial applications (*i.e.*, pilots) (2) at 1200 acres, and therefore the risk is of concern. The ARI's are above one for other scenarios and therefore the risk is not a concern. Chronic dermal or inhalation exposure is not expected for use of tribufos in agricultural areas, hence a chronic risk assessment were not conducted.

As shown in **Table 10**, when used at the current application rates, again the ARI's are below one for mixing/loading liquid for aerial applications (1a); and aerial applications (2) (*i.e.*, pilots) at both 350 and 1200 acres treated, and therefore the risk estimate is of concern. The ARI's are above one for other scenarios and therefore the risk was not a concern.

4.2.2.3 Postapplication Exposure Risk Estimates

As shown in **Table 11**, the short- and intermediate-term postapplication dermal MOEs are greater than 300 on the days the test subjects were monitored in the field and therefore do not exceed HED' level of concern on 15, 17 and 20 DAT.

As shown in **Table 12**, at the lower rate of 1.125 lb ai/A, the current label 24 hour REI corresponds to a range of MOEs from 74 to 180 for various activities, and the MOEs on the proposed REI of 7 DAT range from 340 to 820. The MOEs at the current application rate (1.875 lb ai/A) range from 45 to 110 for 24 REI and 200 to 480 for a REI of 7 DAT.

4.2.3 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 of 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 woman 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.

5 Aggregate Risk Estimates

5.1 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 to 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).

5.2 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.

5.3 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 to 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).

6 Tolerance Reassessment

Provided in Table 13 is a summary of the tribufos tolerance reassessment.

6.1 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. Unless data are provided, the tolerance for milk will be reassessed at 0.01 ppm (currently 0.002 ppm). 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.

6.2 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.

6.3 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.

Table 13. 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	<i>(Cotton, undelinted seed)</i>
Cotton Gin byproducts	none	40	<i>(Cotton, gin byproducts)</i>
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.

¹Negligible residues

7 Data Requirements

7.1 Toxicology

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

7.2 Residue Chemistry

Residue Analytical Method - 171.4(a) - ILV of milk analytical method

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

7.3 Occupational Exposure

Handler exposure 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.

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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 , 44439101 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	

GLN: Data Requirements	Current Tolerances, ppm (40 CFR)	Must Additional Data Be Submitted?	References ¹
171-4 (f): Nature and Magnitude of the Residue in Water	N/A	N/A	
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 (I): 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, 2/11/95, 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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CBRS No.: 8763 and 10031

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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

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

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 for Tribufos
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

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



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Chemical: Tribuphos

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02/12/2001

