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SUBJECT: TRIBUFOS: EXPOSURE UPDATES AND MITIGATION STATUS

Overview

Tribufos (S,S,S-tributyl phosphorotrithioate, CAS Number 78-48-8) is an organophosphate (OP) pesticide registered for use as a cotton defoliant. In plants, tribufos inhibits a key plant esterase that leads to the accumulation of the phytohormone ethylene in the leaves. This in turn causes leaf stress and premature abscission (U.S. EPA, 2015). The principal mechanism of adverse effects of OPs in animals is the irreversible inhibition of the cholinesterase (ChE) enzyme which metabolizes the neurotransmitter acetylcholine. The resultant accumulation of acetylcholine causes overstimulation of the nervous system in target and non-target organisms leading to cholinergic effects, such as ataxia, tremors, paralysis, reduced motor activity, bradycardia or tachycardia, miosis, excessive sweating, and altered mental status, among others. The typical manifestation of OP acute toxicity is often described by the acronym, SLUDGE (salivation, lacrimation, urination, defecation, gastrointestinal upset, emesis). Severe cases of exposure to OPs may lead to death, usually due to respiratory or cardiac failure. Localized effects can also be observed after tribufos exposure (Lewis, 2004).

Regulatory Status – Department of Pesticide Regulation

The California Department of Pesticide Regulation (DPR) completed the first Risk Characterization Document (RCD) for tribufos in 1998 (Lewis, 1998). The RCD used exposure estimates from the Exposure Assessment Document (EAD) published in 1990 and revised in 1995 (Formoli and Wang, 1995). The RCD identified ChE inhibition effects and dermal irritation as the most sensitive non-oncogenic oral and dermal toxicological end points and established a margin of exposure (MOE) of 100 as the level of concern (LOC). Dose-related cancer effects (liver hemangiosarcomas) were identified in mice and the cancer potency was quantified. DPR identified five handler and four fieldworker scenarios. Four of the nine occupational scenarios presented unacceptable risks for acute dermal systemic exposures (MOEs of 40 – 90), and eight

for seasonal exposures (MOEs of 17 – 86). The cancer risk for occupational scenarios ranged from 10^{-4} to 10^{-5} and presented unacceptable risk. The combined risk from diet and ambient air for non-cancer effects for the general public was not of concern (MOEs in the 1,000s), and the oncogenic risk was around 10^{-6} (Lewis, 1998).

In 1999, DPR corrected the method used for calculation of dislogeable residues from cotton bolls as part of tribufos mitigation (Andrews, 1999). Additionally, the dermal absorption rate was revised from 47.5% to 7.1% after DPR reviewed a primate dermal absorption *in vivo* study sponsored by Bayer Corporation, the registrant of the tribufos-containing product, DEF (Thongsinthusak, 2000). These changes prompted recalculation of the occupational exposures and release of a revised EAD, which also included an additional fieldworker scenario for weeders and irrigators (Formoli, 2000). As all exposures had MOEs above 100, it was determined that the label-required personal protective equipment (PPE) for handlers and a restricted entry interval (REI) of 7 days would provide adequate protection to handlers and fieldworkers, respectively. A mitigation completion memorandum was issued in 2002 (Formoli, 2002).

Tribufos was designated as a Toxic Air Contaminant (TAC) in 1999 (Helliker, 1999) after a dedicated exposure and risk assessment process determined that the cancer risk to ambient air exposures for the general public was as high as $7x10^{-7}$ (Lewis, 1999). The target risk level for carcinogens is generally $\leq 1x10^{-6}$.

In response to new toxicology data submitted by the registrant, DPR revised the RCD in 2004 (Lewis, 2004). The exposure estimates in the 2000 EAD were used along with updated points of departure (PoDs) for systemic neurological effects. The LOC of 100 was retained and DPR concluded that the MOEs for acute systemic and localized effects were in the range of 120 – 36,000. DPR found that eight of the ten seasonal occupational scenarios needed mitigation (MOEs of 23 – 75). The oncogenic risks for workers were in the range of 10^{-5} – 10^{-7}. The critical PoDs and occupational risk estimates are discussed further in this memorandum. The combined risk for non-cancer effects from diet and ambient air for the general public was not of concern (MOEs in the 1,000s), and the oncogenic risks were between 10^{-6} and 10^{-8} (Lewis, 2004).

In 2005, DPR issued a Risk Management Directive (RMD) for tribufos, asking staff to monitor the proposed mitigation being developed by the United States Environmental Protection Agency (U.S. EPA) at the time (increased REIs and "other measures"), and if the measures were insufficient, to develop mitigation steps for the occupational and residential risks identified by DPR (Gosselin, 2005).

In 2012, DPR issued an internal mitigation completion memorandum (Sanders, 2012) citing the sharp drop (approximately 10-fold) in tribufos use and few illnesses reported in California in the years between 2000 and 2010 as a reason not to pursue further mitigation of occupational exposures. The memorandum also pointed out that the mitigation measures mandated by U.S.

EPA in its 2006 Reregistration Eligibility Decision (RED) (U.S. EPA, 2006)—requiring closed mixing systems, enclosed cockpit for aerial applications, and an REI of 7 days—were already reflected on the only product label registered in California in 2012.

Other regulatory information:

- Tribufos is a California restricted material per §6400(e) of Title 3 of the California Code of Regulations (3 CCR).
- Tribufos was added to Proposition 65 list as a carcinogen in 2011.

Label Review

There are currently three active labels for products containing tribufos (Table 1). All labels carry the signal word DANGER.

Table 1. Tribufos end-use products registered in California (DPR, 2023a).

Product (year of most recent CA label)	AI %	Registrant	Registration number	REI (days)
DFT 6 EC Cotton Defoliant (2017)	70.5	Loveland Products, Inc.	34704-867-AA	7
Folex 6 EC (2012)	70.5	AMVAC Chemical Corp.	5481-504-AA	7
Tribufos 6 (2012)	70.5	Red Eagle Int., LLC	85678-15-AA	7

The label requirements for workers are:

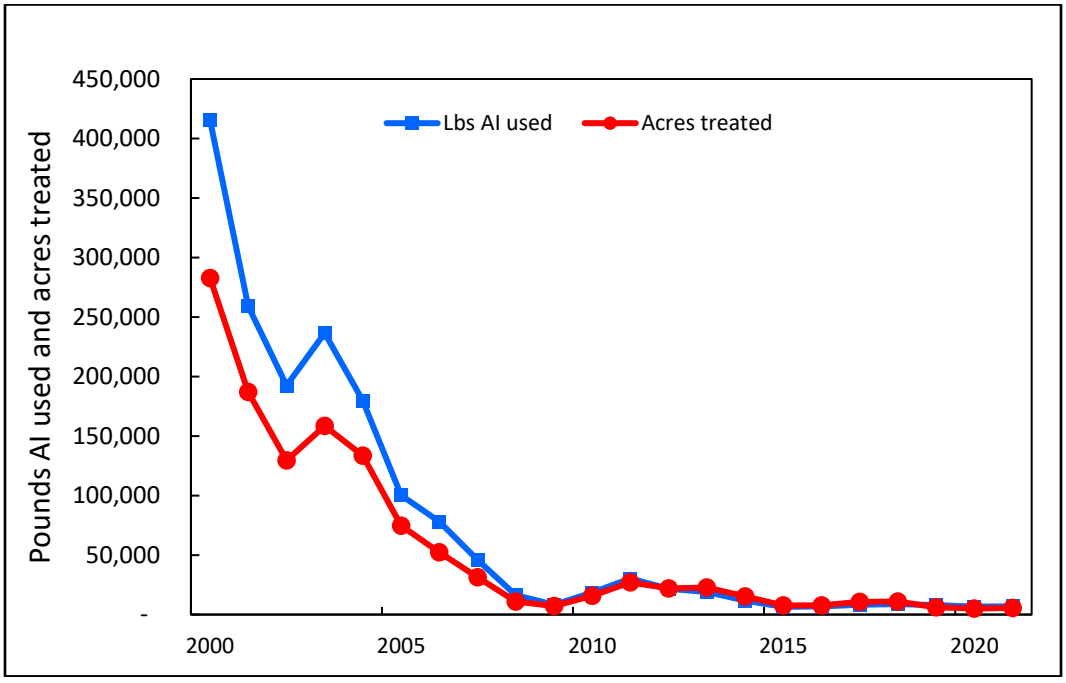
- Closed mixing/loading (M/L) for aerial applications,
- Coveralls over long-sleeved shirt and long pants,
- Chemical-resistant gloves,
- Chemical-resistant footwear plus socks,
- Protective eyewear,
- Chemical-resistant headgear for overhead exposure,
- Chemical-resistant apron when cleaning equipment, mixing, or loading,
- Pilots must use an enclosed cockpit,
- Chemigation is prohibited,
- Respirator with R, P or HE cartridges for outdoor use is required only by the Folex 6 label,
- Hand harvesting is prohibited,
- An REI and preharvest interval (PHI) of 7 days, and
- Maximum application rate of 2.5 pints product/acre/year, equivalent to 1.875 lbs AI/acre/year for California and Arizona.

In addition to the precautionary statements on the label, California regulations provide additional protections for handlers and residents. Tribufos products are Toxicity Category I and the label signal word is DANGER. All labels have warnings about skin corrosivity, and that the products "may be fatal" or "harmful" "if absorbed through skin". Such materials require closed mixing systems in California per 3CCR §6746(c). Per 3 CCR §6470(a)(1), a closed system for mixing and transfer of tribufos is also required, as well buffer zones from schools and residential areas and drift control measures when tribufos is used as a cotton harvest aid. In addition, California regulations require that occupational handlers use protective eyewear when using closed mixing system (3 CCR §6746(e)), thus providing protection to all mixers and loaders, not only those supporting aerial applications as required by the labels.

Tribufos Use

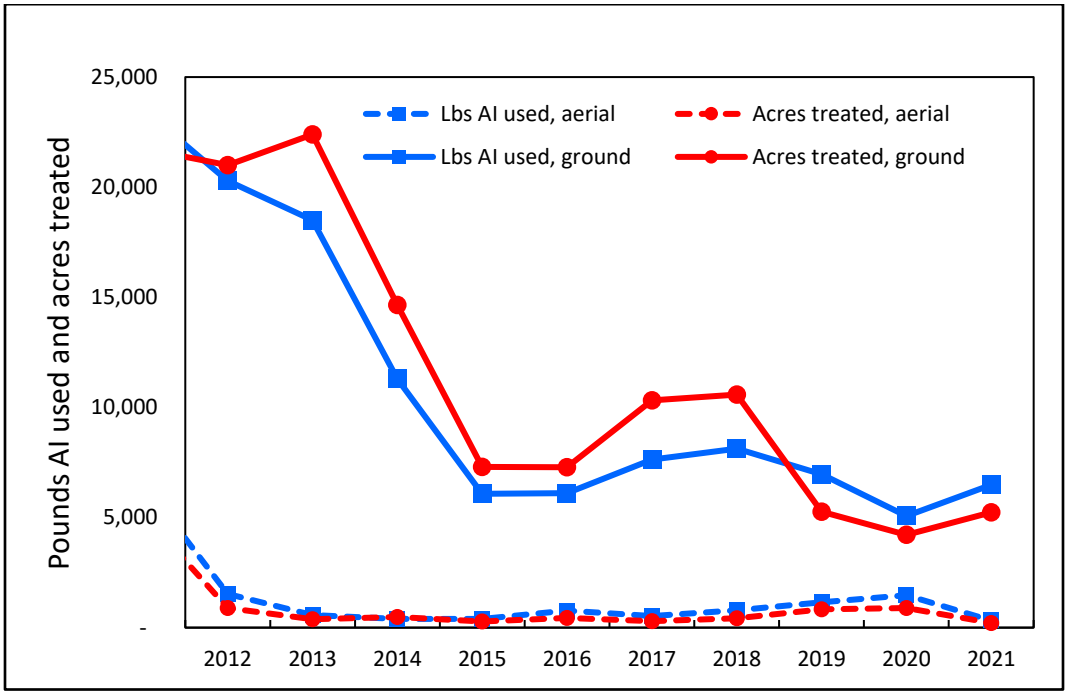
Tribufos is registered only as a cotton defoliant. Its annual use has been in decline over the past two decades (Figure 1); in 2021 (the most recent year that Pesticide Use Reporting (PUR) data were available) it was 6,800 lbs AI—about a 60-fold drop compared to 415,500 lbs AI in 2000 (DPR, 2022a, 2022b; DPR, 2023b).

Figure 1. Annual use of tribufos in California from 2000 – 2021 (lbs AI applied and acres treated) (DPR, 2022a, 2022b; DPR, 2023b).



A total of 104,500 lbs of tribufos AI were used in California in the decade between 2012 and 2021, and applications by ground equipment dominate the use with 92.4% of the amounts AI used and 95.5% of the acres treated (Figure 2). This is a reverse of the trend observed in the 2004 RCD, when most of the applications were made by air (Lewis, 2004).

Figure 2. Annual use of tribufos by ground and air equipment in California from 2012-2021 (lbs AI applied and acres treated) (DPR, 2022a, 2022b; DPR, 2023b).



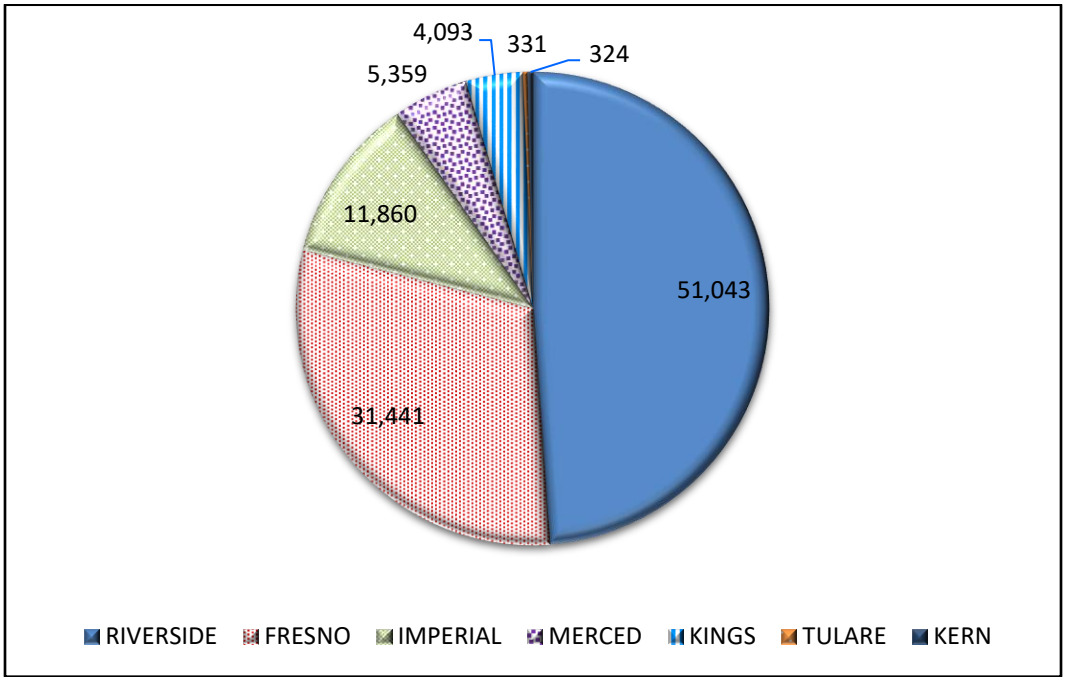
The maximum application rate currently allowed in California on tribufos labels is 1.875 lbs AI/a. As seen from the closing gap between the pounds used and acres treated each year, the mean application rate has fallen steadily over the last two decades (Figure 1). One possible reason is the increased number of ground applications compared to aerial applications, as discussed above. According to PUR data for 2012 – 2021, the mean application rate for ground applications was 0.87 lbs AI/a, and the 95th percentile was 1.50 lbs AI/a. For aerial applications, the mean application rate was 1.39 lbs AI/a, and the 95th percentile was 1.87 lbs AI/a.

Tribufos is used on a small percent of the cotton crop grown in California. A comparison of the total acres treated with tribufos (DPR, 2022a, 2022b; DPR, 2023b) and the acres planted with cotton (CDFA, 2023) shows that this share was around 5% for the 10-year period of 2012 – 2021 (113,400 cumulative acres treated vs 2,357,000 cumulative acres planted). U.S. EPA noted in the 2006 RED that in California approximately 13% of the cotton acres were treated with tribufos (U.S. EPA, 2006). The Pesticide Use Annual Report's 2021 Data Summary (U.S. EPA, 2021) shows that other defoliants, such as the hormonal defoliant thidiazuron and the herbicide/

defoliants, urea dihydrogen sulfate and sodium chlorate, are widely used on cotton. For example, in 2021, thidiazuron was applied on 135,065 acres of cotton, compared to 5,450 acres treated with tribufos.

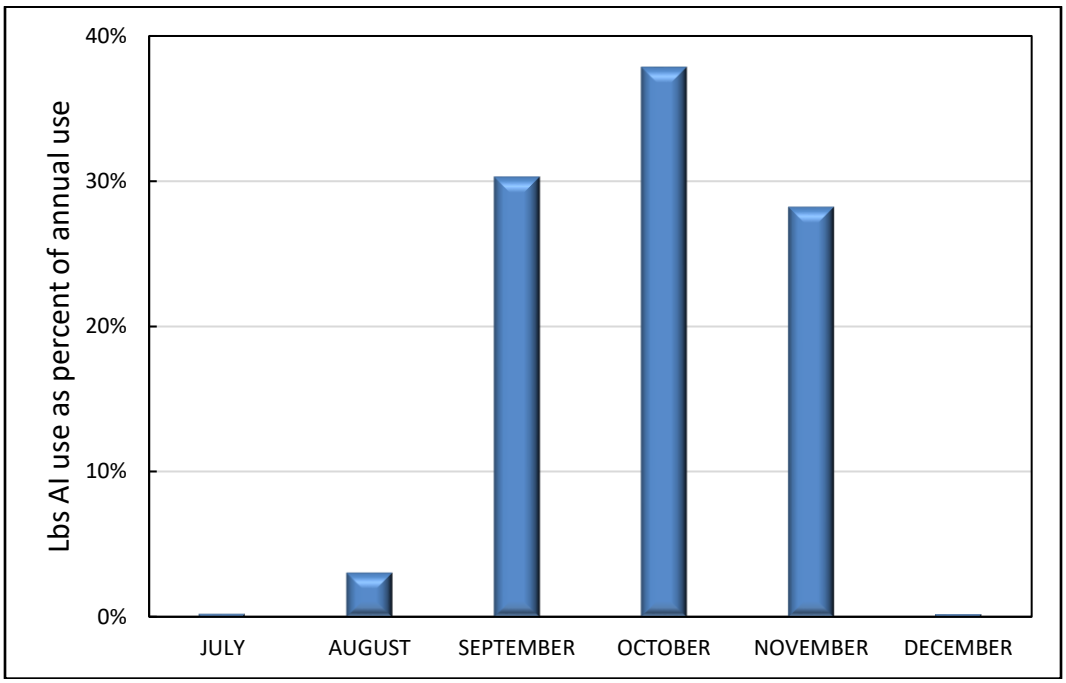
During the 2012 – 2021 period, approximately 79% of tribufos use occured in two counties: Riverside and Fresno (Figure 3).

Figure 3. Tribufos use (in lbs AI) in California by county from 2012 – 2021 (DPR, 2022a, 2022b; DPR, 2023b).



Usually, DPR defines the length of the pesticide use season as the number of consecutive months with AI use at or above 5% of the total annual pesticide use (Beauvais, 2014; Thongsinthusak, 2004). The use season for tribufos is 3 months—September to November (Figure 4). However, according to the 1995 EAD, the seasonal exposure is calculated on a basis of 21 days out of a 45-day season because of the specific climatic conditions (narrow temperature range) for effective cotton defoliation (Formoli, 1995).

Figure 4. Monthly use of tribufos in California from 2012 – 2021 (DPR, 2022a, 2022b; DPR, 2023b).



Illnesses Review

There were no reported illnesses associated with tribufos in the 15-year period between 2006 and 2020 (DPR, 2022c, 2022d). There were 15 illnesses recorded between 1992 and 2005. With the exception of two applicator cases in 1992, the rest of the incidents were due to early reentry or spray drift exposures to fieldworkers. Seven cases stemmed from a single incident in 1999 when the workers were mistakenly allowed to enter a field 5 hours after it was treated with tribufos and sodium chlorate. Some workers were hospitalized or lost days from work. The most recent case (probable relationship, from 2005) involved a farmworker who was sprayed during an aerial application of tribufos, ethephon, urea dihydrogen sulfate, and adjuvant to a neighboring cotton field. This worker experienced dizziness, headache, difficulty breathing, sore throat, and eye and skin irritation, and lost two days from work (DPR, 2022c).

U.S. EPA Status

Tribufos was first registered in the United States in 1961 (U.S. EPA, 2000). It is not a restricted use pesticide at the federal level (U.S. EPA, 2022).

U.S. EPA released the RED for Tribufos in 2006 (U.S. EPA, 2006), which contained the 2000 Tribufos Interim RED and found that the occupational risks exceeded the level of concern. The RED outlined the following mitigation measures for worker exposures:

> 1) The maximum application rate is to be reduced to 1.5 pints/A (1.125 lbs ai/A) in all states, except California and Arizona, which would remain at the higher rate of 2.5 pints/A/year (1.875 lbs ai/A). California and Arizona grow hardier varieties of cotton, which require more defoliant.
> 2) The REI is to be increased from 24 hours to 7 days;
> 3) Tribufos products are to be distributed in closed systems starting with the 2002 season,
> 4) The Agency is also requiring closed systems for aerial applicators (enclosed cockpits). (U.S. EPA, 2006, pp.23-24 of 123).

U.S. EPA published a draft human health risk assessment for tribufos in 2015 (U.S. EPA, 2015), and an addendum with revised human equivalent inhalation dose and inhalation risks in 2016 (U.S. EPA, 2016). In 2019, the U.S. EPA published a review of *in vitro* dermal absorption studies and revised the dermal PoD for tribufos to 1 mg/kg/day (U.S. EPA, 2019a, 2019b), up from 0.16 mg/kg/day (U.S. EPA, 2015).

The toxicological end points and PoDs are listed in Table 2. U.S. EPA selected a steady-state acetyl cholinesterase (AChE) inhibition endpoint for estimating human risk. Steady-state refers to the equilibrium between the concentration of the inhibited AChE and the production of new free enzyme upon repeated exposures. U.S. EPA believes this approach addresses adverse effects from short-term exposures while providing protection for long-term exposures. U.S. EPA classifies tribufos as "'likely' at high doses but 'unlikely' to be a human carcinogen at low doses." Increased carcinogenicity was observed only at extremely high doses (48 and 63 mg/kg/day in male and female mice, respectively). These doses also triggered severe ChE inhibition toxicity and mortality, so U.S. EPA stated that the steady-state risk estimates were "protective of potential carcinogenicity" (U.S. EPA, 2015, p.25).

U.S. EPA defined the levels of concern (LOCs) as MOEs. The LOC for dermal and dietary/oral exposures was an MOE < 1,000 (UF_A=10 for interspecies extrapolation, UF_H=10 for intraspecies extrapolation, and a Food Quality Protection Act (FQPA) safety factor (SF)=10 for data uncertainty for neurodevelopmental adverse effects) (U.S. EPA, 2015). The only exception was an LOC < 100 for dietary exposure of adults ≥50 years old. The LOC for inhalation exposures was an MOE < 300 (UF_A=3, UF_H=10, FQPA SF=10 for neurodevelopmental effects data uncertainty) (U.S. EPA, 2015, 2016). Even if the critical toxicological endpoint (ChE inhibition) was not sex-specific, the exposure calculations used female-specific body weight (69 kg) to account for susceptibility of pregnant women due to the uncertainty in the developmental neurotoxicity database (U.S. EPA, 2015).

Since the LOCs are different for the dermal and inhalation routes of exposure, albeit with similar toxicological endpoints, an aggregate risk index (ARI) was used as a metric of overall occupational handler risk, with a target of ARI<1 (U.S. EPA, 2015). The occupational handler risk for tribufos is driven by the dermal exposures with dermal MOEs several orders of magnitude lower than the target MOE of <1,000 (some MOEs are < 1), while the inhalation

MOEs are in double and triple digits but still below the LOC of 300 (U.S. EPA, 2015, Appendix 5; U.S. EPA, 2016). U.S. EPA concluded that all occupational handler scenarios are of concern (ARI << 1) despite mitigation measures, such as additional PPE, engineering controls, and reduced application rate (1.125 lbs AI/a) (U.S. EPA, 2015). U.S. EPA estimated that all fieldworker dermal exposures were of concern long after the expiration of the label-required REI of 7 days; the MOEs were <1,000 at 30 days post-application.

U.S. EPA evaluated the risk for residential exposures via the dermal (for adults) and dermal and incidental oral (for children) routes resulting from spray drift deposition on turf at a distance up to 300 feet from the application site. The LOC was MOE < 1,000. The estimated risks were of concern (MOEs in the single and double digits) even with decreased application rates and drift reduction measures, such as droplet size and boom height (U.S. EPA, 2015).

In February 2023, U.S. EPA published an updated risk assessment for tribufos (U.S. EPA, 2023). The document summarized the risk estimates outlined in 2015 with the updated dermal PoDs (U.S. EPA, 2019b) and inhalation PoDs (U.S. EPA, 2016). Again, most of the risk estimates (MOEs and ARIs) were well below the LOCs. In parallel, U.S. EPA conducted a "mitigation exercise," hypothesizing that if new approach methods (NAMs) currently under review in the Agency, "support[ed] the conclusion that AChE inhibition is protective of potential neurodevelopmental effects," then the FQPA SF=10 could be removed. In that case, the LOCs may be reduced 10x as shown in Table 2. In addition, a body weight of 80 kg, reflective of the general population, could be applied to the exposure estimates, instead of the female-specific body weight (69 kg) used previously. The recalculated MOEs (Appendix D in U.S. EPA, 2023) indicate that:

- all handler risks remain of concern,
- most occupational reentry risks are of concern, and
- most drift bystander risks to children and adults are of concern.

However, if certain mitigation conditions are met as detailed in Appendix D, some of the exposure scenarios may approach the target LOCs. The Agency noted that these LOC reductions were intended only for "early mitigation discussions and are **not** an indication that … these reductions will be implemented in future assessments for tribufos" (page 44 in U.S. EPA, 2023).

In May 2023, two tribufos registrants—RedEagle and AMVAC—committed to a list of agreed-upon and voluntary measures that would mitigate occupational handler and post-application risks and drift exposures to bystanders (AMVAC, 2023; RedEagle, 2023). These measures include:

- For occupational handlers:
    - reductions in the maximum application rates: 0.75 lbs AI/a for aerial applications and 1.125 lbs AI/a for ground applications,
    - limitations in the amount AI handled daily for aerial applications, equivalent to treatment of 800 acres daily, and

    - requiring closed M/L for ground applications (already required in California per 3CCR §6746(c) and 3CCR §6470(a)(1)).
- For reentry workers: REI of 10 days for applications using rates above 0.75 lbs AI/a. For applications using rates below 0.75 lbs AI/a, the REI remains 7 days.
- For drift exposures:
    - control of droplet size: only medium or coarser droplet size is allowed, and
    - buffer zones of 25-50 ft for residential areas depending on the application method and boom height (1/8-mile from schools and one-half mile from residential areas is required in California per 3CCR §6470(a)(3)(4)).

All end-use products are subject to the mitigation measures outlined above. U.S. EPA accepted the revised product labels in September 2023. Although U.S. EPA has not published risk estimates that have been updated according to the new mitigation measures, the Agency expects that these measures would not fully mitigate all occupational and spray drift risks. U.S. EPA plans to publish a Proposed Interim Decision (PID) for tribufos in 2025, and to complete the registration review process for tribufos in 2025-2026 (Anna Romanovsky, U.S. EPA Chemical Review Manager for tribufos, personal communications, April-May 2023).

Risk Assessment

The critical toxicological endpoints and PoDs selected by DPR and U.S. EPA and corresponding estimated health risks are presented in Table 2.

Table 2. Toxicological endpoints and points of departure selected by DPR and U.S. EPA, and corresponding human health risk estimates.

Criterion	DPR (Lewis, 1999, 2004)	U.S. EPA (2015, unless noted otherwise)
Critical toxicological end points and PoDs		
Oral PoD	• Acute NOEL=2 mg/kg/day for ChE inhibition (RBC and plasma), decreased motor activity and neurological effects in rats. • Oral absorption: 70% (rat). • **LOC=100.**	• Acute dietary $BMDL_{10}$=1.05 mg/kg/day for RBC ChE inhibition in male rat pups (acute study). • Steady-state dietary and oral $BMDL_{10}$=0.19 mg/kg/day for RBC ChE inhibition in adult rats (subchronic study). • Oral absorption: 55-80% (rat). • **LOC=1,000** for children & females (<50 years old) (UF_A=10, UF_H=10, FQPA SF=10 for developmental neurotoxicity data uncertainty); • **LOC=100** for adults (>50 years old) (UF_A=10, UF_H=10);

Criterion	DPR (Lewis, 1999, 2004)	U.S. EPA (2015, unless noted otherwise)
		• **LOC=100** for all age/sex groups (UF_A=10, UF_H=10) (U.S. EPA, 2023).
Dermal PoD	• Acute systemic NOEL=1.4 mg/kg/day (adjusted for oral absorption) from rat neurotoxicity oral study for neurological effects (decreased motor activity & neurobehavioral effects), and ChE inhibition (RBC and plasma). • Acute dermal NOEL=8.3 mg/cm^2 from rabbit dermal irritation study. • Seasonal NOEL=0.1 mg/kg/day (adjusted for oral absorption) from rat neurotoxicity oral study for RBC, plasma, and brain ChE inhibition. • Dermal absorption: 7.1% based on primate *in vivo* study. • **LOC=100.**	• Steady-state PoD=1 mg/kg/day (21-day dermal rabbit study for RBC ChE inhibition in adult females (U.S. EPA, 2019b), adjusted for *in vitro* dermal absorption studies (U.S. EPA, 2019a). • Seasonal PoD=N/D. • Dermal absorption=N/A (PoD is from dermal study). • **LOC=1,000** for all age/sex groups (UF_A=10, UF_H=10, FQPA SF=10); • **LOC=100** for all age/sex groups (UF_A=10, UF_H=10) (U.S. EPA, 2023).
Inhalation PoD	• Not determined. • Where inhalation data available, the inhalation exposure is summed with dermal exposure and risk estimated using oral PoD. • **LOC=N/A.**	• HED=0.16 mg/kg/day (13-wk rat inhalation study for RBC ChE inhibition in adult males, (U.S. EPA, 2016). • HEC=0.0017 mg/L. • **LOC=300** for all age/sex groups (UF_A=3, UF_H=10, FQPA SF=10). • **LOC=30** for all age/sex groups (UF_A=3, UF_H=10) (U.S. EPA, 2023).
Cancer	• Oncogenic potency 4.7x10^{-2} (MLE) and 8.4x10^{-2} (95% upper bound) (mg/kg/day)$^{-1}$ for liver hemangiosacromas in male mice.	• N/D (see above text).
Exposure scenarios and risk estimates[a, b]		
Occupational handlers	• MOEs>100 for all short-term exposures. • MOEs=30-57 for 4/5 seasonal exposures. • Inhalation risk: Not considered separately from dermal risk. • Oncogenic risk: Up to 10^{-5}.	• Dermal MOEs<<1,000 all scenarios. • Inhalation MOEs<300 all scenarios. • ARI<<1. • Oncogenic risk: N/D (N/A).

Criterion	DPR (Lewis, 1999, 2004)	U.S. EPA (2015, unless noted otherwise)
Occupational reentry (fieldworkers)	• MOEs>100 for all short-term exposures. • MOEs=23-75 for 4/5 seasonal exposures. • Oncogenic risk: Up to 10^{-5}.	• Dermal MOEs<1,000. • Oncogenic risk: N/D (N/A).
Bystander/residential	• Ambient air: TAC designation for cancer risk (up to $7x10^{-7}$). REL=42 ng/m^3 (3.3 ppt) for cancer effects. No concern for ChE effects. • Drift spray deposit: N/D.	• Ambient air: N/D. • Drift spray deposit on turf: dermal and incidental oral MOEs<<1,000.

Abbreviations: (A)ChE=(Acetyl) Cholinesterase; ARI=Aggregate risk index. ARI=1 ÷ [(Dermal LOC ÷ Dermal MOE) + (Inhalation LOC ÷ Inhalation MOE)]; BMDL=Benchmark dose lower confidence limit; FQPA SF=Food Quality Protection Act Safety Factor; HEC/D=Human equivalent concentration/dose; LOC=Level of concern; M/L(/A)=Mixer/loader(/applicator); MLE=Maximum likelihood estimate; MOE=Margin of exposure (MOE=PoD/Exposure); N/A=Not applicable; N/D=Not determined; NOEL=No-observed effect level; PoD=Point of departure; RBC=Red blood cell; RCD=Risk characterization document; REL=Reference exposure level; TAC=Toxic air contaminant; UF_A=Uncertainty Factor for interspecies extrapolation, UF_H=Uncertainty Factor for intraspecies extrapolation.

[a] Details about DPR's risk estimates can be found in Table 3 below.

[b] U.S. EPA did not publish recalculated human risks after the adoption of the mitigation measures in May 2023.

As evident from Table 2, there are notable differences in DPR's and U.S. EPA's approaches to occupational and residential exposure risks, resulting in different risk estimates for the exposed population groups.

One significant difference is how the agencies deem tribufos toxicity as a ChE inhibitor: U.S. EPA considers all exposures to be steady-state and, as such, representative of both short- and longer-term durations of exposure (U.S. EPA, 2015). DPR, on the other hand, separated the exposure durations to short-term, seasonal, and long-term based on different PoDs and found that only seasonal exposures present significant occupational risk and require mitigation (Lewis, 2004).

The two agencies also differed in the approaches they adopted to assess dermal and inhalation risk. Although DPR and U.S. EPA selected different toxicologic endpoints, they arrived at similar dermal PoDs. However, the established LOCs differ by 10-fold, as U.S. EPA applied an FQPA safety factor to risks from all exposure routes to account for uncertainty in the developmental neurotoxicity database. U.S. EPA found that dermal exposures are the major driver in the occupational and bystander risks, and that worker risks were orders of magnitude higher than the LOC even with the addition of mitigation measures. DPR's risk estimates showed that occupational risk was at levels below, but close to the LOC. DPR did not identify an

inhalation toxicological PoD, while U.S. EPA derived one from a rat inhalation study. Notably, the inhalation exposures do not drive U.S. EPA's human health risk estimates.

The agencies also differ in their approach to the carcinogenicity of tribufos. U.S. EPA did not estimate the oncogenic risk for tribufos because it is considered to have low carcinogenic potential, while DPR identified dose-related carcinogenic effects and found oncogenic risks of concern for workers, as well as for residents.

Mitigation

Occupational risk

Table 3 presents in detail the seasonal and cancer occupational risk estimates, as listed in the 2004 RCD. These scenarios are included in the table because all of them required mitigation, while the short-term exposures were not of concern (Lewis, 2004). The exposure estimates (short-, intermediate-, and long-term) calculated in the EAD were based on the product application rate used in the respective exposure assessment studies summarized in the EAD (Formoli, 2000). As evident from Table 3, in most cases 1.9 lbs AI/a was used, which was the maximum application rate allowed on the labels at the time.

While DPR uses upper-bound or maximal-value exposure inputs as a health-protective approach (worst case scenario) to calculate short-term exposures, DPR's practice is to use central tendency exposure values (e.g., means) for mid- and long-term exposure estimates because they reflect the typical pesticide use patterns.

DPR updated the mid- and long-term occupational risk estimates identified in the RCD to consider the following factors:

- the typical application rates discussed in the pesticide use section, when applicable, and
- the latest mitigation measures negotiated by U.S. EPA (AMVAC, 2023; RedEagle, 2023) and discussed in the U.S. EPA Status section.

Analysis of the latest 10-year PUR data showed an average application rate for ground use in California at 0.87 lbs AI/a. This value was used to recalculate the risk estimates for handlers participating in ground applications, and for all fieldworkers, because applications by ground equipment represented 90% of tribufos use in the last 10 years.

The average application rate for aerial applications in California was estimated to be 1.39 lbs AI/a. However, for handlers in aerial applications, DPR used the rate capped at 0.75 lbs AI/a by the U.S. EPA mitigation (AMVAC, 2023; RedEagle, 2023).

The typical daily acreage for aerial applications is 1,200 acres. The latest mitigation measures limited the amount AI handled per day to that was sufficient to treat 800 acres (AMVAC, 2023;

RedEagle, 2023). The revised MOEs in Table 3 for handlers involved in aerial applications were also adjusted to reflect this restriction in daily acreage.

U.S. EPA's 2023 mitigation measures also extended the REI to 10 days for fields treated at application rates above 0.75 lbs AI/a. The revised risk values in Table 3 incorporated exposure estimates at day 10 post-application using a log-quadratic regression for residue decay on cotton, as suggested by Formoli (2000).

The results of all the above adjustments are shown in the last column in Table 3. Despite these adjustments, the revised MOEs for M/L supporting ground applications (MOE=55) and irrigator/weeder (MOE=80) remain below 100. All other non-cancer risks were mitigated by the impending label changes.

The RCD found that all but one occupational exposure had unacceptable (above $1x10^{-6}$) cancer risks (Lewis, 2004). The risk for ground applicator was estimated at $9.4x10^{-7}$ by the maximum likelihood estimate (MLE)—one of two methods used in the RCD to calculate cancer potency. The other method—95% upper bound estimate (UB)—showed unacceptable risk at $1.7x10^{-6}$ for this scenario. Adjusting the oncogenic risk estimates for average application rate and for the most recent U.S. EPA mitigation measures did not significantly mitigate the cancer risk values; only one scenario—ground applicator—had a cancer risk estimate lower than 10^{-6} using both the MLE and 95% UB methods for calculating cancer potency ($4.3x10^{-7}$ and $7.7x10^{-7}$, respectively). Table 3 below lists only the worker scenarios with the highest oncogenic risk within each handler and fieldworker category: M/L supporting ground applications and irrigator-weeder.

The PPE and engineering controls applicable to occupational exposures are described in the EAD as follows: ground applicators in enclosed cabs and pilots wear work clothing (long-sleeved shirt, long pants, socks, and shoes); mixer/loaders wear work clothing, gloves, and an apron and use a closed mixing system; and flaggers wear work clothing, coveralls, gloves, hat, and a dust mask (Table 3, Formoli, 2000). In addition, mixer/loaders wore goggles and rubber boots (Formoli, 2000). The EAD does not specify if the pilots were in open or closed cab. The product labels implemented after 2006 require that pilots be in an enclosed cab.

The exposures calculated in the EAD (Formoli, 2000) were based on PPE and REIs which are required by the currently active in California tribufos labels and listed in the Label Review section. These requirements, combined with the California regulations also described in the Label Review section of this Memorandum**,** provide the maximum reasonable protection (PPE and engineering controls) for handlers and fieldworkers.

Table 3. Seasonal and cancer occupational risk[a] for tribufos (Formoli, 2000; Lewis, 2004; and updated in this memorandum). Targets: MOE <100 for non-cancer risks, <1x10^{-6} for cancer risk.

Exposure Group	Work Task	Seasonal and Cancer Risk Estimates (Formoli, 2000; Lewis, 2004)		Revised Seasonal and Cancer Risk Estimates	
		Study Application Rate (lbs AI/a) (Formoli, 2000)	Seasonal MOE[b] (Table 27, Lewis, 2004)	Application Rate (lbs AI/a)	Recalculated Seasonal MOE
Handler, Aerial	Mixer/Loader	1.50[c]	57	0.75[d]	171[e]
	Pilot	1.50[c]	50	0.75[d]	150[e]
	Flagger	1.33[c]	57	0.75[d]	152[e]
Handler, Ground	Mixer/Loader	1.90	30	0.87[f]	55
	Applicator (closed cab)	1.90	400	0.87[f]	874
Fieldworker	Picker operator	1.90	52[g]	0.87[h]	178[e, i]
	Module builder operator	1.90	133[g]	0.87[h]	476[i]
	Raker	1.90	75[g]	0.87[h]	260[e, i]
	Irrigator/Weeder	1.90	23[g]	0.87[h]	80[i]
	Tramper	1.90	31[g]	0.87[h]	107[e, i]
			Oncogenic risk[j]		Oncogenic risk
Handler, Ground	Mixer/Loader	1.90	1.3x10^{-5} (MLE) 2.4x10^{-5} (95% UB)	0.87[f]	6.0x10^{-6} (MLE) 1.1x10^{-5} (95%UB)
Fieldworker	Irrigator/Weeder	1.90	1.7x10^{-5} (MLE)[g] 3.1x10^{-5} (95% UB)[g]	0.87[h]	4.2x10^{-6} (MLE)[i] 7.4x10^{-6} (95%UB)[i]

[a] Only seasonal and cancer estimates are listed here because MOEs for all short-term exposures exceeded the LOC of 100, indicating no unacceptable risk (Lewis, 2004).
[b] MOE=PoD/Seasonal average daily dose (SADD). A subchronic no-observed-effect level (NOEL) of 0.1 mg/kg/day from rat neurotoxicity oral study for plasma, RBC, and brain ChE inhibition was selected as a PoD (Lewis, 2004). SADD was estimated from chemical- and scenario-specific exposure studies under the respective study conditions (Formoli, 2000).
[c] Table 3 of the EAD presented the exposure estimates as a mean between exposures of handler crews applying tribufos at different rates (Formoli, 2000). We calculated the application rate as an average of the application rates used by two crews (1.9 and 1.1 lbs AI/a) for the M/L and pilot scenarios, and by three crews (1.0, 1.9, and 1.1 lbs AI/a) for the flagger scenario.
[d] Maximum application rate allowed for aerial applications (AMVAC, 2023; RedEagle, 2023).
[e] MOEs that exceeded 100 following calculation adjustments as described in the text and footnotes (also shown in green font).
[f] Mean application rate from PUR data for 2012-2021 (see Tribufos Use section).
[g] REI=7 days.

[h] The mean application rate for ground applications was used because approximately 90% of tribufos is applied by ground equipment in California (see Tribufos Use section). The maximum application rate allowed for ground applications is 1.125 lbs AI/a (AMVAC, 2023; RedEagle, 2023).
[i] REI=10 days (AMVAC, 2023; RedEagle, 2023).
[j] Oncogenic risk=Oncogenic potency x Lifetime average daily dose (LADD). Oncogenic potency was calculated by two methods in the RCD (Lewis, 2004): maximum likelihood estimate (MLE) and 95% upper bound estimate (95% UB). Only the highest cancer risk of each handler and fieldworker group, respectively, is listed in the table.

Residential risk

Tribufos is a restricted use material in California and there are no residential uses of the pesticide. Therefore, residential handler and post-application residential exposures are not anticipated. However, residents living in a vicinity of cotton fields treated with tribufos could be exposed to pesticide residues in ambient air (Formoli, 1999).

The analysis of residential exposures showed negligible risk for ChE effects with MOEs in the thousands for combined dietary and ambient air exposure for selected population subgroups (Lewis, 2004). However, tribufos received a TAC designation in 1999 based on identified cancer risks to the general population in Fresno and Kern Counties.

The TAC RCD (1999) established the following reference exposure levels (RELs) for tribufos in ambient air:

- 8.8 $\mu g/m^3$ (0.68 parts per billion (ppb)) for acute and seasonal cholinergic effects,
- 43 $\mu g/m^3$ (3.3 ppb) for other toxicological effects, and
- 42 ng/m^3 (3.3 parts per trillion (ppt)) for cancer effects.

According to the provisions of 3 CCR §6864 (formerly §6890), a pesticide is identified as a TAC if its detected air concentrations "would result in a ten-fold lower risk than that which has been determined by the director to be a negligible risk." (DPR, n.d.).

Ambient air concentrations of several organophosphate pesticides, including tribufos, are being monitored seasonally in four California counties by the joint Air Monitoring Network (AMN) program of DPR and the California Air Resources Board (CARB) starting in 2018. The 24-hr/4 times per week samples are collected in January-March in Imperial County, March-May in Kern County, and June-August in Fresno and Tulare Counties. The most recent report was published in 2019 and contains results from monitoring performed in 2018. Only one sample—in Westmorland, Imperial County—was reported to contain quantifiable concentrations of tribufos (CARB, 2019). This sample was collected on January 16, 2018, and contained 38 ng/m^3 of tribufos—below the TAC REL for cancer effects listed above. Being a cotton harvesting aid, the tribufos use season is in the fall (Figure 4). Therefore, the validity of this sample is debatable, as there were no tribufos applications in Imperial County in January 2018.

To our knowledge there are no other reports of detectable ambient air concentrations of tribufos in California in the past decade.

Conclusions

DPR finalized the risk assessment for tribufos in 2004 and concluded that the MOEs for acute exposures were not of concern. In contrast, most seasonal exposures posed unacceptable risks to workers (Lewis, 2004). The PPE and engineering controls included in the risk estimates are based on then- and currently registered California product labels and provide adequate protection for workers. DPR's updated seasonal MOEs (Table 3), which adjust for the most recent U.S. EPA mitigation measures and for typical application rates in California, mitigate the overall seasonal non-cancer occupational risk, except for two scenarios: M/L supporting ground applications and irrigator/weeder.

Tribufos was added to the TAC list in 1999; at the time there were ambient air detections at levels of concern for cancer risk to residents in Fresno and Kern Counties. The sharp decrease in tribufos use over the last decade and the recent monitoring reports of ambient air concentrations in California suggest that tribufos exposures may not pose unacceptable risk to residents.

In its most recent documents (2015 – 2023), U.S. EPA found that tribufos use presented occupational risks that exceeded the levels of concern. In September 2023, the Agency adopted revised federal product labels containing mitigation measures. U.S. EPA is also collecting information on NAMs, which could help in the future to define chemical-specific safety and uncertainty factors rather than using default factors. U.S. EPA is poised to issue a PID for tribufos in 2025. DPR will continue monitoring the status of tribufos at U.S. EPA, and if necessary, will take appropriate action to ensure the safe use of tribufos in California.

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