ESTIMATION OF EXPOSURE OF PERSONS IN CALIFORNIA TO PESTICIDE PRODUCTS THAT CONTAIN TRIBUFOS

BY

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ABSTRACT

Tribufos (DEF), S,S,S-tributyl phosphorotrithioate is registered in California as a cotton defoliant. There were a total of 20 illness and injury cases, mostly systemic in nature, associated with exposure to tribufos and tribufos in combination with other pesticides in California during 1982 to 1992. There were no reported illness or injury cases in California from 1993 to 1998. Formulated products of tribufos are strong dermal irritants. Tribufos is extensively (47.5 percent) absorbed through the skin of rats, but in primates (monkey) the dermal absorption was shown to be 7.1 percent. Tribufos is absorbed rapidly and metabolized extensively in laboratory animals following oral administration. The absorbed daily dosages (ADD) for workers handling tribufos were estimated to range from 0.7 µg/kg/day for a ground applicator to 8.5 µg/kg/day for a ground mixer/loader. The ADD for workers involved in cotton harvesting ranged from 1.9 µg/kg/day for a module builder operator to 8.3 µg/kg/day for a tramper.

This report is prepared as part of the Department of Pesticide Regulation's risk characterization document for tribufos. Tribufos toxicity studies have shown cholinergic signs in exposed laboratory animals.

HUMAN PESTICIDE EXPOSURE ASSESSMENT

California Environmental Protection Agency
Department of Pesticide Regulation
Worker Health and Safety Branch

TRIBUFOS

August 8, 1990
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Introduction

Tribufos is on the list of the first 200 products under the California Birth Defect Prevention Act of 1984. The Department of Pesticide Regulation (DPR) prepared a risk assessment document for tribufos because the chronic studies have shown possible adverse effects in laboratory animals. Human exposure assessment provides essential information for the risk assessment of pesticides. This human exposure assessment document is an integral part of the Risk Characterization Document of the DPR for tribufos. It also serves as a basis for developing mitigation strategies if exposure to tribufos is found to cause excessive risk.

This document was revised on June 20, 1995 to recalculate estimates of absorbed daily dosages (ADD) using new dermal absorption data, worker exposure studies, and worker protection statements on the product label. The second revision includes data from a new primate dermal absorption study and refines estimates of absorbed dosages based on that dermal absorption rate. This revision also applies a log-quadratic curve to the actual (observed) data to predict cotton boll dislodgeable residue dissipation and revises the estimates of field workers' exposure based on this predicted residue dissipation. In addition, the exposure to field workers such as weeders and irrigators is also added in the second revision.

In the first revision of this document, a log-linear regression curve was used to predict dislodgeable residue dissipation. The staff of Worker Health and Safety Branch (WH&S) determined that the use of a log-linear regression curve resulted in extending the predicted values to a region inconsistent with actual values (Andrews, 1999). The staff recommended using a log-quadratic for a better prediction of dislodgeable residues.

Chemical and Physical Properties

Tribufos (DEF) is the proposed common name for S,S,S-tributyl phosphorotrithioate (CAS No. 78-48-8). It is an organophosphate pesticide that can cause cholinesterase inhibition. Tribufos is marketed in California under the trade names of DEF® and Folex®. Its empirical formula is $(C_4H_9S)_3PO$. Tribufos is a colorless to pale yellow clear liquid with a molecular weight of 314.5, and a vapor pressure of 6.5×10^{-6} mm Hg at 25^{o} C (Talbott and Mosier, 1987). It is soluble in

aliphatic and aromatic chlorinated hydrocarbons, and is practically insoluble in water. It is relatively stable in acid and toward heating, but hydrolyzes slowly under alkaline conditions, producing the highly odorous butyl mercaptan. Tribufos can be stored in a freezer and remain relatively stable prior to analysis. The octanol/water partition coefficient for tribufos is 3.31 x 10^5 at 25^o C (D'Harlingue, 1987). Tribufos contains minute quantities of butyl mercaptan. Butyl mercaptan is a colorless liquid with a strong skunk-like odor. It is highly volatile with a vapor pressure of 35 mm Hg at 20 ^{o}C (GPC, 1982).

U.S. EPA and California Status

In 1981, the U.S. EPA issued a decision not to initiate the Rebuttable Presumption Against Registration (RPAR) review of tribufos with respect to its neurotoxicity concerns (U.S. EPA, 1981). The U.S. EPA concluded that even though laboratory animal testing indicated potential neurotoxic effects, under actual field use conditions there has not been unreasonable adverse effects to man. Moreover, the U.S. EPA obtained agreement from the registrants for label changes that specify protective clothing for workers to further reduce the exposure. The U.S. EPA contended in its 1981 decision document that the safety margins for various groups of workers were found adequate. At this time, the U.S. EPA is in the process of completing the registration eligibility document (RED) for tribufos.

In California, tribufos was placed into reevaluation on August 9, 1991 since available acute toxicity studies were inadequate to determine whether possible adverse effects were sufficiently mitigated by the signal word and precautionary language on the labels. Additional acute toxicity studies submitted by the registrant indicated that the signal word and precautionary statements on the labels were not adequate to mitigate possible eye and skin irritation hazards. The reevaluation resulted in revising the precautionary statements and changing the toxicity signal word from 'Warning' to 'Danger'. In 1998, the Department of Pesticide Regulation (DPR) completed a risk characterization document (RCD) for tribufos. In 2000, the Department issued permit conditions for the use of tribufos, requiring a seven-day entry restriction to treated areas for workers that could come in contact with foliage. The use permit condition will be in affect until it can be incorporated into the product label.

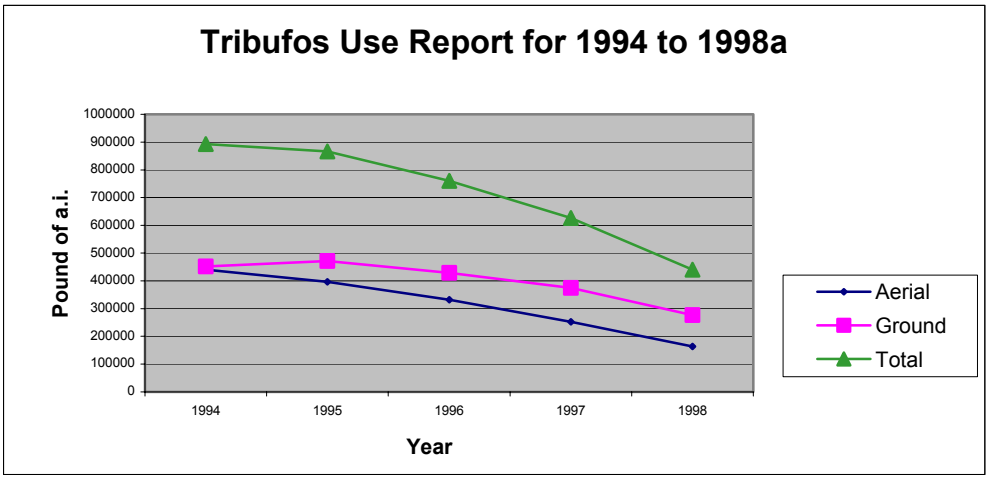
Formulations

To date, there are two tribufos-containing products registered in California. They are DEF® 6 Emulsifiable Defoliant and Folex® 6 EC Cotton Defoliant. Both products are emulsifiable concentrates, each containing 70.5 percent of the active ingredient (a.i.); which is equivalent to six pounds (lb.) of tribufos per gallon. Folex was originally formulated with slightly different a.i. (S,S,S-tributyl phosphorotrithioite), but was reformulated several years ago. Currently registered Folex contains tribufos as an a.i. and there is no pesticide product registered in California that contains S,S,S-tributyl phosphorotrithioite.

Usage

Tribufos is used exclusively on cotton for defoliation. The recommended application rate is 1.0 to 2.5 pints of the product (0.75 to 1.9 lb. a.i.) per acre. According to label directions, tribufos can be applied as a dilute spray in five to ten gallons of water per acre by air, or ten to 25 gallons of water per acre with ground equipment. It cannot be used through any type of irrigation system. In the past, tribufos was applied predominantly by air in California, but since 1995, ground application appears to be the primary method of application. The total yearly use of tribufos in California has been in steady decline since 1994 (DPR, 2000). Nearly 900,000 lb of tribufos was used in 1994, compared to approximately 400,000 lb used in 1988 (see Figure I). Under favorable conditions tribufos gives effective defoliation of cotton within four to seven days after application. When continued low temperatures prevail at night (below 60 ^{o}F), complete defoliation may require nine to 14 days.

Figure I



a- DPR, 2000

Label Precautions

Both DEF® 6 and Folex® 6 EC are toxicity category I products, bearing the signal word Danger on their labels. The precautionary statements on both labels inform users of ingestion and inhalation hazards. The labels also warn users of possible eye and skin injuries. The statement of personal protective equipment (PPE) on the product labels on file requires applicators and other handlers to wear the following:

- Coveralls (over long-sleeved shirt and long pants).
- Chemical resistant gloves.
- Chemical resistant footwear plus socks.
- Protective eyewear.

- Chemical resistant headgear.
- Chemical resistant apron when mixing/loading and cleaning equipment.
- MSHA/NIOSH-approved respirator in enclosed areas, or MSHA/NIOSH-approved dust/mist filtering respirator for outdoors.

According to the federal worker protection standards (WPS) for agricultural pesticides [40 Code of Federal Register, Section 170.240(d)(4-6)], when using closed mixing/loading system, enclosed cabs, or enclosed cockpits, the PPE requirements for mixer/loaders may be reduced to work clothing (long-sleeved shirt and long pants), chemical resistant apron, and chemical resistant gloves and for applicators may be reduced to work clothing.

Based on the WPS labels, restricted reentry interval to treated areas is 24 hours. The product label requires a preharvest interval of seven days. Tribufos is a restricted material in California. California Code of Regulations (CCR), Title 3, Section 6470 requires a one-half mile buffer zone from residential areas or schools in session (or due to be in session) for all tribufos applications. The regulations also require the use of a closed mixing/loading system for tribufos. The level of butyl mercaptan in tribufos-formulated products must not exceed 0.1 percent according to CCR, Title 3, Section 6361.

Human Illnesses and Injuries

There were a total of 20 illness and injury cases associated with exposure to tribufos and tribufos in combination with other pesticides in California during 1982 to 1992 (Orr, 2000). Of the 20 cases, 13 were systemic and the remaining 7 involved respiratory, eye, or skin illness/injuries. From 1993 to 1998, there were no reported illness or injury cases that were associated with exposure to tribufos.

In a 1977 report from the California Department of Food and Agriculture, several hundred complaints of human illness were summarized (Maddy, 1977). The illnesses were characterized by wheezing, coughing, nausea, and other discomforts that could be linked to the foul odor of butyl mercaptan, a degradation product of the cotton defoliant. Due to improvements in the manufacturing process of tribufos, a very low odor formulation is available now and has, to some extent, minimized the odorous problem associated with the use of this cotton defoliant. However, this report also emphasized that after the low-odor cotton defoliant has been sprayed onto the field, foul odorous material is generated and may persist for up to 48 hours due to photodegradation and other field conditions (Maddy, 1977). Thus, removing the impurities of the defoliant product alone does not totally eliminate the foul odor.

There are no available clinical reports in this country on human illness due to tribufos exposure. An article entitled "Merphos Poisoning or Mass Panic?" reported a chemical spill on a ship in Mexico on route to Sydney, Australia (McLeod, 1975). Six hundred and forty-three exposed persons were seen at a local hospital. The most serious problem appeared to be the inhalation toxicity of the butyl mercaptan. It was estimated that the airborne concentration of butyl mercaptan exceeded 0.5 ppm, and in some situations, exceeded 10 ppm (American Conference of Government Industrial Hygienists threshold limit value {(ACGIH) TLV} for butyl mercaptan

was 0.5 ppm time-weighted average (TWA.) Reportedly, there was no cholinesterase inhibition among the tested individuals. In addition to the symptoms usually seen following exposure to mercaptan, the author emphasized that panic, fear, anxiety, and exhaustion play a major role in exhibiting or intensifying some of the symptoms. Since caustic soda was used for the decontamination process of chemical spill, more butyl mercaptan was generated, thus, resulting in a continuous supply of foul odorous chemical. The author concluded that there was no significant human illness resulting from organophosphate poisoning in this episode.

Kilgore *et al*. conducted medical examination and psychological testing of 14 aerial applicator personnel who were exposed to tribufos (Kilgore *et al*., 1984). These volunteers were pilots, flaggers, mixer/loaders and other personnel. Medical examination included a general physical, chest X-ray, EKG, total and RBC cholinesterase, blood chemistry, and urinalysis. There were no significant medical findings noted in any of the 14 workers. A battery of psychological tests was utilized to measure the neuropsychological functions of the exposed persons. These particular measures were selected because they were considered to be subtle measures of organic brain dysfunction. The test found no significant differences between the pre- and post-exposure scores on any of the psychological measures utilized.

An epidemiological study was conducted by the Department of Health Services on acute health effects associated with the exposure of cotton defoliants (Scarborough, 1989). The study surveyed by phone 460 residents of agricultural communities in the San Joaquin Valley during cotton defoliation. The study found a positive association between the various symptoms and spraying of cotton defoliants for people living or working near a sprayed field. These symptoms included "respiratory allergy", eye irritation, rhinitis, throat irritation, shortness of breath, wheezing, "asthma symptoms", nausea, and diarrhea. In this epidemiological survey it is not known whether the regulation requiring a one-half mile buffer zone between residential areas and the sprayed fields had been enforced during tribufos applications.

Although very low exposure to tribufos is unlikely to cause a toxicological effect, the presence of an infinitesimal amount of the degradative product (butyl mercaptan) causing foul odor is likely to be associated with the various symptoms and complaints. The TLV - TWA for butyl mercaptan is 0.5 ppm which indicates exposure at this level or below should not result in untoward acute health effects (ACGIH, 1988). However, the offensive odor which can be detected at 0.001 ppm (Amoore and Hautala, 1983) may have caused the various discomforts and reported illness.

Dermal Irritation/Sensitization

Technical tribufos is a moderate dermal irritant (category III) to rabbits (Sheets and Fuss, 1991). The formulated products are strong dermal and eye irritants (Sheets and Phillips, 1992; Crawford, 1971), which may be due to the inert ingredients. A skin sensitization study with technical grade tribufos found no evidence of dermal sensitization in guinea pigs (Sheets, 1990).

Animal Metabolism

Indirect information indicates differential metabolism (degradation) occurs via various routes of administration. This is likely due to the consequence of kinetics of metabolism. When administered orally tribufos undergoes hydrolysis in the GI tract to produce n-butyl mercaptan, causing late acute effects in test animals without producing neurohistopathological changes. When applied dermally, tribufos does not undergo hydrolysis, thus the late acute effects caused by n-butyl mercaptan are virtually absent. This may explain why topically administered tribufos in large dosages is more effective in producing neurotoxic effects. Other studies also demonstrate that dermally administered DEF was more effective in the inhibition of neurotoxic esterase (NTE) and induction of cytochrome P-450 than orally administered tribufos in adult hens (Abou-Donia, 1979, Lapadula *et al*., 1984, Abou-Donia, *et al*., 1986).

[^{14}C] Tribufos was absorbed rapidly and metabolized extensively by rats when administered orally (gavage) as a single dose of 5 or 100 mg/kg or multiple doses of 5 mg/kg (Kao *et al*., 1991). At least 57 percent of the administered dose was excreted in 24 hours. Approximately 96 percent of the administered dose was excreted in urine and feces within 72 hours. Urinary excretion accounted for 55 to 80 percent of the administered dose. Elimination in feces was 15 to 42 percent of the administered dose. The highest residues in tissues were found in the liver following administration. Of the 18 metabolites detected in urine only one was identified (butyl-gamma-glutamylcysteinylglycine disulfide), accounting for one to four percent of the total dose. No tribufos was found in urine. In feces, the parent compound accounted for 15 to 31 percent of the dose. There was no evidence of bioaccumulation in rats. Metabolism studies in laying hens and lactating goats also showed that tribufos is absorbed rapidly and metabolized extensively (Sahali, 1991; and Hall, 1991).

Dermal Absorption, Route of Exposure, and Toxicity

A dermal absorption study of tribufos in rats showed substantial dermal absorption in treated animals (Schroeder, 1992). Adult male Sprague-Dawley rats weighing 200 to 238 grams were used in this study. The back of each animal was shaved and the treated skin site was enclosed with a rubber ring. The animals were placed in individual metabolism cages to allow the separate collection of urine and feces during the study. Rats were treated at three dose levels of 1.93, 12.4, and 100 ug/cm^2. The dosing solution was tribufos-1-^{14}C (98.9% purity) mixed in distilled water with DEF 6 blank formulation and non-labeled tribufos as needed. The treated skin site was protected with a non occlusive cover made of a Teflon-laminated filter and a carbon-impregnated material. Rats were exposed for 10 hours or until sacrificed whichever came first. A group of four rats from each dose level were sacrificed at 1, 4, 10, and 168 hours. All sampling media such as non occlusive cover, ring wash, treated skin site, cage wash, carcass, urine, feces, and blood were collected for analysis. Recoveries of the administered doses ranged from 89 to 106 percent. Tribufos was apparently readily absorbed because the skin residues for all dose levels and exposure periods were similar. Dermal absorption was calculated as the sum of percent dose in urine and feces at asymptote and percent dose recovered in, carcass, cage wash, and blood. The dermal absorption values after correction for recoveries were 47.5, 47.9, and 33.9 percent for the low, medium, and high doses, respectively.

A monkey dermal absorption study, submitted by the tribufos registrant, was reviewed by DPR (Thongsinthusak, 2000). Five male rhesus monkeys, ages 1.4 to 3.2 years and weighing 3.2 to 3.8 kg, were used in this study. A sufficient area of the back of each monkey was shaved and cleaned for dose administration. A mean dose of 83.3 μg/24 cm^2 of [C^{14}]-DEF 6 was administered dermally to the animals. Intravenous injection was unnecessary since the recovery of radioactivity was greater than 90%. The application site was covered with an aluminum dome for an exposure period of 8 hours. After the exposure, the test site was washed with a series of 16 soap/water-soaked and 2 dry cotton swabs. Tape stripping of the skin was performed 48 hours after dosing. Urine and feces samples were collected at various intervals up to 120 hours and at 24-hour intervals thereafter until the recovered radioactivity measured greater than 80%.

Total recovery of radioactivity from individual animals ranged from 101 to 109% with a mean of 105%. The mean percent recoveries in various samples were 6.24 (urine), 0.72 (feces), 0.48 (food biscuits), 1.25 (dermal dome), 2.73 (Duoderm®), 93.8 (dermal swabs), and 0.08 (tape strips). Cumulative dose recovered in urine, feces, and biscuits (food left on the feces collection screen) was used to develop an excretion profile by employing the exponential saturation model. The excretion profile showed that the maximum excretion of the administered dose was 8.1%, after adjusting for average recovery of 105%. The observed cumulative dose recovered in urine, feces, and biscuits was 7.1% of the administered dose. A dermal absorption rate of 7.1% was recommended for use in the calculation of absorbed dose.

Dislodgeable Foliar Residue

A cotton boll residue study was conducted in conjunction with a cotton harvester exposure study (Eberhart and Ellisor, 1993). The harvester exposure portion of the study is discussed in the Worker Exposure section of this document. The residue portion of the study was conducted as follows. Cotton boll residue samples were collected at two locations (California and Mississippi). Two separate residue trials were conducted at each location. In California, cotton boll samples (50 grams each) were collected from the fields harvested during the worker exposure monitoring portion of the study. The fields were treated with DEF 6 at the maximum label rate (2.5 pints/acre) either aerially or by ground equipment. Triplicate samples were taken from the aerially-treated field prior to the application and at 0, 1, 2, 4, 7-13, 15, and 17 days post application. Triplicate samples were also taken from ground-treated fields at the same intervals and 16, 18, and 20 days post application. The cotton boll samples were placed in a container with 200 mL of Nekal/water solution and shaken for 20 minutes. The solution was decanted into a pre-labeled container. Control and field fortified samples were also collected. The study was performed according to the U.S. EPA's Good Laboratory Practice (GLP) standards. The study combined the cotton boll residue data from California and Mississippi to predict residue degradation. Residue degradation is highly environmentally dependent. We prefer to use California data when readily available. In the first revision of this exposure assessment document dated June 20, 1995, the predicted residue levels were derived from log-linear regression analysis of observed residues in California over time. The staff of WH&S determined that the use of a log-linear regression curve resulted in extending the predicted values to a region inconsistent with actual values (Andrews, 1999). The staff recommended using a log-quadratic curve for a better prediction of dislodgeable residues (Table 1).

In a defoliated cotton field, cotton bolls could be the primary source of pesticide exposure for cotton harvesting crews entering the treated field. Cotton boll residues are not necessarily dislodgeable foliar residues (DFR) as conceived with other crops, but can be used for an indirect estimate of exposure of workers involved in harvesting.

Table 1. Tribufos Residue Levels on Cotton Bolls in California (μg/g)[a]

Post Application	Observed residue		Predicted residue[b]	
Days	*ground*	*aerial*	*ground*	*aerial*
0	3.91	2.36	3.252	4.851
1	2.59	2.62	2.249	2.796
2	1.18	1.39	1.583	1.661
4	0.57	1.39	0.829	0.652
7	0.38	0.23	0.363	0.216
8	0.40	0.14	0.286	0.163
9	0.17	0.15	0.230	0.129
10	0.14	0.14	0.189	0.106
11	0.14	0.02	0.158	0.091
12	0.15	0.05	0.135	0.082
13	0.18	0.06	0.118	0.076
15	0.09	0.05	0.095	0.074
16	0.06	n.c.	0.088	0.076
17	0.09	0.14	0.082	0.081
18	0.10	n.c.	0.079	0.088
20	0.06	n.c.	0.077	0.107
		R Square (r^2)	0.952	0.843

a – Eberhart and Ellisor, 1993.
b - Predicted using a log-quadratic curve
n.c. - No samples were collected
Predicted ln residue = $\beta_0 + \beta_1$* day + β_2* day^2
β_0 = Intercept, β_1 = Slope, β_2 = Coefficient of quadratic

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Worker Exposure

Handler Exposure:

1. Handler Exposure Study (Peoples *et al.*, 1981)
   Two aerial applicator firms cooperated in this study. Monitoring included inhalation and dermal exposure of mixer/loaders, pilots, and flaggers during the applications of DEF and Folex in the San Joaquin Valley of California in 1979. Closed system transfer was used during this study by both firms. However, the containers were rinsed by hand, and the rinse water was hand-poured into the mix tank by mixer/loaders of one firm (firm #2). The application rate of the defoliants was 0.22 and 0.25 gallon (approximately one pound a.i. per acre) in 10 gallons of water per acre.

Mixer/loaders wore rubber boots, socks, a shirt, pants, and a washable cap. Clean long-sleeved and long-legged coveralls were required daily. The mixer/loaders wore neoprene gloves when hooking up, loading, and washing the aircraft. They removed the gloves between mixing/loading operations and while cleaning the nozzles. The pilots wore shoes and socks, a helmet, and clean long-sleeved shirts and long-legged cloth pants, which were changed daily. They are expected to wear rubber gloves when adjusting spray nozzles. Some pilots did not wear gloves when adjusting spray nozzles. The flaggers wore clean coveralls (with long sleeves and legs) and washable caps.

Inhalation exposure was monitored by placing a Dupont Constant Flow Sampler P-4000 pump on each worker with the air intake placed in the breathing zone. Air sampling tubes containing Amberlite XAD-4 resin were used as the sampling media. Dermal exposure was measured with patches made of an outer layer of cloth and an inner layer of gauze taped together. The outer layer represented the protective factor of clothing and the inner layer represented the skin surface. Patches were taped to the clothing and skin areas. The residues on the head and neck surfaces were measured as the sum of the inner and outer patches. Hand exposure was monitored at the end of the workday by rinsing the hand with ethyl alcohol, after removal of gloves when applicable.

The estimates of exposure were normalized to seven hours. The monitoring days were selected so that at least seven hours of continuous applications were expected but the monitoring period varied from a few hours to 7 hours. The actual application time was 6 to 12 hours daily. Gas chromatography (GC) was used for the analysis of tribufos following solvent extraction. Table 2 shows estimated dermal and inhalation exposure of workers to tribufos during aerial application.

Table 2. Estimates of Absorbed Daily Dosage of Workers Exposed to Tribufos During Aerial Application

Work Activity (n)	Exposure[a] (µg/person/day)					ADD[b] (µg/kg/day)
	Head/ Neck	Body	Hand	Total Dermal	Inhalation	
Mixer/Loader[c] (10)	1965	2169	5617	11398	257	12.4
Pilot[c] (11)	518	1790	4699	8354	124	8.6
Flagger[c] (11)	1266	202	175	1897	313	3.8

a - Geometric mean (log-normally distributed) and seven-hour workday.

b - Dermal absorption of 7.1 percent (Thongsinthusak, 2000), respiratory uptake of 50 percent (Raabe, 1988), inhalation rate of 14 L/minute, and body weight of 75.9 kg (Thongsinthusak, *et al*., 1993).

c – For pilots wearing work clothing (long-sleeved shirt, long pants, socks, and shoes), mixer/loaders wearing work clothing, gloves, and apron and used a closed mixing/loading system, and flaggers wearing work clothing, coveralls, gloves, hat, and a dust/mist respirator. Coveralls, gloves, hat, and apron, each provide 90 percent dermal protection to the covered areas (Thongsinthusak, *et al*., 1993), and a dust/mist respirator assumed to provide 50 percent respiratory protection (Raabe, 1988).

(n) - Number of observations.

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2. Handler Exposure Study (Eberhart, 1993)
Dermal exposure, inhalation exposure, and cholinesterase activity of handlers were monitored during tribufos application to cotton at two locations in the San Joaquin Valley, California and one location in Glendora, Mississippi.

Four commercial applicator crews were monitored in California. At the first location, two crews, each consisting of a pilot, a mixer/loader, and two flaggers, applied DEF® 6 by air at 2.5 pints (1.9 lb. a.i.)/acre and 1.5 pt (1.1 lb. a.i.)/acre. A total 1710 gallons of DEF® 6 was applied aerially to 6705 acres of cotton during the monitoring. At the second location, two crews, each consisting of one mixer/loader and one applicator applied DEF® 6 by ground rig boom sprayers equipped with closed cabs and air conditioning at 2.5 pints/acre. A total of 165 gal. of DEF® 6 were applied to 531 acres of cotton. Closed mixing/loading systems were used at both locations in California. In Mississippi, only mixer/loaders of two aerial crews were monitored during open mixing-loading operations.

Dermal and inhalation exposure of workers was monitored during four one-half day (approx. 4 hours) periods. Each worker wore a dosimeter garment (a long-sleeved tee-shirt and a pair of tights) under a single layer of coveralls (as work clothing), and a hat. All mixer/loaders wore additional protective clothing consisting of nitrile gloves, goggles, and rubber boots. Gauze patches were attached to the coveralls at the chest, back, and front of the cap to estimate exposure to uncovered areas such as neck, face and head. Hand exposure was measured via ethanol hand washes at the end of each monitoring period. An air sampling pump connected to an OVS-2 tube (glass fiber filter backed by two sections of XAD-2 resin) was used to monitor air residues in workers' breathing area. All collected samples were placed on dry ice and shipped via over-night delivery to the laboratory. RBC and plasma cholinesterase activities of three to five workers in each job category were monitored weekly for a 3-4 week period during the rest of the cotton defoliation season in California. The workers participating in cholinesterase monitoring were not necessarily all participants of the exposure monitoring portion of the study. The rate of applications varied during cholinesterase monitoring. Blood samples were analyzed as soon as possible, mostly within 48 hours of collection.

Control and field fortified samples were prepared on each day of monitoring. The study was performed according to the U.S. EPA's GLP standards. Blood cholinesterase analyses were performed in a manner consistent with GLP. All exposure results were corrected for field recoveries. Most field recoveries were over 90 percent. Head and neck surface area as described in the U.S. EPA Subdivision U Guidelines (U.S. EPA, 1987) were used in calculating dermal exposure to those exposed areas. The exposure values were reported as µg/lb. handled, µg/hour, and µg/replicate.

Table 3. Mixer/loader, Applicator, and Flagger Exposure to Tribufos During DEF 6 Application to Cotton in San Joaquin Valley, California

Job Category (n)	Exposure[a] (µg/person/hour)					ADD[b] (µg/kg/day)
	Head/ Neck	Body	Hands	Total Dermal	Inhalation	
Aerial Application						
Mixer/Loader (8)[c]	182.2	199.8	181.9	629.6	9.5	4.6
Pilot (8)[c]	67.8	100.2	542.7	748.1	5.0	5.1
Flagger (16)[c]	520.5	43.6	78.1	657.7	11.6	4.8
Ground Application						
Mixer/Loader (8)[c]	243.0	252.2	434.0	1075.8	8.0	8.5
Applicator (8)[d]	4.6	58.8	19.6	86.8	1.4	0.7

a - Geometric mean (log-normally distributed).

b - Dermal absorption of 7.1 percent (Thongsinthusak, 2000), respiratory uptake of 50 percent (Raabe, 1988), inhalation rate of 14 L/minute, and body weight of 75.9 kg (Thongsinthusak *et al.*, 1993), and workday of 7 hours for aerial crews and 8 hours for ground crews.

c - For pilots wearing work clothing (long-sleeved shirt, long pants, socks, and shoes). Mixer/loaders wearing work clothing, gloves, and apron and used a closed mixing/loading system. Flaggers wearing work clothing, coveralls, gloves, hat, and a dust mask. Coveralls, gloves, hat, and apron, provided 90 percent dermal protection to the covered areas (Thongsinthusak et al., 1993). Dust mask assumed to provide 50 percent respiratory protection (Raabe, 1988).

d - In enclosed cab wearing work clothing.

(n) - Number of observations.

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3. Handler Exposure Study (Lotti *et al*., 1983):

Lotti, *et al*. reported a worker exposure study consisting of seven workers during aerial application of DEF in cotton fields. The dermal exposure data generated from this study was neither meant for, nor appropriate, to the whole body dose extrapolation. The primary objective of this study was to determine whether the measurement of neurotoxic esterase (NTE) inhibition was useful in monitoring workers exposed to organophosphates that can cause delayed neurotoxicity.

In addition to dermal exposure and air monitoring, a series of tests to monitor peripheral nerve function and nerve enzyme activity were conducted. These tests emphasize the subclinical aspects of worker exposure. By definition, subclinical effects denote the subtle changes of enzyme markers or electrophysiological changes of nerve function which by themselves do not lead to demonstrable clinical symptoms.

Prior to conducting these tests, workers were exposed to the defoliants for a lengthy period (averaging 27 days), and thus the test results are considered reliable as indicators of subtle effects following season long exposure. The exposure did not result in any detectable clinical effect on the peripheral nervous system, nor was there any cholinesterase inhibition detected in any of the exposed workers. The lymphocyte NTE activity was significantly inhibited in most of the exposed workers. This inhibition appears to be correlated to the

length of exposure and did rebound, approaching normal values three weeks after the exposure was terminated. The significance of the NTE inhibition and the potential of developing neuropathy are not known. However, the measurement of NTE during the exposure to organophosphate may be a useful biomarker and serve as a warning signal for overexposure.

Exposure of Cotton Harvesters:

1. Cotton Harvester Exposure Study (Roberts and Smith, 1980; Cox *et al*., 1980a, b, c)
   Mechanical cotton picker operators' dermal and respiratory exposure to tribufos was studied in California at four locations. Closed cab, two-row type mechanical cotton pickers were used to harvest cotton. Respiratory samples were collected inside the cab at the operator's breathing zone, using air sampling pumps calibrated at 1.0 liter per minute. Dermal exposure was monitored by attaching gauze pads with polyethylene backing to the front thigh clothing areas of the operators.

   Only one pad was used for each operator to monitor dermal exposure. The weather conditions prior to and during this study were unusual (low temperature, high humidity, rain) for the season and not typical of California. The study authors concluded that the unusual weather conditions could contribute to reduced exposure levels. In the presence of more reliable data (Eberhart and Ellisor, 1993), the information from this study may not be appropriate for estimating tribufos exposure to cotton picker operators.

2. Cotton Harvesters Exposure Study (Eberhart and Ellisor, 1993)
   In a more recent study, dermal exposure, inhalation exposure, and cholinesterase activities of five cotton harvesting crews were monitored in San Joaquin Valley, California. DEF® 6 was applied to the cotton fields at the label rate of 1.9 lb. a.i./acre either by aerial or ground equipment (Eberhart, 1993).

   All crews used mechanical harvesters to harvest cotton. Three crews used mechanical module builders to compact the harvested cotton. The other two crews compacted the harvested cotton by the old fashioned method of physical tramping. Workers of each crew were divided into three job categories as harvesters (picker operators), compactors (module builder operators or trampers), and rackers who also picked loose cotton on the ground. Crews with mechanical module builders entered the cotton fields 15 and 17 days after a single aerial application. Crews with trampers entered cotton fields 20 days after a single ground application. Dermal and inhalation exposure of workers was monitored during two 4-hour periods. Each worker wore the dosimeter garments (a long-sleeved T-shirt and a

Table 4. Dermal and Inhalation Exposure of Workers to Tribufos During Cotton Harvesting (Eberhart and Ellisor, 1993)

	Dermal Exposure (µg/person/hr)[a]				Inhalation[a]	ADD[b]
Job Category	Exposed	Covered	Hands	Total	(µg/person/hr)	(µg/kg/day)
15 Days After Aerial Application:						
Picker Operator	19.3	33.8	32.1	85.2	4.0	0.9
Module Builder Operator	10.6	61.2	7.7	79.4	4.2	0.8
Raker	22.6	74.9	32.2	129.8	4.7	1.2
17 days After Aerial Application:						
Picker Operator	12.8	60.6	63.8	137.2	1.9	1.1
Module Builder Operator	4.0	9.3	7.3	20.6	1.7	0.2
Raker	9.9	31.7	11.8	53.4	1.1	0.5
20 Days After Ground Application:						
Picker Operator	21.6	74.4	116.9	212.9	1.8	1.7
Tramper	15.0	122.6	108.7	246.3	4.0	2.1
Raker	6.6	58.4	38.2	103.3	2.5	0.9

a - All data are arithmetic means (data mostly normally distributed).
b - Absorbed daily dosage; based on dermal absorption of 7.1 percent (Thongsinthusak, 2000), respiratory uptake of 50 percent(Raabe, 1988), inhalation rate of 14 L/minute, body weight of 75.9 kg (Thongsinthusak *et al*., 1993), and workday of 8 hours.
Clothing: Long-sleeved shirt, long pants, socks, and shoes for all workers.

Formoli, WH&S, 2000

pair of tights) under a single layer of coveralls (as work clothing). A hat was also worn that held a gauze patch. Gauze patches were attached to the coveralls at the chest, back, and front of the hat to estimate exposure to uncovered areas such as neck, face and head. Hand exposure was measured by taking ethanol hand washes at the end of each monitoring period. An air sampling pump connected to an OVS-2 tube (glass fiber filter backed by two sections of XAD-2 resin) in worker's breathing zone was attached to the belt of each worker to monitor inhalation exposure. RBC and plasma cholinesterase activities of five workers in each job category were monitored weekly for a 5-6 week period during the rest of cotton harvesting season. All exposure results were corrected for field recoveries. The participating workers spend 31 to 35 days per year performing cotton harvesting activities. Average body weight for workers (nine males and seven females) was 75±13 kg. Table 4 shows the estimates of exposure for these workers.

Mean five-week plasma and erythrocyte cholinesterase values for each worker were within 88 to 107 percent of his/her baselines. The two lowest erythrocyte cholinesterase activities observed were both 77 percent of the baseline for two module builder operators on the fifth week of monitoring. The next lowest erythrocyte cholinesterase observed was at least 83 percent of the baseline. The lowest plasma cholinesterase activity observed was 79 percent of the baseline for another module builder operator on the fourth week of monitoring and

raised to 85 percent of the baseline on the fifth week of monitoring. While cholinesterase activity is a general indicator of exposure, it is not a gauge to specifically quantify exposure.

To estimate the dermal exposure of harvesters entering treated fields seven days after tribufos application, a dermal transfer factor was calculated from the estimate of dermal exposure of workers in Table 4 and the level of residues in cotton bolls (Table 1) on the day worker exposure was measured. Table 5 shows the estimate of exposure of harvesters entering treated fields immediately after the expiration of the preharvest interval. The indirect estimation of field workers' exposure from dislodgeable foliar residues is an acceptable method in exposure assessment; however, cotton boll residues are not dislodgeable foliar residues as conceived with other crops. Cotton boll residues are probably distributed throughout the boll while dislodgeable foliar residues are only surface residues.

Table 5. Tribufos Estimated Dermal Transfer Factors and ADDs for Workers Involved in Cotton Harvesting Following Ground or Aerial Application

Days After Application & Application Type	Dermal Exposure Observed[a] µg/hr	Cotton Boll Residue Predicted µg/g	Transfer Factor g/hr	Dermal Exposure Calculated µg/hr	ADD[b] Calculated µg/kg/day
Picker Operator:					
15 aerial	85.2	0.07	1217		
17 aerial	137.2	0.08	1715		
20 ground	212.9	0.08	2661		
Average			1864		
7 Ground		0.36	1864	671	5.0
Module Builder Operator:					
15 aerial	79.4	0.07	1134		
17 aerial	20.6	0.08	258		
Average			696		
7 Ground		0.36	695	250	1.9
Raker:					
15 aerial	129.8	0.07	1854		
17 aerial	53.4	0.08	668		
20 ground	103.3	0.08	1291		
Average			1271		
7 Ground		0.36	1271	458	3.4
Tramper:					
20 ground	246.3	0.08	3079		
7 Ground		0.36	3079	1108	8.3

a – Eberhart and Ellisor, 1993

b - Absorbed daily dosage; assuming dermal absorption of 7.1 percent (Thongsinthusak, 2000), body weight of 75.9 kg (Thongsinthusak *et al*., 1993), 8-hour workday, and workers wearing work clothing.

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Exposure of Weeders and Irrigators:

The DEF label requires a restriction of entry of four to seven days for activities involving human contact with foliage. This period allows cotton defoliation to occur under ordinary environmental conditions and minimizes human contact with foliage. Under extraordinary environmental conditions (such as continuous low nightly temperatures) when defoliation may require more than seven days, irrigators and weeders entering treated fields could come in contact with the foliage treated with tribufos. Irrigators may enter the cotton fields to remove the irrigation pipes before harvest. Weeders remove any weeds so the field will be prepared for harvest. There are no chemical specific (tribufos) and crop-specific (cotton) irrigator or weeder exposure data available. In addition, there are no chemical specific cotton dislodgeable foliar residue data available. Therefore, an estimate of exposure for workers entering treated fields must be made, using surrogate data and default assumptions.

In the absence of actual DFR values for tribufos, a uniform foliar deposition value can be used as DFR for exposure assessment and can be calculated based on the maximum application rate of 1.9 lb a.i./acre. The calculated foliar deposition is equivalent to 10.6 ug/cm^2, immediately after the application. This is based on the assumption that the amount of tribufos applied will be distributed uniformly on the field and on the cotton foliage (front and back of the leaves). Assuming that the degradation of foliar deposition follows the degradation pattern of cotton boll resides, the foliar deposition values after four and seven days will be 25% and 11% of the initial deposition, respectively. Based on the calculated initial foliar deposition of 10.6 ug/cm^2, the foliar deposition values after four and seven days of a ground application will be 2.65 ug/cm^2 and 1.17 ug/cm^2. The Science Advisory Council for Exposure recommends a generic default transfer factor (transfer coefficient) for irrigators that range between 1,000 to 4,000 cm^2/hour, depending on the crop in which the work is performed (SACE, 1998). For cotton scouts, the recommended default transfer factor also ranges between 1,000 to 4,000 cm^2/hour. A transfer factor of 1,000 cm^2/hour is recommended for weeding and hoeing. Using a methyl parathion exposure study (Ware *et al*., 1975), a dermal transfer of 1,288 cm^2/hr can be calculated for cotton scouts wearing work clothing such as long-sleeved shirts, long pants, and footwear. To estimate dermal exposure to cotton irrigators and weeders entering treated fields four to seven days after tribufos application, a dermal transfer factor of 1,288 cm^2/hour was used (Table 6).

Table 6. Tribufos Estimated Dermal Transfer Factors and ADD for Workers Entering Treated Fields Postapplication

Worker Activity	Days After Application	DFR[a] (µg/cm^2)	Transfer Factor (cm^2/hour)	Dermal Exposure[b] (µg/person/day)	ADD[c] (µg/kg/day)
Irrigators/ weeders	4	2.65	1,288	27,305	25.5
Irrigators/ weeders	7	1.17	1,288	12,056	11.3

a – Estimated dislodgeable foliar residues at reentry, four and seven days after tribufos application.
b – Based on an 8-hour workday and workers wearing long-sleeved shirts, long pants, socks and footwear.
c – Absorbed daily dosage; based on a dermal absorption of 7.1% (Thongsinthusak, 2000) and body weight of 75.9 kg (Thongsinthusak *et al*., 1993).

Cotton defoliation is a seasonal activity in California. It starts in early September (Southern San Joaquin Valley) and ends in mid October (Central San Joaquin Valley), depending on the weather conditions and crop maturity (Vargas, 1993; Wright, 1993). According to the product label, tribufos effectiveness is limited by temperature. The climatic conditions favorable for effective use of tribufos normally occur during the first two to three weeks of the defoliation season (Wright, 1993). A worker may handle tribufos an average of four to five workdays during the season (Haskell, 1993). Three weeks (21 workdays) in a season may be the maximum. The seasonal average daily dosage (SADD) and annual average daily dosage (AADD) in Table 7 are based on three weeks of exposure in a 45-day season and in a 365-day year respectively for both tribufos handlers and cotton harvesting crews.

Table 7 is a summary of the estimates of exposure for tribufos handlers, field workers, and cotton harvesting crews. The estimates of ADD for mixer/loaders and pilots in Table 7 are based on the Eberhart (1993) exposure study since the closed system technology and the work habits in this study are more representative of the current use of tribufos. During Peoples, *et al*., 1981 study, protective clothing was worn irregularly. Some pilots adjusted the nozzles without gloves. Mixer/loaders removed their gloves during handling and the mixing/loading procedure of one crew involved hand pouring. The estimate of ADD for flaggers is based on weighted-average of both studies.

Table 7. Estimated Absorbed Daily Dosage (ADD), Seasonal Average Daily Dosage (SADD) and Annual Average Daily Dosage (AADD) for Tribufos Handlers, and Field workers

Job Category	ADD µg/kg/day	SADD[a] µg/kg/day	AADD[b] µg/kg/day
During application:			
Mixer/loader (aerial)	4.6	2.1	0.3
Pilot	5.1	2.4	0.3
Flagger	4.4[c]	2.1	0.3
Mixer/loader (ground)	8.5	4.0	0.5
Applicator (ground)	0.7	0.3	0.1
Four days postapplication:			
Irrigators and weeders	25.5	11.9	1.5
Seven days postapplication			
Irrigators and weeders	11.3	5.3	0.6
Seven days postapplication:			
Picker Operator	5.0	2.3	0.3
Module Builder Operator	1.9	0.9	0.1
Raker	3.4	1.6	0.2
Tramper	8.3	3.9	0.5

a - A 21-workday tribufos application or harvesting in a 45-day season was assumed.
b - A 21-workday tribufos application or harvesting in a 365-day year was assumed.
c - Weighted average of ADDs in Tables 2 and 3 (Peoples *et al*., 1981 and Eberhart, 1993)

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Exposure of Non-Applicator Personnel and Crews:

1. Drift Study (Lowrimore *et al*., 1985)
   The primary objectives of this study were to measure the air drift capacity of tribufos, and to monitor the potential dermal exposure by measuring the deposition of tribufos on denim cloth under field study conditions. This study was conducted in Pickins, Arkansas, on six cotton fields ranging from 46 to 70 acres. The results indicated that at one kilometer (0.6 mile) downwind and within 0 - 60 minutes after spraying, the amount of tribufos found on denim ranged from 0.03 to 0.34 $\mu g/cm^2$, with the majority of the samples below 0.1 $\mu g/cm^2$. Table 8 shows the average levels of tribufos in denim patches and air monitors. There was no attempt at odor surveillance in this study.

Table 8. Exposure of Non-Applicator Personnel and Crews to Tribufos (Lowrimore *et al*., 1985)

Distance	Within 0 to 60 minutes After Application		Within 60 to 180 minutes After Application	
Downwind (meters)	Denim Patch ($\mu g/100\ cm^2$)	Air ($\mu g/M^3$)	Denim Patch ($\mu g/100\ cm^2$)	Air ($\mu g/M^3$)
10	993	10	9	2
50	119	8	4	1
100	46	6	5	1
1000	10	not reported	4	not reported

Wang, WH&S, 1990

2. Drift Study (Oshima *et al*., 1980)
   The California Department of Food and Agriculture (CDFA) conducted this study in September and October of 1979 in Fresno and Merced Counties to monitor tribufos downwind drift during and following aerial applications. The CDFA also monitored ambient air of residential areas (Mendota and Dos Palos) for tribufos. Tribufos levels in the air during applications ranged from 14.5 $\mu g/m^3$ to 0.95 $\mu g/m^3$ between 30 and 400 meters downwind from the field. Tribufos levels several hours after the termination of applications were close to the background (0.6 $\mu g/m^3$) that was detected prior to the field applications. No tribufos was detected in the ambient air samples of residential areas.

3. Drift Study (Seiber *et al*., 1983)
   This study monitored ambient air levels of several cotton harvest aid chemicals including tribufos during commercial aerial applications in the San Joaquin Valley. Air samples collected during and following the application of tribufos were analyzed for tribufos, n-butyl mercaptan, and dibutyl disulfite. Samples collected during application of tribufos at 50 meters distance contained 1.19, 0.002, and 0.015 $\mu g/m^3$ of tribufos, dibutyl disulfite, and butyl mercaptan, respectively. Residues decreased to 0.45, 0.0005, and 0.004 $\mu g/m^3$ of tribufos, dibutyl disulfite, and butyl mercaptan, respectively, 24 hours following application.

4. Ambient Air Monitoring Study (Seiber *et al.*, 1988)
   Ambient air monitoring for tribufos was conducted during September and October 1987 at four residential areas in Fresno County (Tranquility, San Joaquin, Five Points, and Huron) and two urban background locations in cities of Fresno and Bakersfield. The four locations were in the proximity of cotton fields ranging from 10 to 400 meters from the edges of the fields. High volume air samplers equipped with XAD-4 resin sampling tubes were used. A total of 164 field samples were collected. No tribufos was detected (MDL = 0.001 $\mu g/m^3$) at urban sites except for two days in Bakersfield and four days in Fresno where the tribufos concentrations were above the MDL. Tribufos levels at four residential areas ranged from a minimum of below the MDL to a maximum of 0.34 $\mu g/m^3$.

The data generated from these studies indicate that the exposure to work crews in adjacent and near-by fields is minimal compared to that of workers involved in handling tribufos or harvesting tribufos treated cotton. The potential exposure of the general population to tribufos is assessed in a separate document (Formoli, 1999) prepared under the Toxic Air Contaminant program (Food and Agriculture Code, 14021).

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